Liposarcoma of the Colon: A Case Report and Review of the Literature

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Liposarcoma is a malignant mesenchymal tumor frequently located in the retroperitoneum and rarely presents as an isolated lesion in the colon. To our knowledge, only three cases of primary colon liposarcoma have been reported in the world literature to date. In this article, we report a case of liposarcoma of the colon in a 46-year-old man. The patient presented with abdominal pain and a palpable mass. Abdominal ultrasonography and computed tomogram confirmed the presence of a large intra-abdominal fatty tissue mass, but the colon origin of the tumor was revealed only on laparotomy. During surgery, a voluminous (12 cm × 11 cm × 10 cm) lesion situated in the subserosa of the ascending colon was found, and a right hemicolectomy with radical lymph node dissection was performed. The pathological diagnosis of the resected tumor revealed primary colon liposarcoma (myxoid subtype). The postoperative course was uneventful, and the patient remained free of disease for 12 months. No adjuvant therapy was performed. Diagnostic and therapeutic problems related to this type of neoplasm as well as literature reviews are reported. Curative R0 resection remains the main treatment for primary and recurrent liposarcomas. (J GASTROINTEST SURG 2006;10:652–656)

KEY WORDS: Colon, liposarcoma, mesocolon

Liposarcoma, the most common soft tissue sarcoma, represents 20% of the mesenchymal malignancies and tends to occur in the retroperitoneum and deep soft tissues of the trunk and extremities.[1,2] It infrequently arises in the gastrointestinal system, and colon liposarcoma is extremely rare. Our review of the literature revealed that only three cases of these uncommon neoplasms have been reported to date.[3–5] Sporadic case reports make it difficult to determine the true diagnostic features and appropriate treatment of this rare tumors.

Herein, we report the additional case of a primary colon liposarcoma that was successfully resected and review diagnostic and management strategies previously reported in the literature. To our knowledge, this represents the fourth case reported in the world literature, and the first case of primary liposarcoma presenting with a voluminous extraluminal colonic mass. Moreover, this report, for the first time, provides a computed tomography image of primary liposarcoma of the colon.

CASE REPORT

A 46-year-old man with abdominal pain was admitted to the hospital. His previous history, as well as family history, was unremarkable. Physical examination revealed a large soft mass palpable in the right half of the abdomen (in the right lower quadrant).

Laboratory data on admission were within normal limits. The tumor markers, including carcinoembryonic antigen (CEA), CA 125, and CA 19.9 were normal. An abdominal ultrasound showed the presence of a hyperechoic mass with well-defined margins in the right abdomen. A computed tomography (CT) scan showed a homogeneous, smoothly outlined, low attenuation mass (22–25 UH; Fig. 1). A tentative diagnosis of intra-abdominal fat-containing tumor (lipoma, liposarcoma) without regional or distant metastases was made.

A laparotomy was performed with a midline incision. No ascites or peritoneal dissemination was

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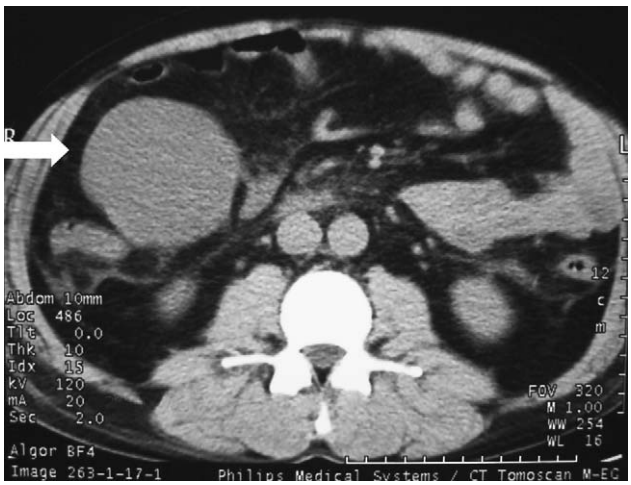


Fig. 1. Abdominal computed tomographic scan showing a well-circumscribed, homogeneous mass of low attenuation, located in the iliac area (*arrow*).

observed. The tumor was situated in the subserosa of the ascending colon, had a diameter of 11 cm, and showed well-defined borders. There were some enlarged lymph nodes in the colonic mesentery, but the paraaortic and superior mesenteric nodes were not involved. The patient underwent a right hemicolectomy with radical lymph node dissection.

Macroscopic examination of the specimen revealed a yellowish capsulated mass measuring 12 cm × 11 cm × 10 cm (Fig. 2, *A*). The mass was located in the subserosa of the ascending colon, and colonic mucosa was not involved by the tumor at any place in the resected specimen (Fig. 2, *B*). Pathologic examination revealed myxoid-type liposarcoma of the colon (Fig. 3). There was no evidence of necrosis, vascular invasion, or lymph node metastases.

The postoperative course was unremarkable, and 12 months after the operation, the patient was well without evidence of disease.

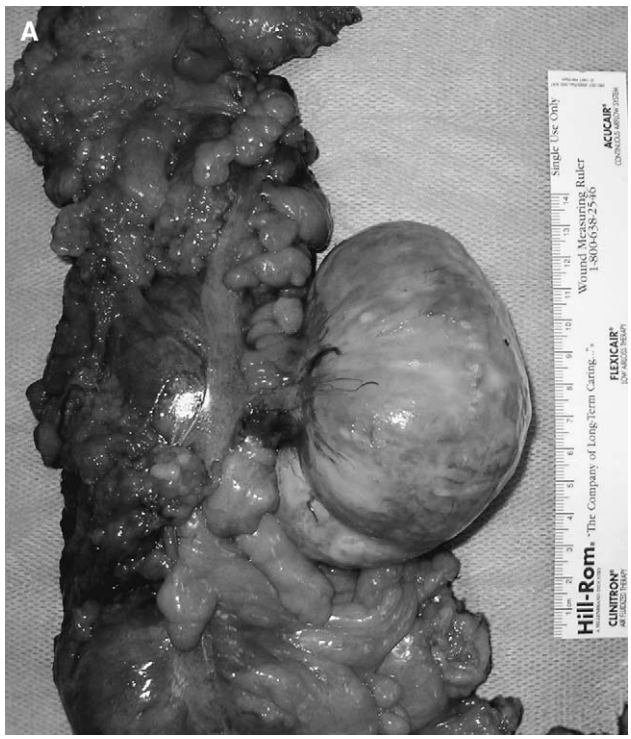
DISCUSSION

The first case of primary liposarcoma of the colon was reported by Wood and Morgenstern.[3] Since then, only three well-documented cases, including our patient, have been reported.[4,5] The clinicopathologic characteristics of these four reported cases are summarized in Table 1.

From a histopathologic point of view, these neoplasms take their origin from primitive mesenchymal cells and are rarely encountered in fat-rich areas such as the subserosa of the intestinal tract.[2] In the recent World Health Organization classification, liposarcomas are divided into five major histological subtypes: atypical lipomatous tumor (well-differentiated liposarcoma), myxoid liposarcoma, pleomorphic liposarcoma, dedifferentiated liposarcoma, and mixed type liposarcoma. The well-differentiated type occurs in 40%–45%, the myxoid in 35%–40% and the pleomorphic in 5% of all the liposarcomas.[1] Only three histopathologic subtypes of colon liposarcoma were described to date: well differentiated (case 3), the myxoid type (cases 1 and 4), and the pleomorphic type (case 2). According to the WHO classification (2002),[1] the definition of myxoid liposarcoma is "neoplasms composed of uniform round to oval shaped primitive nonlipogenic mesenchymal cells and a variable number of small signet-ring lipoblasts in a prominent myxoid stroma with a characteristic branching vascular pattern." Our case satisfies these criteria and is thus considered as a primary liposarcoma of the colon.

The primary liposarcoma of the colon tends to occur in adults (mean ± SD age of 51.2 ± 3.9 years; range, 45–62). In general, liposarcoma occurs almost exclusively in adults, with a peak incidence between the 5th and 6th decades. Surprisingly, in all previously reported cases, these neoplasms predominantly affect female patients, which is not consistent with the slight male predominance observed in the soft tissue liposarcomas. Our report represents the first case of primary colon liposarcoma in a male patient. Most tumors (75%) were located in the right colon. The size and growth pattern of primary colon liposarcoma influence the clinical presentation. In the reported cases, the symptoms are variable, nonspecific, and include abdominal pain, diarrhea, weight loss, anemia, and hematochezia.[3–5] An abdominal mass may be palpable.

The optimal diagnostic program for colon liposarcoma cannot yet be defined due to the small number of published cases. Endoscopy can highlight a polypoid submucosal mass.[5] Studies based on CT and magnetic resonance (MR) imaging of liposarcomas demonstrated the correlation of the histological subtypes of these neoplasms with the radiological findings. CT density and MR signal reflect the amount and distribution of fat in the neoplasms. Tumors of higher histological grade are more vascular and contain less fat. Myxoid, pleomorphic, and round cell liposarcomas have little fat and simulate other partly necrotic nonfatty tumors.[6] In our case, CT scan confirmed the presence of a large intraabdominal fatty tissue mass but did not show broad fixation of the tumor to the wall of the colon. To the best of our knowledge, the CT appearance of primary colon liposarcoma has not been previously described in the literature, so accurate preoperative diagnosis is not possible in all cases, and only surgical resection and histopathologic examination are



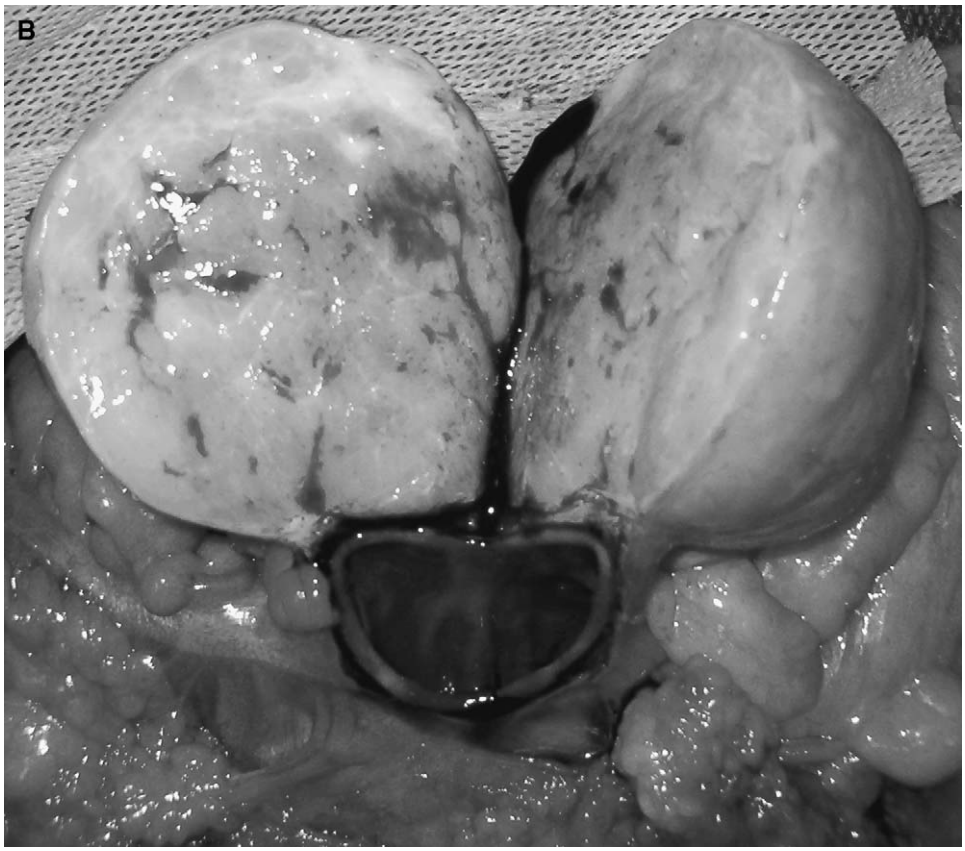


Fig. 2. Macroscopic view of the resected specimen (**A**) large extraluminal mass of the ascending colon (**B**) yellowish-white in color on cut section; the tumor was situated in the subserosa without involving of mucosa.

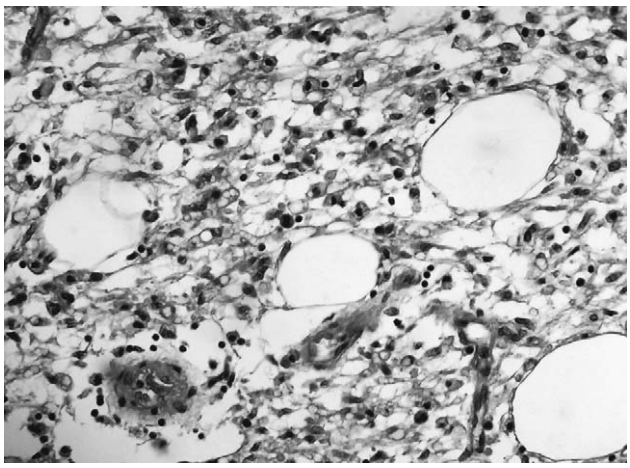


Fig. 3. High-power view of histological findings of the resected tumor (H & E stain × 200).

required to confirm the nature of lesions.[3–5] Not surprisingly, most of the lesions are often voluminous at the time of diagnosis, because characteristic signs and symptoms are often absent. All published cases are of large tumors that ranged in greatest dimension from 6 to 12 cm. These features are common among liposarcomas in general.[2] Our case demonstrated that, despite substantial lesion size, only extraluminal localization of the colon liposarcoma might induce atypical presentation and a long disease-free interval.

The growth pattern of colon liposarcoma is typically intraluminal.[3–5] On gross examination in most of the cases, the tumor consisted of a polypoid, yellow-to-gray tan mass protruding into the lumen of the colon. Recently, Chen[5] reported a case of colon liposarcoma that formed a dumbbell-shaped lesion with an intraluminal polypoid and a mesocolic component. In an analogical situation, this lesion may resemble primary liposarcomas of the mesocolon.[7,8] To our knowledge, ours is the first reported case of primary liposarcoma presenting with an extraluminal colonic mass.

The protocol for treatment of liposarcoma of the colon has not been well established. However, most authors have recommended complete wide excision, which is the treatment of choice for such tumors.[3–5] The role of adjuvant or neoadjuvant therapy in colon liposarcoma is, however, still unclear and a controversial subject. Chemotherapy after resection of a recurrent tumor was reported only in one case.[1]

Histological subtyping of liposarcomas has shown to correlate with clinical behavior. Available data suggest that a well-differentiated subtype is considered to be a low-grade malignancy, whereas the pleomorphic type is considered to have a high propensity to exhibit malignant behavior. The myxoid types are intermediate.[2] In general, liposarcoma should be considered to have a malignant potential. Not surprisingly, this neoplasm has a remarkable tendency to recur after surgical excision, it rarely metastasizes.[1,2] It is a well-established fact that myxoid liposarcoma usually metastasizes in the lungs and bone.[2] A more recently study demonstrated that this histopathologic subtype has a particular propensity for soft-tissue metastases.[9] On the other hand, only one case, reported by Wood and Morgenstern,[3] demonstrated that tumor recurrence developed 3 years later after surgery for myxoid colon liposarcoma. However, only one reported case (case 3) had regions of mesocolic lymph node metastasis.[4]

The prognosis of primary colon liposarcoma is difficult to predict because of the small number of reported cases. Well-differentiated tumors have the most favorable outcome, with a 5-year survival rate estimated between 75% and 100%. Round cell and pleomorphic liposarcomas have the worst prognosis with 0 to 20% survival rate at 5 years.[1] Patients with myxoid liposarcoma who are surgically treated demonstrate good survival even 10 years after surgery. Three parameters have been correlated with poor prognosis: age (greater than 45 years), the presence of round cells, and necrotic areas within the

Table 1. Review of cases with colon liposarcoma

Case No.	Author (yr)	Age/ Sex	Presentation	Location	Tumor size, cm	Histological type	Recurrence	Follow-up
1	Wood and Morgenstern (1989)[3]	62/F	Pain + palpable mass	ICV, C, AC	12	ML	Yes (36 mo)	Died 48 mo
2	Parks et al. (1994)[4]	45/F	Abdominal discomfort + diarrhea + weight loss + anemia	AC	6 × 5 × 4	PL	NA	NA
3	Chen (2004)[5]	52/F	Pain + hematochezia	DC	7.5 × 5.5 × 5	WDL	No	Alive 24 mo
4	Current case	46/M	Pain + palpable mass	AC	12 × 11 ×10	ML	No	Alive 12 mo

AC = ascending colon; C = cecum; DC = descending colon; ICV = ileocecal valve; ML = myxoid liposarcoma; NA = not available; PL = pleomorphic liposarcoma; WDL = well-differentiated liposarcoma.

mass; the grade of the neoplasm influences the incidence of metastasis and its recurrence.[2] In our case, absence of necrotic areas within the mass, myxoid subtype, and complete resection of the tumor could provide a good survival free of recurrences.

In summary, primary colon liposarcoma represent the difficulties in differential preoperative diagnosis because of the nonspecific nature of the symptoms and inconclusive findings of imaging modalities. In agreement with other authors, we believe that surgical resection offers the only chance of cure and prolongs survival. Special guidelines for the treatment of these exceedingly rare neoplasms may be defined after collection of a larger number of cases.

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Malakoplakia Occurring in Association With Colon Carcinoma

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Malakoplakia, characterized by histiocytes with Michaelis-Gutmann bodies, is a rare entity. It is particularly so in the gastrointestinal tract, where it has been described in association with colon cancer, with about 20 cases described worldwide. The significance of this condition lies in its potential effect upon the preoperative staging and treatment of associated colorectal cancer. Its presence may lead to preoperative clinical and radiological over staging and more extensive resection, as well as the use of neoadjuvant therapy or a decision to undertake palliative care. This condition is more common in males. We present the case of the oldest reported patient with this association. The patient was a 90-year-old female who was treated with a sigmoid resection for an obstructing sigmoid lesion. At operation, the left ureter was embedded within an inflammatory pericolic mass but was not grossly involved with tumor. The tumor was a Dukes' stage B adenocarcinoma and occurred in association with malakoplakia. (J GASTROINTEST SURG 2006;10:657–661)

KEY WORDS: Malakoplakia, colon cancer

Malakoplakia, a rare condition first described in the early 1900s, is a chronic inflammatory condition characterized by a histiocytic infiltrate with concentrically layered intracytoplasmic inclusions called Michaelis-Gutmann bodies. It is most commonly seen in the genitourinary tract; the gastrointestinal tract is the second most common site of occurrence. The colon seems to be the most common site, accounting for nearly all reported cases. It has been described in association with a wide range of conditions, such as adenocarcinoma, colonic adenomas, ulcerative colitis, and diverticulosis. When it occurs in association with colon cancer, it may potentially alter the preoperative staging, and thus, the treatment of colon cancer. Its natural history is unknown. It has not been previously described as occurring in association with colon cancer in the very elderly. We present a case of the oldest reported patient to have colon cancer occurring in association with malakoplakia of the colon. We also review all reported cases of this association.

CASE REPORT

The patient was a 90-year-old female who presented with weight loss, change in bowel habits, and bleeding per rectum. Her past medical history was significant for hypertension, myocardial infarction, and complete heart block requiring pacemaker placement three years prior to surgery. There was no history of steroid use. Physical examination was essentially normal. A digital rectal exam revealed heme-positive stool. She underwent a colonoscopy that revealed an obstructing stricture in the sigmoid; a subsequent barium enema confirmed a partially obstructing lesion in the proximal part of the sigmoid colon (see Fig. 1). Multiple diverticula were seen in the distal sigmoid. A CT scan revealed a nonspecific soft tissue thickening in the rectosigmoid area (see Fig. 2), with no liver lesions. She underwent an open sigmoid resection. At laparotomy, a sigmoid mass was noted. This was not fixed and there was no obvious evidence of extension beyond the colonic wall. There was significant surrounding inflammation in the pericolic fat within which the left ureter was embedded. This was identified, dissected free, and carefully preserved during the course of the resection.

Macroscopically, a $4 \times 4 \times 1$ cm circumferential fungating tumor was found in the proximal sigmoid colon (Fig. 3). It was a low-grade adenocarcinoma that extended through the bowel wall into the subserosal tissue. There was no tumor involvement of the proximal, distal, or radial margins. No

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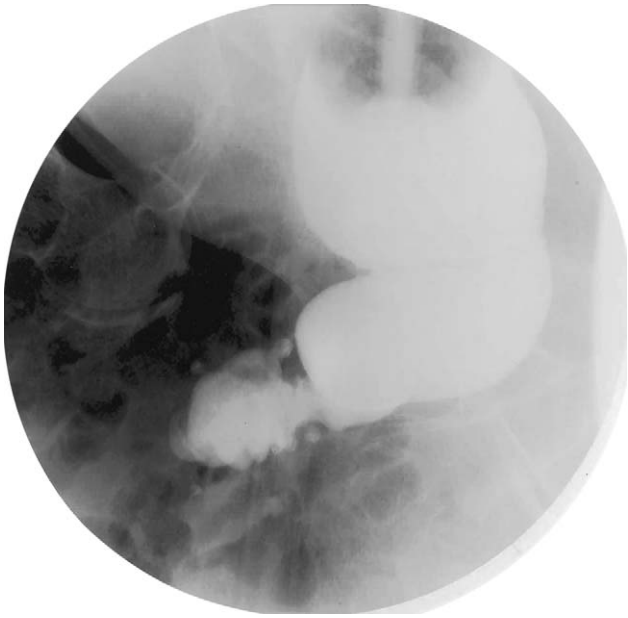

Fig. 1. Obstructing lesion in sigmoid colon.

lymphovascular invasion was recognized, and 31 lymph nodes were negative for malignancy.

The infiltrating tumor was associated with a diffuse inflammatory infiltrate consisting predominantly of sheets of histiocytes. Numerous Michaelis-Gutmann bodies characterized on the hematoxylin and eosin stain as round layered intracytoplasmic inclusions were recognized, which are diagnostic of malakoplakia (see Fig. 4).

DISCUSSION

In 1902, Michaelis and Gutmann described inclusion bodies that could be recognized on hematoxylin and eosin stained sections.[1] The term "malakoplakia vesicae urinariae" was coined by von Hansemann in 1903.[2] This term was derived from the Greek words "malakos," which means soft, and "plakos" referring to the soft plaques he described in the urinary bladder of four patients. Macroscopically, malakoplakia tends to appear as an umbilicated plaque. Histologic examination reveals a homogenous infiltrate of macrophages, with eccentrically disposed nuclei, and eosinophilic granular cytoplasm containing 5–10 μm basophilic targetoid intracytoplasmic inclusion bodies[3] or Michaelis-Gutmann bodies. The infiltrate is usually mixed with neutrophils, lymphocytes, and plasma cells, and there may be large amounts of granulation tissue.[4] Malakoplakia is a rare condition whose pathogenesis is not well understood. The frequent association with urinary tract infection led some authors to speculate that infectious agents such as coliform bacteria were responsible for this entity [3]. An alteration in the immune state of the reticuloendothelial system was proposed by Curtis et al. [5] while an altered macrophage response was proposed by Lou et al. [6]. Michaelis and Gutmann

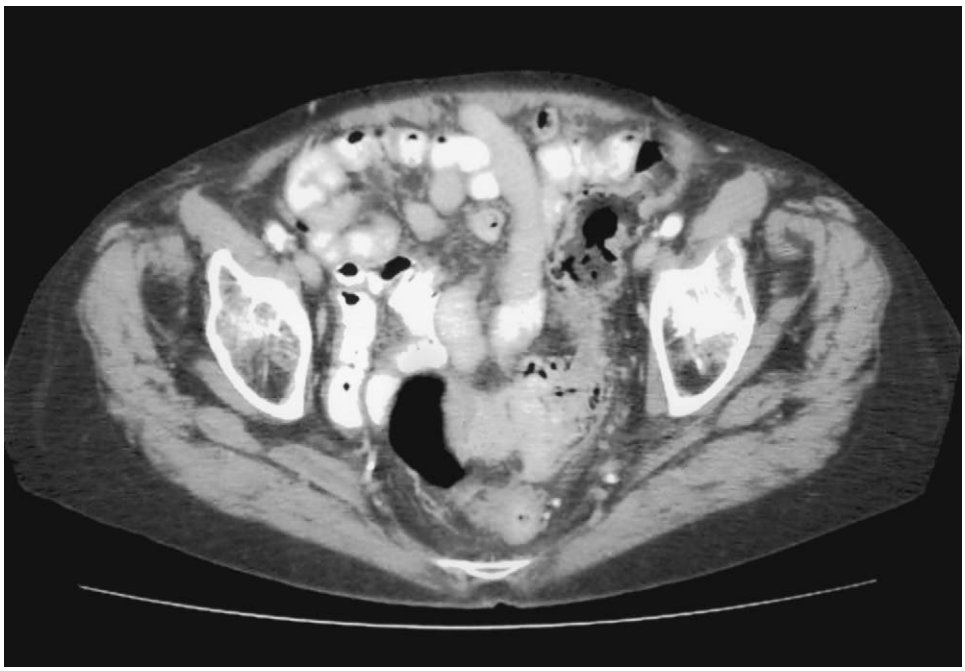

Fig. 2. CT scan showing thickening in mid sigmoid.

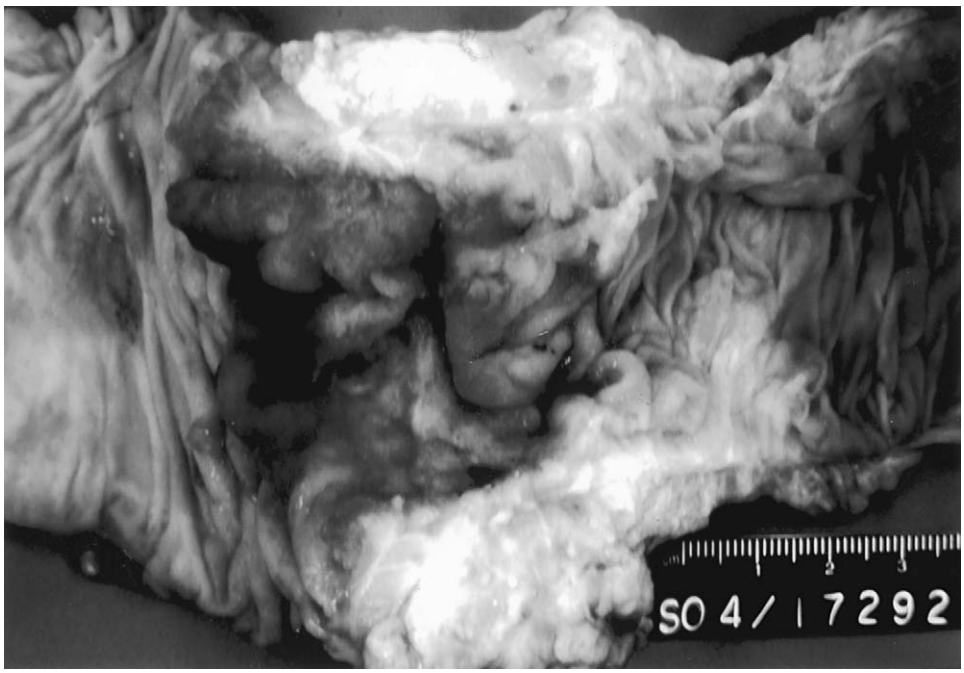

Fig. 3. Sigmoid colon with tumor.

thought that malakoplakia was a manifestation of a benign neoplasm.[2] Malakoplakia was first noted in the genitourinary tract; this remains the most common site of its occurrence. Various other sites have been described, such as the brain, thyroid, and bone.[7–9] The frequent association with urinary tract infection led some authors to speculate that infectious agents such as coliform bacteria were responsible for this entity.[3] An alteration in the immune state of the reticuloendothelial system was proposed by Curtis et al.,[5] whereas an altered macrophage response was proposed by Lou and Teplitz.[6]

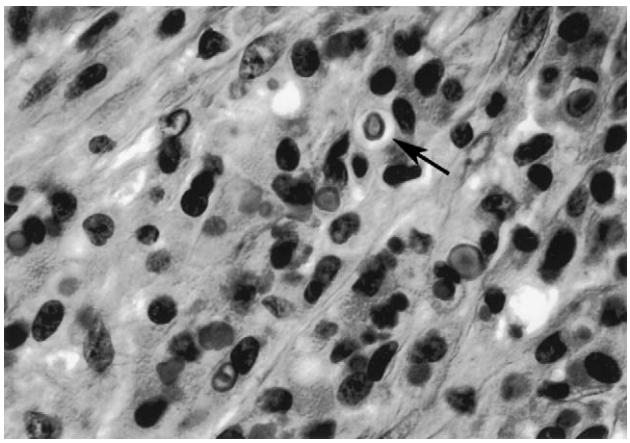

Fig. 4. Michealis-Gutmann body (*arrow*).

The gastrointestinal tract is the second most frequent site of occurrence, with an incidence of 11%.[10] Within the gastrointestinal tract, malakoplakia has been associated with carcinoma, adenoma, and ulcerative colitis, as well as diverticulosis. In keeping with what has been reported in the literature, our patient was found to have carcinoma as well as diverticulosis. Malakoplakia within the gastrointestinal tract seems to follow one of two patterns: it may be localized and occur in association with a tumor, or it may have a diffuse presentation in the setting of underlying autoimmune disease or immunocompromised states.[10] Local alterations in gut flora as well as the host's stromal response to tumor against the background of a locally deficient host immune response have been implicated as being factors in the development of malakoplakia.[11,17] Malakoplakia may simulate colon carcinoma or may coexist with it, and the rectosigmoid seems to be the commonest site.

A review of the literature revealed only 24 cases of malakoplakia (Table 1)—in association with adenocarcinoma of the colon—reported to date, including our case.[10–21] There have been three reports of colon adenomas occurring in association with malakoplakia.[12] There are only six reported cases of colorectal cancer associated with malakoplakia occurring in females, including our patient. A review of all reported cases gives a male to female ratio of 4:1 and a mean age of 69 years. Our patient was significantly older

Table 1. Demographics pathology, and distribution of reported cases

Reference	Age/Sex	Site	Tumor stage	Distribution
Asiyanbola (2004)	90/F	Sigmoid	Dukes' B	Pericolic fat
Pillay (2002)	64/M	Cecum/ascending colon	Dukes' B	Pericolic fat and lymph nodes
Pillay (2002)	55/F	Rectum	Dukes' B	Pericolic fat and lymph nodes
Pillay (2002)	62/M	Descending colon	Dukes' B	Pericolic fat and lymph nodes
Pillay (2002)	61/M	Rectum	Dukes' B	Pericolic fat and lymph nodes
Perdiki (2002)	75/M	Cecum	Dukes' B	Not known
Matter (2001)	65/M	Rectosigmoid	Dukes' B	Pericolic fat/perirectal tissue/bladder
Bates (1997)	64/M	Rectum	Not Known	Not known
Bates (1997)	72/M	Rectum	Not Known	Not known
Bates (1997)	71/F	Transverse colon	Dukes' B	Gastric wall
Bates (1997)	83/M	Rectum	Dukes' B	Pericolic fat
Bates (1997)	65/M	Sigmoid	Dukes' B	Pericolic fat
Bates (1997)	67/M	Sigmoid	Dukes' B	Pericolic fat
Sandmeier (1993)	74/M	Cecum	Dukes' C	Single nodule
Moran (1989)	77/M	Rectosigmoid	Dukes' B	Single nodule
Moran (1989)	51/M	Sigmoid	Dukes' B	Single microscopic focus
Alfonso (1989)	Not Known	Rectum	Not Known	Not known
McClure (1981)	59/F	Rectum	Dukes' B	Not known
McClure (1981)	73/M	Rectum	Dukes' B	Pericolic fat
McClure (1981)	79/M	Rectum	Dukes' B	Pericolic fat and lymph nodes
Dockety (1972)	88/M	Sigmoid	Dukes' B	Not known
Rywlin (1968)	45/F	Rectum	Not Known	Colonic serosa
Finally-Jones (1968)	80/M	Rectum	Dukes' B	Pericolic fat
Finally-Jones (1968)	82/F	Rectosigmoid	Dukes' B	No extramural spread

than this at 90 years, thus becoming the first documented case of a patient of this age. Over the years, an association between steroid use and malakoplakia has been documented. Mater et al.[12] found a 20% association between patients with colorectal adenocarcinoma and malakoplakia and a history of steroid use. Our patient had no history of steroid use. Clinicopathologic staging revealed our patient to have a Dukes' stage B lesion; this was in keeping with the majority of cases reported in the literature.

The clinical significance of malakoplakia, when it occurs with colorectal carcinoma, lies in its possible effect upon the staging and treatment of this cancer. Preoperatively, when it occurs in conjunction with colorectal carcinoma, it may lead to over staging and more extensive resection. Malakoplakia may be locally aggressive and infiltrative, and extensive malakoplakia can infiltrate adjacent structures like the bladder and sacrum; however, resection of grossly involved tissue seems to be adequate.[12] In our patient, there was no direct involvement of adjacent organs, though the pericolic tissues adjacent to the sigmoid were densely adherent to the sigmoid and the patient's left ureter. Malakoplakia has not been noted to recur after resection of an associated tumor, and its presence does not appear to have prognostic significance in colon carcinoma.[11] The preoperative picture may lead to the decision to refer a patient for neoadjuvant therapy. The effect of radiation on malakoplakia is unknown; it has been postulated that this may be responsible for some of the cases of good response to neoadjuvant chemoradiation[12] Alternatively, a diffuse malakoplakia surrounding a carcinoma may simulate advanced diseases, leading to palliative therapy.[22] The treatment and prognostic implications of its occurrence are not fully understood, partly due to the rarity of coexistent colorectal carcinoma and malakoplakia, and partly due to the uncertain pathogenesis and natural history of this condition.

CONCLUSION

Malakoplakia was first described over 100 years ago. Unfortunately, its etiology, pathogenesis, and natural history are all still unclear. Malakoplakia may occur in association with colon cancer. This association may occur in patients up to 90 years of age. Its presence may potentially alter the staging and treatment of colon cancer.

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An Approach to Analyze Mechanisms of Intestinal Adaptation Following Total Proctocolectomy

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We hypothesized that epithelial cells of the remnant small intestine display "colonic" phenotype after total proctocolectomy. The aims of the present study were to identify preferentially expressed molecules in the colon or in the small intestine and to evaluate mRNA levels of those in the ileal pouch. Differential gene expression was investigated between the small intestine and the colon by using cDNA microarray and was confirmed by Northern blotting. Expression of three colonic mRNAs (3-hydroxy-3-methylglutaryl-coenzyme A synthase 2, deleted malignant brain tumors 1, carcinoembryonic antigen-related cell adhesion molecule 1) and one "small intestinal" (microsomal triglyceride transfer protein) mRNA were compared between the control and the ileal pouch mucosae by quantitative reverse transcriptase-polymerase chain reaction. Seventy-four clones were differentially expressed with more than a threefold difference. Differential expression was confirmed in all mRNAs examined, including 3-hydroxy-3-methylglutaryl-coenzyme A synthase 2 and microsomal triglyceride transfer protein. The mucosal expression of carcinoembryonic antigen-related cell adhesion molecule 1 mRNA in the ileal pouch was enhanced in humans. The remnant ileum develops some, but not all, colonic phenotype after total proctocolectomy. Comparative study of epithelial gene expression between the small intestine and the colon enables us to analyze mechanisms of intestinal adaptation after total proctocolectomy. (J GASTROINTEST SURG 2006;10:662–671)

KEY WORDS: Total proctocolectomy, intestinal adaptation, intestinal epithelial cell gene expression, carcinoembryonic antigen-related cell adhesion molecule 1

Total proctocolectomy followed by ileo-anal (canal) anastomosis is an established surgical treatment for ulcerative colitis and familial adenomatous polyposis.[1] The patients who undergo this procedure are cured of their diseases by the removal of the entire colon, without receiving a permanent ileostomy. Adaptive changes of systemic hormone levels, renal function, and intestinal absorption are essential to compensate for the absent colon, to keep water and electrolyte balance, and to ensure a high quality of life after surgery.

We previously studied the mechanisms of intestinal adaptation in conditions characterized by postoperative diarrhea, dehydration, and sodium depletion. Because the renin-angiotensin-aldosterone pathway plays a major role in regulating electrolyte balance and water homeostasis, we investigated epithelial expression of the aldosterone-associated molecules by using a total colectomized rat model. We demonstrated that epithelial cells in the remnant ileum induced epithelial sodium channel (ENaC), prostasin, 11β-hydroxysteroid dehydrogenase type 2, and sodium/glucose cotransporter 1 (SGLT1) mRNAs after total proctocolectomy.[2–4] ENaC has a major role in sodium absorption via the luminal surface. Prostasin is a novel serine protease suspected of functioning in conjunction with ENaC to accelerate sodium absorption.[5] 11β-hydroxysteroid dehydrogenase type 2 metabolizes glucocorticoids, permitting aldosterone to bind to mineralocorticoid receptors.[6,7] SGLT1 is essential for glucose absorption and cotransports sodium and water across the membrane in the small intestine.[8] Induced expression of these molecules has been linked to functional changes. Studies using

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an Ussing chamber revealed activation of electrogenic sodium transport,[2] increased reactivity to aldosterone,[3] and enhanced glucose-coupled sodium absorption (S.H. and K.F., unpublished data 2005) in the ileal mucosae after total proctocolectomy. Interestingly, with the exception of SGLT1, these molecules are highly expressed in the colon and contribute to fundamental functions unique to this organ. These data suggest that epithelial cells in the remnant small intestine may acquire certain colonic functions as an adaptation to the lack of the entire colon. Concomitantly, cells may lose certain of their small intestinal functions after surgery. Acquired and/or lost epithelial cell functions occur as a result of altered gene expression in the remnant small intestine, and such alterations may be critical for physiological adaptation and/or pathological events. The aims of the present study were (a) to identify molecules which possibly determine the features of the colon (e.g., colonic molecules) or the small intestine (e.g., small intestinal molecules) in epithelial cells by using differential gene screening and (b) to test the hypothesis that mucosal epithelial cells in the remnant small intestine induce and repress the expression of colonic and small intestinal molecules, respectively, after total proctocolectomy.

MATERIAL AND METHODS

Isolation of Epithelial Cells From the Murine Small Intestine and Colon

Mice served as the source of epithelial cells to identify colonic and small intestinal molecules because (a) samples of the small intestine and the entire colon free of inflammatory or malignant lesions are easily accessible, (b) the presence of factors influencing epithelial gene expression, for example, foods and genetic background, are minimal and (c) many murine counterparts of human genes have been studied extensively. Male ICR, BALB/c, MCH-ICR mice (8 weeks of age) were obtained from Clea Japan Inc. (Tokyo, Japan) and housed in the animal room at Tohoku University Institute for Experimental Animals, Sendai, Japan. The details of the isolation of epithelial cells have been described previously.[9] In brief, small and large intestines were removed, washed with Hanks balanced salt solution, and everted. The intestines from four animals were cut into 2 cm lengths and incubated in Hanks balanced salt solution with 1.5 mg/ml dithiothreitol for 15 minutes at room temperature. The pieces were subsequently incubated in Hanks balanced salt solution with 1 mmol/L ethylenediamine-tetraacetic acid at room temperature for three consecutive 10-minute periods. At the end of each period, the pieces were agitated rapidly with a glass rod. The supernatants containing enterocytes were collected and washed twice with RPMI 1640. After determining that the homogeneity of the cell suspensions and cell viability (trypan blue exclusion) exceeded 95%, the total RNA was extracted. Mononuclear cells constituted the primary cellular contaminant.

Isolation of RNA

Total RNA was extracted from isolated epithelial cells by using a cesium chloride gradient. The quality and quantity of RNA were confirmed by 260 nm ultraviolet absorbance and gel electrophoresis with ethidium bromide staining, respectively.

Extraction of Poly (A) From Total RNA and Detection of Differentially Expressed Genes by Microarray Analysis

Poly (A) RNA was extracted from the total RNA from the isolated small intestinal and colonic epithelial cells of ICR mice by using the Oligotex-dT30 (Super) mRNA Purification Kit (Takara Biomedicals, Tokyo, Japan). Microarray analyses of the Poly (A) RNAs were performed by Incyte Genomics (Palo Alto, CA). Gene expression between the small intestinal and colonic epithelium was compared. Labeled cDNAs were subjected to mouse GEM microarrays, containing 8638 sequence-verified clones.[10] Hybridization was performed in competition with Cy3- and Cy5-labeled cDNAs as previously described.[11] Expression sequence tag clones were used to perform a homology search of the BLAST program.[12]

Northern Blot Analysis to Confirm Differential Expression

Northern blotting was performed to confirm differential gene expression. Samples from BALB/c and MCH-ICR mice were used in some experiments to determine whether or not differential expression occurred regardless of mouse strain. Twenty μg of total RNA from colonic and small intestinal epithelial cells were fractionated by electrophoresis and transferred onto nylon transfer membrane (Amersham, Tokyo, Japan). Photographs were taken of the gels after staining with ethidium bromide. Eleven genes were selected on the basis of their signal intensity in the microarray. We prepared probes from 11 clones obtained from Incyte Genomics (underlined in Tables 3 and 4) by restriction enzyme digestion and purification after gel electrophoresis. The blots were hybridized according to a protocol described previously.[13]

Table 1. Outline of the patients for evaluation of mucosal gene expression

	Control	Ileal pouch
Number (M:F)	8 (5:3)	12 (4:8)
Mean age (range)	40.3 (21–68)	38.8 (21–62)
Presunisolone	7/8	0/12
Duration after IC (range)	-	26.1 months
	-	(3–83 months)

IC = ileostomy closure.

Mucosal Sampling From the Control Ileum and the Ileal Pouch After Total Proctocolectomy

Ileal mucosae (1 cm oral side from ileo-cecal valve) were obtained at surgery from patients with ulcerative colitis subjected to total proctocolectomy and ileal J-pouch anal anastomosis. Mucosal biopsies were obtained from the ileal pouch more than 3 months after closure of the covering loop ileostomy. Patient outlines are listed in Table 1. Absence of mucosal inflammation in the pouch was determined endoscopically according to the criteria of the modified Pouchitis Disease Activity Index.[14] Samples were immediately frozen in liquid nitrogen, homogenized in guanidine isothionate buffer, and RNA was extracted using a cesium chloride gradient. Ethics approval for this study was obtained from the Ethics Committee at Tohoku University School of Medicine.

Measurement of 3-Hydroxy-3-Methylglutaryl-Coenzyme A Synthase 2, Deleted Malignant Brain Tumors 1, Carcinoembryonic Antigen-Related Cell Adhesion Molecule 1, and Microsomal Triglyceride Transfer Protein mRNAs by Quantitative Reverse-Transcriptase Polymerase Chain Reaction

The amounts of 3-hydroxy-3-methylglutaryl-coenzyme a synthase 2 (HMGCoA S2), deleted malignant brain tumors 1 (DMBT1; a human homologue of murine CRP-ductin), and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1; a human homologue of murine CEACAM2) mRNAs in the ileal mucosa were measured to test the hypothesis that epithelial cells in the remnant ileum induce expression of colonic molecules after total proctocolectomy. HMGCoA S2, DMBT1, and CEACAM1 were selected as representative molecules for metabolic enzymes, molecules associated with innate immunity, and cell adhesion molecules, respectively. The level of microsomal triglyceride transfer protein (MTTP) mRNA, a small intestinal molecule, was also measured. Total RNA (1 μg) from mucosal biopsies was reverse-transcribed, and mRNA was quantitated in duplicate in a twofold dilution of the reverse transcriptase mixture by using a QuantiTect SYBR Green PCR Kit (Quiagen K.K., Tokyo, Japan) and ABI GeneAmp 5700 (Applied Biosystems Japan, Tokyo, Japan) according to the manufacturers ' protocols. The primer sequences for quantitative RT-PCR were determined with Primer Express software (PE Applied Biosystems, Foster City, CA) and are listed in Table 2. The level of villin mRNA, a tissue-specific actin-binding protein expressed in the epithelial cells of the intestine, was also measured as an internal standard.[15] Preliminarily amplified products of human HMGCoA S2, DMBT1, CEACAM1, MTTP, and villin cDNA were inserted into a pCRII TOPO cloning vector (Invitrogen, K.K., Tokyo, Japan), and the sequence was confirmed. The standard curves for HMGCoA S2, DMBT1, and CEACAM1 mRNAs were constructed using a serial dilution of total RNA (1, 0.2, 0.04, 0.008 μg) extracted from a human colon resected for colonic cancer. Diluted RNA from an ileum resected for ascending colon cancer was used for constructing the standard curves for MTTP and villin measurements. Relative quantitation of target mRNAs was calculated using the comparative threshold cycle number for each sample fitted to a five-point standard curve. Finally, expression levels were normalized to villin mRNA.

Statistics

All values were expressed as medians and percentiles. Data were tested for significance using the Mann-Whitney U test with $P < 0.05$ being indicative of a statistically significant difference.

Table 2. Primer sequences used for semi-quantitative RT-PCR

	Up-stream	Down-stream
HMGCoA S2	5′-TGGCCAAAGGACGTGGGCAT-3′	5′-GCAGTACCACCGTAGCAGGC-3′
DMBT1	5′-CCGTGTGACTGTGATCTTCAGAG-3′	5′-GAGAGGGGAACTGCGGTG-3′
CEARCAM1	5′-CCAAAATCCAAGGCAATTCC-3′	5′-ATCAGAAGCTGGTTCCCTCC-3′
MTTP	5′-GAAGCTCCATTCAGGCAATTTG-3′	5′-GCGGGAATTCACATCCTGC-3′
Villin	5′-CCCTGGAGCAGCTAGTGAACA-3′	5′-GAAGGCAGCTGGAGTCATCC3′

Table 3. Forty-one genes preferentially expressed in the colon

DB	Ac No.	P1(CL)	P2(SI)	GeneName
22.9	AA030116	22663	990	3-hydrox-3 methylglutaryl-Coenzyme A synthase 2
18.2	AA512372	15501	852	carbonic anhydrase 1
12.3	AA266579	10138	827	Mus musculus flavo-binding protein mRNA. complete cds
10.9	AA122925	11879	1092	carbonic anhydrase 2
10.5	AA473158	5807	554	ESTs (hydroxyacid oxidase 3)
10.2	AA239093	14593	1436	ESTs (resistin-like molecule beta)
10.1	AA414831	5107	505	hypoxia induced gene 1
9.6	AA544948	13780	1438	mini chromosome maintenance deficient 7 (S. cerevisiac)
8.9	AA177949	2116	239	solute carrier family 20, member 1
6	WJ8397	5828	976	EST (regenerating islet-derived family, member 4)
5.6	AA253908	7742	1393	ESTs (hydroxyacid oxidase 3)
5.3	AA200392	4089	768	ESTs (myeloid lymphoid or mixed-lineage leukemia 3)
5.2	AA277736	14245	2736	CEA-related cell adhesion molecule 2
5.1	W64798	14452	2855	epithelial membrane protein 1
4.9	AA498457	9719	1972	guanvlate cyclase activator 2 (guanylin 2, intestinal, heatstable)
4.8	AA498773	35316	7410	crp-ductin
4.7	AA519027	6042	1284	myelin and lymphocyte protein; T-cell differentiation protein
4.2	AA403841	11470	2734	lectin, galactose binding, soluble 3
4.1	AA396298	3587	878	Mus musculus mRNA for RNase 4, complete cds
3.9	AA451058	4208	1070	ESTs (oncoprotein induced transcript 1)
3.9	AA244536	5468	1405	3'-phosphoadenosine 5'-phosphosulfate synthase 2
3.8	AA259661	951	253	gamma-glutamyl hydrolase
3.8	AA237829	1842	480	angiogenin
3.8	W33809	8219	2151	EST (similar to 3(20)alpha-hydroxysteroid/dihydrodiol/indano/dehydrogenase)
3.7	AA277314	3382	911	ESTs (angiogenin 4)
3.7	AA245546	18958	5140	CEA-related cell adhesion molecule 1
3.7	AA146215	3122	836	cytochrome P450, 2c40
3.5	AA238618	6227	1801	ESTs (weakly similar to coded for by C. elegans cDNA CEESW58F [Celegans])
3.5	AA277565	1849	527	ESTs (cytochrome P450, family 2, subfamily C. polypeptide 44)
3.4	AA239480	1602	472	ESTs (cystathionine beta-synthase, transcript variable 1)
3.3	A1425791	2417	741	ESTs (hypothetical DNA/RNA non-specific endonuclease containing protein)
3.2	W99102	3010	946	prion protein
3.2	W98963	4403	1357	CD9 antigen
3.2	W36584	1227	383	ESTs (syndecan bindingprotein (synthenin) 2)
3.1	AA138546	1546	495	Mus musculus brain cDNA, clone MNCb-3763, similar to AC004410 fos39554_1
3.1	AA175547	1131	368	Mus musculus mRNA for hypothetical thymus-expressed acidic protein (TEAP gene)
3.1	AA116528	3426	1097	ESTs (syncollin)
3	AA177549	496	168	toll-like receptor 1
3	A1466979	780	262	glutamine synthetase
3	AA509566	2244	743	esterase 1
3	AA272836	4203	1381	aquaporin 8

DF = Differential expression; Ac No = Accession number; P1 (CL) = Probe from colonic RNA; P2(SI) = Probe from small intestinal RNA; Underlines indicate the clones used for Northern blotting.

RESULTS

Differential Gene Expression Between Epithelial Cells From the Small Intestine and the Colon

Epithelial cell gene expression in the small intestine and the colon was successfully compared (Fig. 1). Seventy-four clones (less than 1% of genes examined) exhibited more than a threefold difference in signal intensity (Tables 3 and 4). Highly expressed genes in the colon included metabolic enzymes such as HMGCoA S2, carbonic anhydrase I, hydroxy acid oxidase 3, and gamma glutamyl hydrolase. Other detected genes display functions in cell adhesion (CEACAM1 and 2), cell growth (regenerating

Table 4. Thirty-three genes preferentially expressed in the small intestine

DE	Ac No.	P1(CL)	P2(SI)	Gene Name
−18.9	W13053	259	4908	microsomal triglyceride transfer protein
−14.6	AA097421	340	4958	apolipoprotein A-IV
−13.1	AA123026	2275	29811	rat generating islet-derived, mouse homolog 3 gamma
−11.4	AA473899	2286	26142	pancreatitis-associated protein
−9.2	AA521545	696	6378	ESTs (lectin, galaclose-binding, soluble 2)
−9.2	AA245959	264	2422	kallikrein 3, plasma
−9	W17543	372	3356	ESTs (Dullard homolog)
−8.5	AA061550	1584	13392	retinol binding protein 2, cellular
−8.3	AA272807	473	3933	histocompatibility 2, class II antigen A, alpha
−8	AA209065	448	3574	ESTs (apolipoprotein B)
−7.2	W17866	705	5104	uterine-specific proline-rich acidic protein
−6.9	AA183327	171	1174	granzyme B
−6.7	AA237541	187	1258	dipeptidylpeptidase 4
−6.4	AA244590	218	1404	glutamyl aminopeptidase
−6.3	W50759	432	2713	heat shock protein, 84 kDa 1
−6.1	AA271959	463	2828	apolipoprotein CII
−5.9	W14138	364	2145	kallikrein 3, plasma
−5.4	AI605638	875	4751	diacylglycerol acyltransferase
−5.3	AA087125	440	2318	ESTs (alkaline phosphatase 1, intestinal, homolog)
−5.2	AI385452	1759	9233	sodium-glucose cotransporter
−4.5	AA245078	2293	10255	fatty acid binding protein 2, intestinal
−4.5	AA268120	530	2359	cytochrome P450, steroid inducible 3a11
−4.4	AA212964	197	873	ESTs (cytochrome P450, family 4, subfamily V, polypeptide)
−4.3	AA213062	256	1113	ESTs (mitochondrial carrier, ornithine transporter)
−3.4	AA080332	2701	9255	ESTs (aldo-keto reductase family 1, member C21)
−3.4	AI325330	331	1116	cytochrome P450, 2bI0, phenobarbitol inducible, type b
−3.3	AA030193	773	2519	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7
−3.3	AA108640	1147	3798	glycerolphosphate denydrogenase 1, cytoplasmic adult
−3.2	AA237916	511	1627	ATP-binding cassette, sub-family G (WHITE), member 5
−3.2	AA061397	797	2535	retinol dehdrogenase 7
−3.1	AA175329	539	1682	histocompatibility 2, class II antigen A, beta 1
−3	W89845	830	2485	ESTs (similar to aspartate beta-hydroxylase)
−3	AA254389	781	2330	ESTs (apolipoprotein B)

DF = Differential expression; Ac No = Accession number; P1 (CL) = Probe from colonic RNA; P2(SI) = Probe from small intestinal RNA; Underlines indicate the clones used for Northern blotting.

islet-derived family member 4, epithelial membrane protein 1), or mucosal defense (resistin-like molecule β, CRP-ductin, angiogenin). In the small intestine, highly expressed mRNAs were associated with nutrient absorption, such as MTTP, retinol binding protein 2, apolipoprotein A-IV, dipeptidyl peptidase IV, glutamyl aminopeptidase apolipoprotein CII, sodium glucose cotransporter, and fatty acid binding protein 2.

Confirmation of Differential Gene Expression by Northern Blotting

Northern blotting clearly demonstrated differential expression of 11 genes initially detected by cDNA microarray analysis. HMGCoA S2 mRNA was highly expressed in the colon but not in the small intestine (Fig. 2, *A*). Positive signals for resistin-like molecule β, approximately 0.8 kb in size, were noticed in both the small intestine and the colon, although a much stronger intensity was observed in the latter (Fig. 2, *B*). We confirmed preferential expressions of regenerating islet- derived family member 4, hydroxy acid oxidase 3, CEACAM 2, guanylate cyclase activator 2, 5′-phosohosulfate synthase 2, and aquaporin 8 in the colon, regardless of mouse strain (Fig. 3, *A–C* and Fig. 4, *A–C*). In contrast, several mRNAs were highly expressed in the small intestine rather than in the colon, including MTTP, galactose-biding lectin soluble 2, and proline-rich acidic protein (Fig. 5, *A–C*). We confirmed differential expression in all transcripts examined.

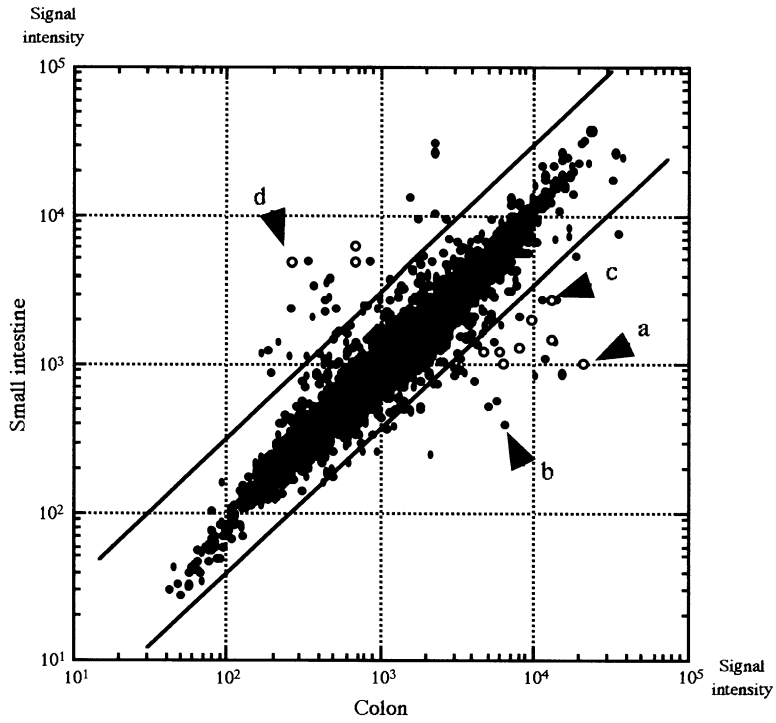

Fig. 1. A scatter graph of gene expression. Each point indicates one gene, and points lying outside of the lines represent differential expressions in excess of threefold. Open circles indicate genes whose differential expression was confirmed by Northern blotting. *Arrowheads* a, b, c, and d indicate HMGCoA S2, CRP-ductin, CEACAM 2, or MTTP, respectively. Expression of the homologous human genes was determined in biopsy samples from the ileal pouch.

Comparative Study of HMGCoA S2, DMBT1, CEACAM1, and MTTP mRNA Expressions Between Control and Ileal Pouch Mucosa After Total Proctocolectomy

Human mucosal tissues from the control ileum and the ileal pouch were used to evaluate the expression of colonic (HMGCoA S2, DMBT1, CEACAM1) and small intestinal (MTTP) molecule mRNAs (Fig. 6, *A–D*). On the one hand, levels of CEACAM1 mRNA were significantly higher in the ileal pouch than in the control tissue. On the other hand, the remaining molecules did not show any differences in mRNA levels. We did not find any correlation between levels of specific mRNAs and the duration after ileostomy closure (data not shown).

DISCUSSION

Epithelial cells serve as gatekeepers, sitting at the interface between the body 's internal milieu and the environment. In the gastrointestinal tract, epithelial cells continuously transport water, electrolytes, nutrients, minerals, and defensive molecules to maintain homeostasis in a site-dependent fashion. Removal of the entire colon results in a decrease in water and sodium absorption,[16] and possibly the impairment of other functions contributing to physiological and pathological events after total proctocolectomy. The former includes watery diarrhea and enhanced mineralocorticoid action.[2–4] The latter may contribute to the onset, relapse, and/or exacerbation of pouchitis, a nonspecific inflammation that develops in the ileal pouch.

In the present study, we initially hypothesized that epithelial cells in the remnant small intestine induce the expression of colonic molecules and repress the expression of small intestinal molecules after total proctocolectomy. To identify appropriate colonic and small intestinal molecules, we examined differential gene expression in isolated epithelial cells by using cDNA microarray technology. A comparison of the small intestine and colon identified 74 genes with more than a threefold difference, including those that participate in cell adhesion, cell growth, mucosal defense, nutrient absorption, and energy metabolism. Bates et al.[17] previously investigated segmental gene expression along the anterior-posterior (proximal-distal) axis in the gastrointestinal tract. They extracted tissue RNAs from each part of the murine gastrointestinal tract and compared gene expression in the hind stomach, duodenum,

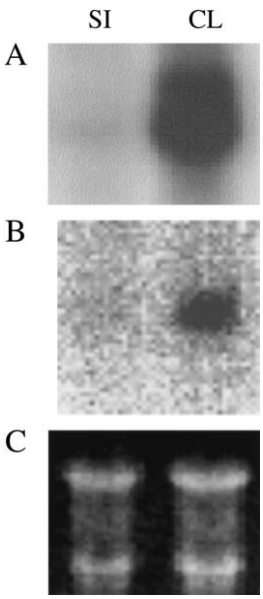

Fig. 2. Differential mRNA expression was confirmed by Northern blotting in two genes. Epithelial RNA was obtained from the small intestine (SI) and the entire colon (CL). (**A**) The HMGCoA S2 cDNA (AA030116) was used as a probe. The band, approximately 3.2 kb in size, was detected only in the colon. (**B**) The EST clone (AA239093, a partial sequence of resistinlike molecule β cDNA) was used as a probe. The band, approximately 0.8 kb, in size was noticed in both the small intestine and the colon, with stronger intensity in the latter organ. (**C**) Ethidium bromide staining.

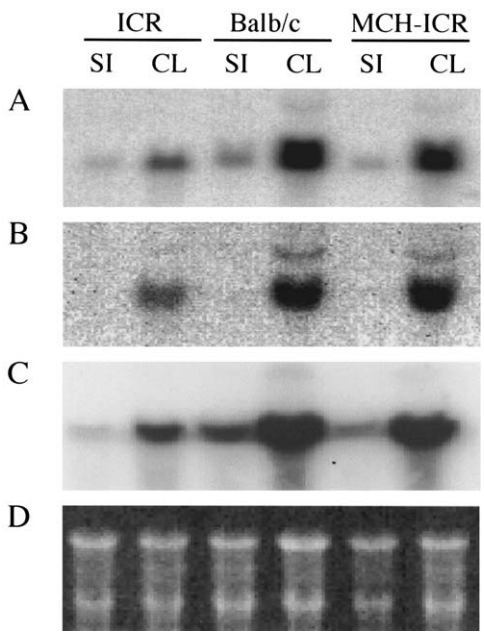

Fig. 3. Differential mRNA expression was confirmed by Northern blotting in three genes. Epithelial RNA was obtained from the small intestine (SI) and the entire colon (CL) of ICR BALB/c and MCH/ICR mice, respectively. (**A**) The EST clone (W18397, a partial sequence of regenerating islet-derived family, member 4 cDNA) was used as a probe. The band, approximately 1.0 kb in size, was noticed in both the small intestine and the colon, with stronger intensity in the colon in all mouse strains. (**B**) The EST clone (AA253908, a partial sequence of hydoxy acid oxidase 3 cDNA) was used as a probe. The band, approximately 2.0 kb in size, was noticed only in the colon in all strains. (**C**) The cDNA of CEA-related cell adhesion molecule 2 (AA277736) was used as a probe. The band, approximately 1.0 kb in size, was noticed in both the small intestine and colon, but the signal intensity was stronger in the colon in all mouse strains. (**D**) Ethidium bromide staining.

jejunum, ileum, cecum, proximal colon, and distal colon. In the present study, we used RNAs extracted from isolated mucosal epithelial cells rather than from whole tissue because we focused on altered epithelial cell functions after total proctocolectomy, that is, aldosterone-mediated sodium transport. We used epithelial RNA from the whole jejunum and ileum or the entire colon because the entire colon is removed in total proctocolectomy. Therefore, it is not surprising that the differentially expressed genes selected in the present study are different from those selected by Bates et al.

Forty-one genes were selected as colonic, and 33 genes were identified as small intestinal molecules. The signal intensities observed on microarray analysis correctly reflected gene expression levels because we confirmed differential expression by Northern blotting. We also tested our hypothesis that epithelial cells in the remnant small intestine induce the expression of colonic molecules and/or repress the expression of small intestinal molecules after total proctocolectomy. We measured the expression of mRNAs for HMGCoA S2 as a metabolic enzyme, DMBT1 as a defensive molecule for innate immunity,[18] CEACAM1 as a cell adhesion molecule, and MTTP as a small intestinal metabolic enzyme in control and pouch mucosae. Biopsy samples were obtained from ileal pouches devoid of inflammation at least 3 months after the ileostomy closure. Villin mRNA expression, rather than β-actin or glyceraldehyde-3-phosphate dehydrogenase, was used as an internal standard. Quantification of target mRNAs in specific cell populations in whole mucosal biopsies is difficult because samples contain variable and unknown numbers of epithelial cells, lymphocytes, macrophages, endothelial cells, fibroblasts, and smooth muscle cells.[19] Villin, a member of the gelsolin family, is produced only by differentiated epithelial cells in the intestinal mucosa[15,20] and used as an intestinal marker.[15] Therefore, target mRNA expression was normalized to the levels of villin mRNA.

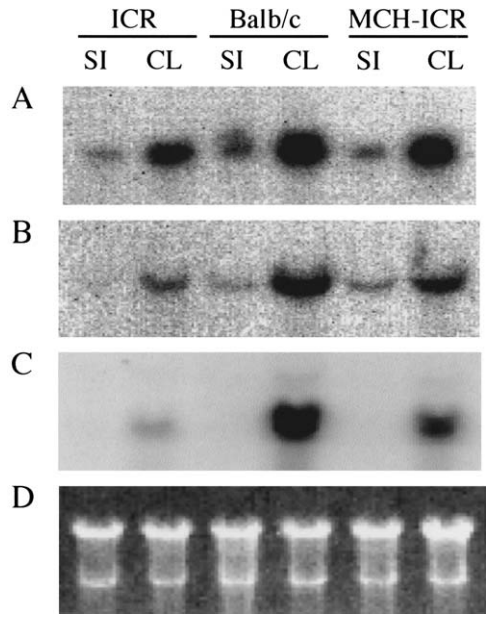

Fig. 4. Differential mRNA expression was confirmed by Northern blotting in three genes. Epithelial RNA was obtained from the small intestine (SI) and the entire colon (CL) of ICR BALB/c and MCH/ICR mice, respectively. (**A**) The cDNA of guanylate cyclase activator 2 (AA498457) was used as a probe. The band, approximately 1.0 kb in size, was noticed in both the small intestine and the colon, but with stronger intensity in the latter organ in all mouse strains. (**B**) The cDNA of 3′-phosphoadenosine 5′-phosohosulfate synthase 2 (AA244536) was used as a probe. The band, approximately 3.5 kb in size, was noticed in both the small intestine and the colon, with stronger signal intensity in the latter colon in all mouse strains. (**C**) The cDNA of aquaporin 8 (AA272836) was used as a probe. The band, approximately 1.4 kb in size, was detected in the colon in all strains. (**D**) Ethidium bromide staining.

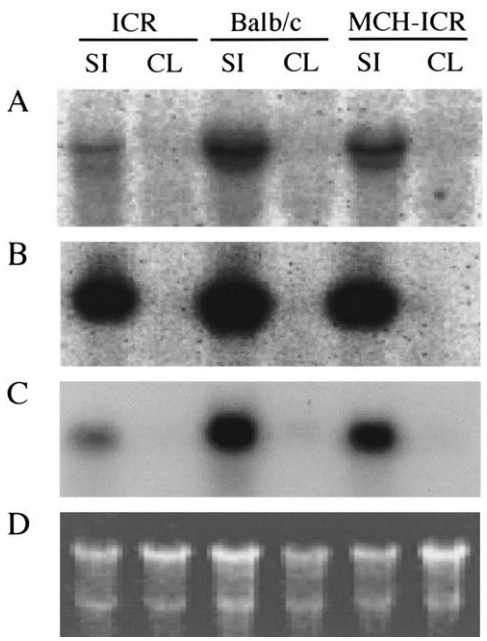

Fig. 5. Differential mRNA expression was confirmed by Northern blotting in three genes. Epithelial RNA was obtained from the small intestine (SI) and the entire colon (CL) of ICR BALB/c and MCH/ICR mice, respectively. (**A**) The cDNA of triglyceride transfer protein (W13053) was used as a probe. The band, approximately 2.9 kb in size, was noticed in both the small intestine and the colon, but with greater signal intensity in the colon in all mouse strains. (**B**) The EST clone (AA521545, a partial sequence of galactose-binding lectin, soluble 2 cDNA) was used as a probe. The band, approximately 0.6 kb in size, was noticed in both the small intestine and the colon, with stronger signal intensity in the latter colon in all mouse strains. (**C**) The cDNA of proline-rich acidic protein (W17866) was used as a probe. The band, approximately 0.7 kb in size, was detected in the colon in all strains. (**D**) Ethidium bromide staining.

Increased expression of CEACAM1 mRNA in the pouch mucosae suggests that some, but not all, colonic molecules are induced after total proctocolectomy. There are many factors that may influence mRNA expression in epithelial cells in the ileal pouch, including the time of the biopsy after ileostomy closure, the presence or absence of mucosal inflammation, bacterial composition in the pouch, foods, medication, and/or the genetic background of the patients. The time of sampling is highly suspected to be one of the most critical factors, because intestinal adaptation seems to be time-dependent. The absence of significant differences in HMGCoA S2, DMBT1, and MTTP mRNA levels may reflect varied sampling times, although we did not observe a correlation between the expression of these mRNAs and the interval between ileostomy closure and sampling. Nonetheless, the present approach permitted us to detect induction of CEACAM1, a candidate molecule that may contribute to intestinal adaptation after total proctocolectomy. However, it is unlikely that the phenotype of the mucosal epithelial cells in the ileal pouch changes completely from that of the small intestine to the colon.

CEACAM1 is a cell surface transmembrane glycoprotein that belongs to the carcinoembryonic antigen family of adhesion molecules. CEACAM1 is found in epithelial cells in various tissues and organs, including the esophagus, stomach, small intestine, colon, pancreas, bile duct, urinary bladder, and others.[21,22] In the small intestinal and colonic mucosae, CEACAM1 protein and mRNA are expressed in mature enterocytes and not in other cell types in the lamina propria.[22] Therefore, the ratio of CEACAM1 mRNA/villin mRNA correctly reflects epithelial

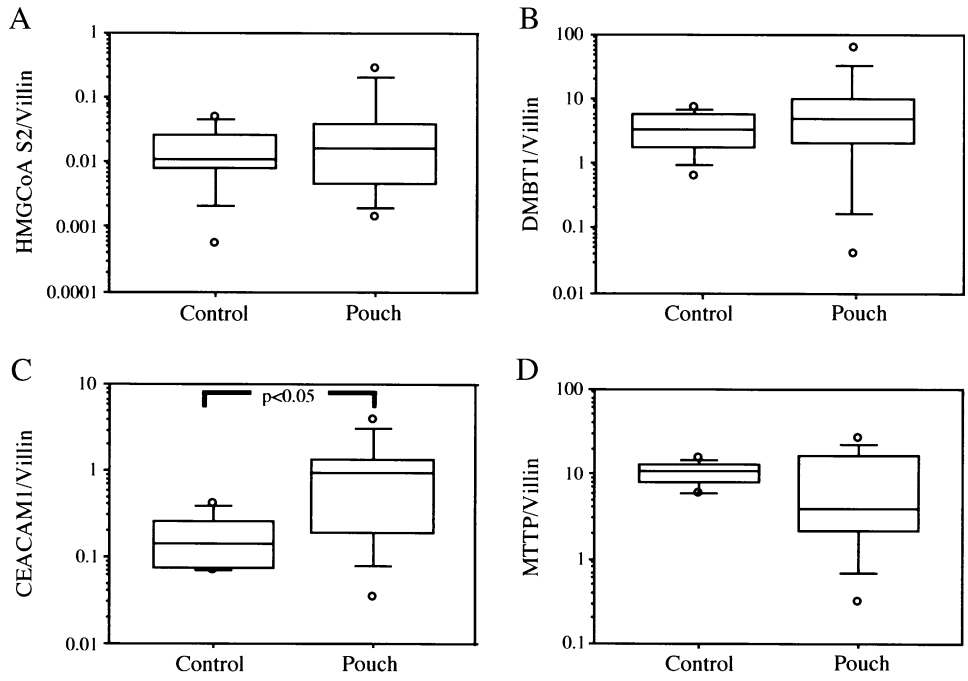

Fig. 6. Expression of (**A**) HMGCoA S2, (**B**) DMBT1, (**C**) CEACAM1, and (**D**) MTTP mRNAs was evaluated by quantitative RT-PCR. A significant difference ($P < 0.05$) was noticed in CEACAM1 between the control tissue and the ileal pouch.

CEACAM1 expression, and it is relatively unaffected by other cell types in the samples. The significance of CEACAM1 induction in the ileal pouch after total proctocolectomy remains unresolved. However, a recent report suggests that epithelial CEACAM1 expression is modulated by bacterial infection and proinflammatory cytokines, such as TNF-α.[22] *Neisseria gonorrhoeae* expressing opacity-associated protein adhesins triggers CEACAM1 upregulation through activation of the transcription factor nuclear factor κB in nontransformed cells in primary cultures.[23] Induction of CEACAM1 in the ileal pouch may be associated with bacterial infection, colonization, and/or dormant inflammation.[24] Further investigation is required for determining possible roles of CEACAM1 expression in the normal pouch and pouchitis with or without microbial infection.

Adaptation of the remnant intestinal mucosa is a compensatory mechanism for the loss of functions caused by the removal of the entire colon. A comparison of epithelial gene expression between the small intestine and the colon permitted us to identify epithelial molecules modulated after total proctocolectomy and candidate molecules that may contribute to intestinal adaptation. Epithelial cells of the remnant ileum partially develop a colonic phenotype as evidenced by the induction of certain mRNAs characteristic of the normal colon. Analysis of intestinal adaptation may lead to the development of new therapies for postoperative dysfunction or complications. The present approach facilitates an analysis of the mechanisms of intestinal adaptation after total proctocolectomy.

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Pancreatic Cancer in Sweden 1980–2000: A Population-Based Study of Hospitalized Patients Concerning Time Trends in Curative Surgery and Other Interventional Therapies

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Progress has been made during the last few decades in the treatment of patients with pancreatic cancer. In this population-based study, the time trends in curative surgery and the choice of palliative invasive therapies in Sweden over two decades are analyzed. Patients treated for pancreatic carcinoma in Sweden during 1980–2000 were identified in the Swedish Hospital Discharge Register and the Cancer Register. These data were matched with those in the Register of Causes of Death in Sweden. Data were identified and analyzed for 16,758 patients for three periods: 1980–1986 (n = 5775), 1987–1993 (n = 6096), and 1994–2000 (n = 4887). The rate of pancreatic resection increased 7.2%, 10.9%, and 15.1% ($P < 0.0001$) during the three respective periods. Palliative interventions decreased from 46.8% in the first period to 41.7% in the last period. On comparing the first and the last periods, biliary bypass operations were found to decrease (from 45.9% to 18.1%), as well as gastric bypass procedures (from 33.8% to 22.8%; $P < 0.0001$). Interventions by percutaneous transhepatic cholangiography (PTC) remained constant (10%–11%). Endoscopic therapy increased from 10.8% to 49.0%, as did the number of procedures per patient, from 1.3 to 1.7 ($P < 0.0001$) in the first and last periods, respectively. In 1980, the mean hospital stay was 40 days after resection and 30 days after palliative intervention. In 2000, the corresponding numbers were 26 days and 18 days ($P < 0.001$), respectively. During the past two decades, the rate of pancreatic resections in Sweden increased significantly. There was also a dramatic drop in palliative open surgery and a simultaneous increase in endoscopic interventions. Hospital stays decreased by more than a third. (J GASTROINTEST SURG 2006;10:672–678)

KEY WORDS: Pancreatic cancer, resection, palliative intervention, supportive care

Pancreatic carcinoma is an aggressive disease, and the majority of patients are not operable at diagnosis due to advanced tumor stage or age, in combination with other medical disorders. Thus, attempted curative resection can only be offered to 10%–20% of the patients, whereas the majority receive palliative treatment.[1,2]

Over time, there has been much development in the treatment of patients with pancreatic carcinoma.[3] The diagnostic workup has been refined to identify potentially resectable patients, and the indication for surgery is based on computerized tomography as well as magnetic resonance imaging.[4–6] During recent years, pancreatic resections have also become more centralized.[7–9] Palliative measures are often needed to relieve obstructive jaundice. It seems as if there has been a shift from percutaneous transhepatic cholangiography (PTC) to endoscopic retrograde cholangiography (ERC) to insert biliary stents, and the recently developed self-expandable metal stents may provide life-long patency.[10] Thus, biliary bypass operations are now less common, but they still remain as an alternative for patients with a long expected survival.[11] Duodenal obstruction may also require surgery, but stenting is also a therapeutic option.[12]

Our aim in the present series was to study all patients in Sweden who were treated for pancreatic carcinoma during 1980–2000, with a focus on trends over time in the choice of therapy. The frequency of

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pancreatic resection was analyzed, as well as the types of palliative interventional therapy for obstructive jaundice and an impaired gastric outlet. The percentage of patients with pancreatic carcinoma not receiving any type of invasive therapy was recorded. The length of hospital stays after different types of treatments were also recorded. To our knowledge, no such other large national population-based study has been published.

MATERIAL AND METHODS

Databases

The Swedish Hospital Discharge Register (SHDR) is kept by the Swedish National Health and Welfare Board. It includes only patients hospitalized in Sweden; those treated in an outpatient department are not included. We have selected from the Cancer Register (CR) all patients with the diagnosis of pancreatic duct carcinoma during the period 1980–2000. We have matched the two registers (SHDR and CR) with the Register of Causes of Death, Statistics Sweden. Data from Statistics Sweden were used to classify the Swedish population by sex and age. The vital population statistics are based on a census of the population. The nominator is known, and therefore, we can give unbiased estimates of the annual population. The population of Sweden was 8.6 million in 1990.

The diagnoses in the SHDR were coded according to the International Classification of Diseases 8, 9 and 10 during the period in question. The hospital morbidity data file allows up to six diagnoses and six operations in each case. The SHDR contains data about the patient and the admitting clinic and hospital, as well as the hospitalization and medical findings. In 2003, we did a retrospective analysis of all data in the CR on patients with pancreatic duct carcinoma during 1980–2000. The SHDR covers the entire country and provides an opportunity to study various groups of patients on the basis of their diagnoses.

The Swedish National Health and Welfare Board considers the data in the SHDR to be reliable. The Board continuously scrutinizes incoming data, looking for omissions and other errors, and it also compares incoming data with those in other relevant registers. The main diagnosis was missing in a mean of 1.2% of the cases in the 8-year period studied. Specialists in the classification of diagnoses have concluded that 8%–11% of the diagnoses are incorrectly classified. Many of these misclassifications are erroneous only at the most detailed level, often being classified correctly in their diagnostic groups.

Patients

During the period 1980–2000, 16,758 patients with pancreas duct carcinoma were registered in the CR, 48% being men and 52% women (the aged-standardized incidence for pancreatic cancer was higher in men, the female dominance caused by a larger amount of women in the older age groups more likely to develop the disease). The age-specific incidence for men with pancreatic cancer was 2 per 100,000 at the age of 40 years, 9 at 50, 26 at 60, 57 at 70, and a peak of 86 per 100,000 at 85 years of age. Corresponding numbers for women were, 1, 6, 20, 42, and 76 per 100,000 at 85 years of age. The median age range was 70–74 years, the same as the mean age range.

According to the coding of interventional procedures, the patients were divided into three groups: patients undergoing pancreatic resection, a palliative intervention group (biliary or gastric bypass, PTC, and ERC), and patients not undergoing invasive therapy.[13a–c]

The study period was divided into three 7-year intervals: 1980–1986, 1987–1993, and 1994–2000. The latter portion of the last interval (1997–2000) could be analyzed separately because there was a shift in the coding of the procedures in 1997.

The health care system in Sweden is public and there has been no change during the study period. In Sweden, patients with pancreatic cancer are, with few exceptions, managed in hospitals, a policy which was the same throughout the study.

Statistical Analysis

The x^2 analysis was applied for differences in the distribution of absolute numbers of patients. Regression analysis was used to calculate changes in hospital stay by calendar year (Fig. 1).

RESULTS

Type of Therapy

During the whole study period, 1819 pancreatic resections were performed (10.9%). Palliative procedures were used in 7457 (44.5%) patients, and no intervention was performed in 7482 (44.6%; Table 1) patients.

During the three periods 1980–1986, 1987–1993, and 1994–2000, the resection rate increased significantly at 7.2%, 10.9%, and 15.1%, respectively ($P < 0.0001$). Palliative procedures decreased from 46.8% to 44.6% in the second period ($P < 0.05$), and further to 41.7% ($P < 0.01$) in the last period. The proportion of patients in whom no intervention

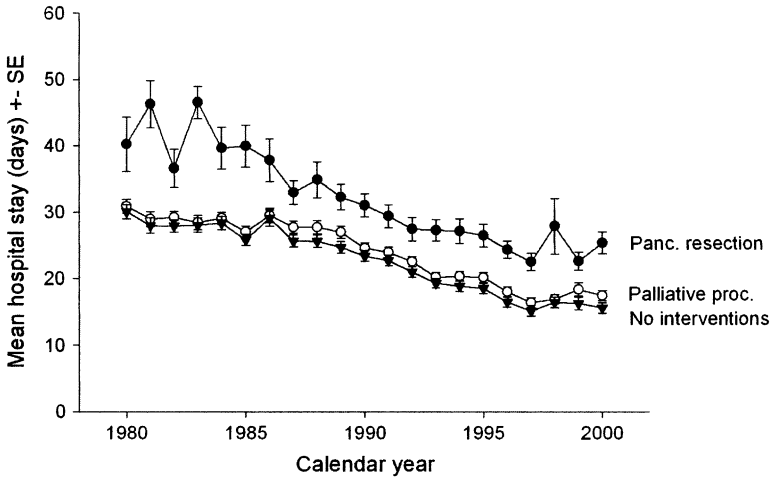

Fig. 1. Length of hospital stay for patients who underwent pancreatic resection (n = 1819), palliative procedures (n = 7457), and patients in the nonintervention group (n = 7482).

was possible decreased 46.0%, 44.5%, and 43.2%, in the respective periods ($P < 0.01$; Table 1). There were no differences in gender distribution between the resection group, the palliative procedure group, and patients in whom no intervention was performed.

Palliative Procedures

In the first period, 1980–1986, 2702 patients underwent 3497 palliative procedures. During the next period, 1987–1993, 4098 procedures were performed in 2717 patients. In the last period, 1994–2000, 2038 patients were subjected to 3446 procedures. The ratio of procedures per patient increased during the three periods was 1.3, 1.5, and 1.7, respectively (Table 2). Thus, the same patient had several procedures, that is, gastric bypass and biliary bypass operations or ERC interventions, on several occasions.

Open surgery decreased significantly. The frequency of biliary bypass operations in the three periods was 45.9%, 37.3%, and 18.1%, respectively ($P < 0.0001$). The corresponding numbers for gastric bypass operations were 33.8%, 28.6%, and 22.8% ($P < 0.0001$). Contrarily, the ratio of ERC interventions increased significantly, 10.8%, 23.1%, and 49.0%, respectively, in the three periods ($P < 0.0001$). However, the rate of PTC procedures remained constant over the different periods, 10.5%, 11.0%, and 10.1%, respectively (Table 2).

In the latter part of period three, 1997–2000, 2144 palliative procedures were performed. There were 287 (13.1%) biliary bypass operations, 398 (18.6%) gastric bypass procedures, 220 (10.3%) PTC interventions, and 1244 (58.0%) of the palliative procedures were performed by using the ERC technique. These changes in the frequency of the intervention type were highly significant ($P < 0.0001$), except for the PTC approach, which was used to the same extent.

Hospital Stay

The length of hospital stays over time is shown in Fig. 1, comparing patients who underwent pancreatic resection and palliative procedures and those in whom no intervention was performed. There was a significant reduction in hospital stay in all three groups ($P < 0.001$). Patients resected for pancreatic

Table 1. Types of treatment in 16,758 patients diagnosed with pancreatic duct carcinoma in Sweden during 1980–2000

Operative procedure	1980–1986 (n = 5775)	1987–1993 (n = 6096)	1994–2000 (n = 4887)
Pancreatic resection (n = 1819)	416 (7.2%)*	665 (10.9%)*,**	738 (15.1%)*,**
Palliative procedure (n = 7457)	2702 (46.8%)†	2717 (44.6%)†,‡	2038 (41.7%)‡
No intervention (n = 7482)	2657 (46.0%)‡	2714 (44.5%)	2111 (43.2%)‡

*$P < 0.0001$.
**$P < 0.0001$.
†$P < 0.05$.
‡$P < 0.01$.

Table 2. Palliative procedures in 7457 patients with pancreatic carcinoma in Sweden treated during 1980–2000

Palliative procedure	1980–1986 (n = 2702)	1987–1993 (n = 2717)	1994–2000 (n = 2038)
Biliary bypass operation (n = 3756)	1604 (45.9%)*,**	1527 (37.3%)*	625 (18.1%)*,**
Gastric bypass operation (n = 3106)	1147 (33.8%)*,**	1174 (28.6%)*	785 (22.8%)*,**
PTC procedure (n = 1165)	367 (10.5%)	451 (11.0%)	347 (10.1%)
ERC procedure (n = 3014)	379 (10.8%)*,**	946 (23.1%)*	1689 (49.0%)*,**
Total number of procedures (n = 11,041)	3497	4098	3446
Procedure/patient	1.3*	1.5*,†	1.7†

All procedures have been recorded, thus a patient may have been treated by several methods. PTC = percutaneous transhepatic cholangiography; ERC = endoscopic retrograde cholangiography.
*$P < 0.0001$.
**$P < 0.0001$.
†$P < 0.01$.

carcinoma had longer hospital stays than those receiving palliative procedures or no intervention ($P < 0.001$). Hospital stays were equal in the two latter groups. In the beginning of the study period, the mean hospital stay for resected patients was 40 days, and in the year 2000, patients undergoing pancreatic resection stayed only 26 days in the hospital. In the palliative procedure and no-intervention groups, the mean hospital stay decreased from 30 days in 1980 to 18 days in 2000.

DISCUSSION

Each individual in Sweden has a unique personal identification number that is included in every type of registration when a patient is admitted to the hospital. The documentation in the registers used in our study is reliable, and thus, information regarding surgical resections and other invasive therapies is readily accessible. We were also able to identify pancreatic cancer patients not connected with a coded invasive procedure. In the present series of 16,758 patients, 44.6% did not undergo any type of intervention. This compares well with the study by Bramhall et al.[14] reporting 42.7% and 47.8% of patients receiving only supportive care during two periods, 1957–1976 and 1977–1986, respectively. However, in contrast to our study, their rate of palliative care increased over time. Pasquali et al.[15] reported that 32.8% of their patients were treated without invasive procedures. The high proportion of patients not undergoing any type of invasive intervention may be explained by the fact that many pancreatic cancer patients are old, and their general condition precludes any type of intervention. Also, pancreatic carcinoma can be found in 2% of patients at autopsy.[16,17]

During the study period 1980–2000, there was a great worldwide improvement in the results after resection surgery for pancreatic carcinoma. Survival has improved, and postoperative mortality has decreased from up to 45% to below 5% in specialized units.[8,14,18–22] Along with these achievements, the rate of resection has increased up to 20%.[23,24] This is consistent with the present series, in which the resection rate increased from 7.2% in the first part of the study up to 15.1% in the last part. Advances in the diagnostic workup, operative technique, and perioperative care have made pancreatic resection safer and the indications wider (also including elderly patients), and have thus increased the resection rate.[8,9] Oncological therapy is also improving, and through chemoradiotherapy, downstaging of pancreatic carcinoma has been possible, which in turn has made surgical resection possible in selected patients with previously inoperable tumors.[25] Extended operations, also including portal vein resection, are also performed.[7,26,27] However, the volume of these procedures could not be evaluated in the present series.

Palliative invasive treatment is predominant in pancreatic carcinoma and is needed particularly when jaundice or duodenal obstruction is present. In our series, a palliative surgical procedure or radiological interventional therapy was performed in 7457 patients (44.5%). Over time, there was a decrease in palliative procedures, apparently because of an increased resection rate. Although it is well known that the resection rate has increased, it has not been demonstrated that palliative procedures have actually decreased in a large population. With the introduction of endoscopic techniques, it might be expected that a larger proportion of patients would undergo interventional procedures and balance those being resected. Thus, in the present series, the noninterventional group decreased, but not enough to compensate for the increased resection rate. There was a dramatic shift over time in the type of palliation of obstructive jaundice in our series. During 1980–1986, 45.5% of the palliative procedures were biliary bypass surgery, and only 10.8% were

ERC interventions. Corresponding numbers for the period 1997–2000 were 13.1% and 58.0%. In contrast to many other countries, patients with obstructive jaundice in Sweden are usually managed by surgeons who, in most cases, also perform the interventional ERC. Thus, there is a free choice between endoscopic procedures and surgery, but still this shift in therapy has occurred. Apparently, there has been a worldwide increase in ERC-based techniques, but the impact has not been demonstrated previously in a large population. There will always be an indication for biliary bypass surgery, that is, for patients in whom nonsurgical intervention fails, good surgical candidates with inoperable disease, and those who are found not to be resectable at attempted curative resection.[28]

Clogging of endoscopic stents is common, and it was shown in our series that the number of interventions per patient increased during the study period; this is probably explained by the need for repeated ERC intervention in cases of stent failure. This increase in procedures per patient, which is probably due to the shift to ERC techniques, has not been demonstrated previously in a population-based study. A more frequent use of metal stents in patients with a longer life expectancy may reduce the need for reinterventions.[10]

Interestingly, the frequency of PTC remained constant over the study period (10%–11%). In the first part of the study, ERC interventional therapy was not widely available in Sweden, and PTC was probably performed most often as a primary procedure. Contrarily, it may be assumed that PTC was employed in the last period when ERC techniques had failed. Duodenal obstruction is also a common problem in pancreatic cancer patients.[22] Some authors claim that duodenal overgrowth is common enough in open surgery for biliary bypass to justify prophylactic gastroenteroanastomosis, which may also cause complications.[29,30] On the other hand, some recent studies show that gastric bypass surgery can be performed safely to prevent potential future obstruction.[28] In the present series, there was a significant decrease in the rate of gastroenteroanastomosis, which paralleled the decrease in biliary bypass surgery.

There was a pronounced reduction of hospital stays that was similar in the resection group, patients treated by palliative intervention, and the nonintervention group. Although there has been a dramatic decrease in hospital mortality after pancreatic resection, postoperative morbidity remains high, up to 40%.[8,18,20] Pancreatic resections can also be performed in elderly patients without increased morbidity or prolonged hospital stay.[9,31] Although significant problems remain in pancreatic surgery,[8,18,32,33] the length of hospital stays has decreased in most series.[8,34] In a large survey, Goodney et al.[35] report a series from 1994–1999 in which the mean hospital stay was 19.8 days in small institutions and 15.3 days in larger ones. This is slightly less than in our study, which comprises a mix in the size of the hospitals. Our numbers are lower compared with a series reported by Pasquali et al.[15] in which the mean hospital stay was 57.7 days. Neoptolemos et al.[36] reported a median hospital stay of 11–36 days in specialist units, but even a hospital stay of less than 10 days after resection has been documented.[8] Many factors account for this decrease in hospitalization, for example, the preoperative evaluation, perioperative management, and centralization of pancreatic surgery.[3]

Older series demonstrate that palliative open surgery carries high morbidity, mortality, and long hospitalization.[29,37] This is also true of PTC procedures.[38] Numbers in more recent series are more favorable, but ERC procedures are still associated with a shorter hospital stay, although they necessitate further hospitalization due to recurrent jaundice and gastric outlet obstruction.[11,28,30] Thus, the shift in our series to ERC-based therapy has surely contributed to shorter hospital stays, as demonstrated in the palliative group. Economic pressure on the health system, which may have contributed to the development of patient care outside the hospital in the patients home as well as in palliative units, is also important.[39]

CONCLUSION

It was shown in the present series that the management of patients with pancreatic carcinoma in Sweden has changed dramatically over a 20-year period. The resection rate has increased and ERC techniques have replaced biliary bypass surgery to a large extent. There is a need to relieve duodenal obstruction, but the number of procedures has decreased. The PTC frequency was constant, and it is obvious that a multidisciplinary approach is required. Along with shorter hospitalization periods, the number of procedures per patient increased. In the future, the development of new oncological methods[40] will probably dominate changes in surgical or interventional techniques.

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Fibromatosis of the Remnant Pancreas After Pylorus-Preserving Pancreaticoduodenectomy

Eric S. Weiss, M.D., Ashlie L. Burkart, M.D., Charles J. Yeo, M.D.

Intra-abdominal fibromatosis or desmoid tumors are rare forms of connective tissue cellular dysplasia characterized by proliferation of fibroblasts and abundant collagen. Most often these tumors associated with familial adenomatous polyposis or Gardner's syndrome. Those tumors not associated with polyposis are termed sporadic desmoids and tend to be locally aggressive in nature. Sporadic intra-abdominal desmoids involving the pancreas are quite rare, as only six previously reported cases exist. In this report we present a seventh case of a sporadic intraabdominal desmoid involving the pancreas. The patient, a 63-year-old white man, developed the desmoid tumor following a pylorus-preserving pancreaticoduodenectomy for an insulinoma. The patient was managed via further pancreatectomy, consisting of a distal pancreatectomy with en bloc splenectomy, sparing a 6-cm portion of pancreatic neck and proximal body. Finally, we present a complete review of the six previous cases of sporadic pancreatic fibromatosis. (J GASTROINTEST SURG 2006;10:679–688)

KEY WORDS: pancreas, fibromatosis, desmoid, pancreaticoduodenectomy

Deep-seated fibromatoses or desmoid tumors are a rare form of neoplasia commonly associated with familial adenomatous polyposis (FAP) or Gardner's syndrome (GS) (incidence, 1:8000 and 1:1 million, respectively) and occur at a rate approaching 38% in these two syndromes. Those not coupled with FAP or GS are termed sporadic and are much less common, occurring at a rate of approximately 2.4 to 4.3 cases per million people per year.[1] The sporadic intra-abdominal desmoid is rarer, with fewer than 100 cases having been reported in the English literature.[2] Finally, of these sporadic intra-abdominal desmoids that have been described, only six cases have involved the pancreas.

In this report we describe a seventh case of a sporadic intra-abdominal desmoid involving the pancreas of a 63-year-old white man who had previously undergone a pancreaticoduodenectomy for neuroendocrine neoplasia. In addition, we describe the successful resection of this desmoid tumor via distal pancreatectomy and splenectomy, while leaving the unaffected mid-portion of the pancreas in situ. We further present a complete review of the literature on intra-abdominal desmoids affecting the pancreas. The report serves not only to describe an unusual case but also to educate the medical community about this rare neoplastic disease.

CASE REPORT

The patient is a 63-year-old white man of Italian ancestry whose past medical history is significant for a bleeding duodenal ulcer responding to medical management, a traumatic fracture of the back requiring orthopedic stabilization, and a cerebral hemorrhage from traumatic injury, all three of which occurred more than 15 years earlier and left the patient with no sequelae. In April 2002, he presented with spells of diaphoresis, weakness, and intermittent seizures. Laboratory analyses revealed severe hypoglycemia, while more extensive testing demonstrated fasting serum glucose and insulin levels to be 42 mg/dl and 12 μU/ml, respectively. In addition, his C-peptide was elevated at 6.8 ng/ml (normal <1.0). With the diagnosis of hypoglycemia related to hyperinsulinemia, he was referred to our institution in August 2002.

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At our institution, the patient had an abdominal computed tomography (CT) scan that was read as normal (Fig. 1, *A*). However, endoscopic ultrasound with fine needle aspiration identified a well-defined 1.5 × 1.0 cm hypoechoic mass deep in the pancreatic head, which tested positive for CD 56 and chromogranin, findings consistent with a well-differentiated neuroendocrine tumor. With the presumed diagnosis of a pancreatic insulinoma, the patient underwent a pylorus-preserving pancreaticoduodenectomy on September 16, 2002. Final pathology from this first operation revealed a 1.5-cm well-differentiated neuroendocrine pancreatic neoplasm (Fig. 2), which tested positive by immunoperoxidase stains for chromogranin and synaptophysin and was equivocal for insulin on special staining. All resection margins and lymph nodes were negative for tumor, and a repeat CT scan showed no evidence of residual disease (Fig. 1, *B*). The patient's postoperative course was complicated by a small bile leak at the biliary-enteric anastomosis, which sealed after the placement of a percutaneous transhepatic biliary catheter. After the resection, the patient's fasting glucose returned to the normal level of 105 mg/dl, his fasting serum insulin level was measured at an appropriate level of 2.3 μU/ml, and his C-peptide level decreased to 1.3 ng/ml. Subsequent follow-up has proved him cured of his insulinoma, without further episodes of symptomatic hypoglycemia.

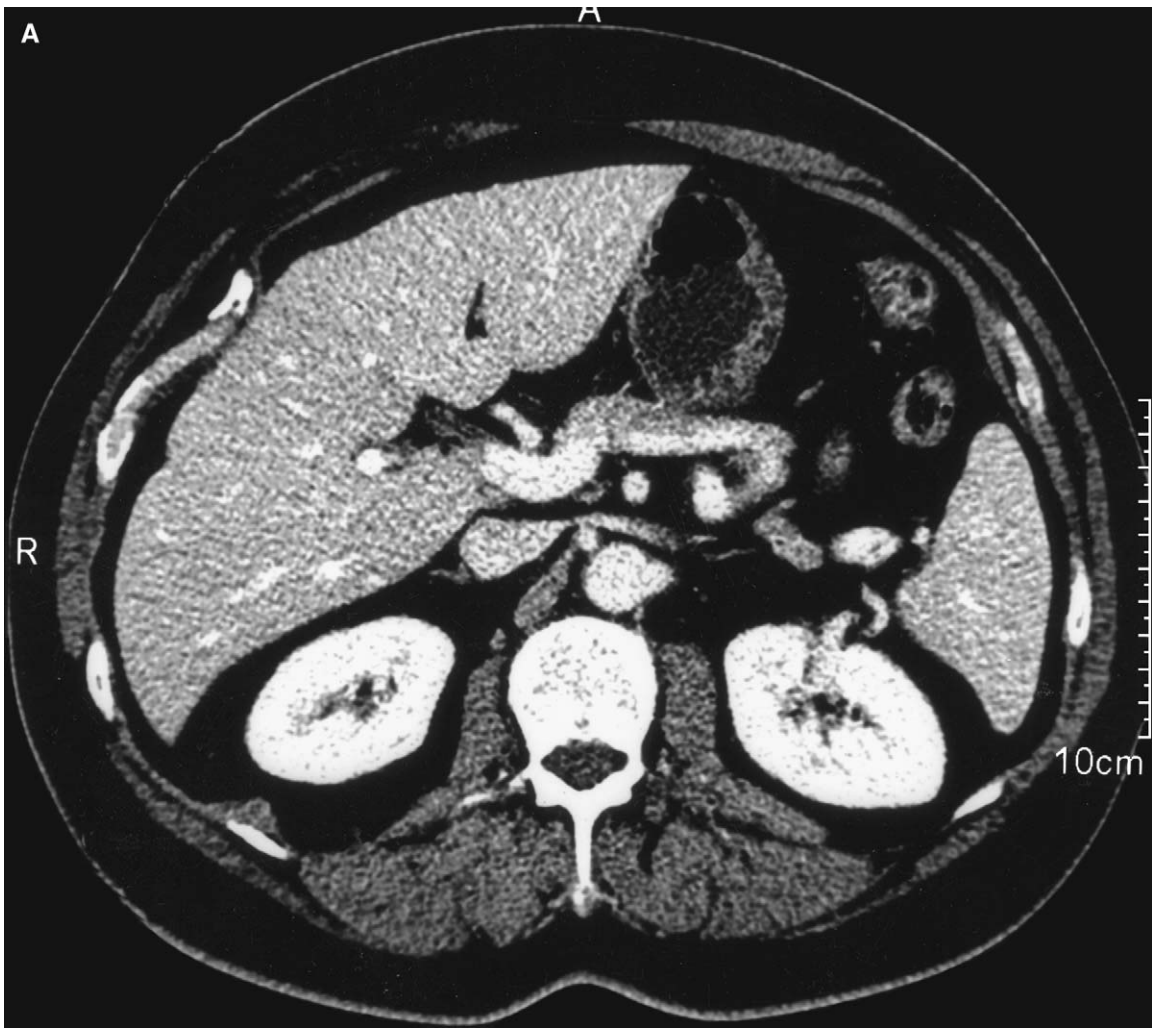

Fig. 1. Computed tomography scans at three stages in the patient course. (**A**) CT scan obtained at initial presentation, with no neuroendocrine tumor visualized, and normal body and tail of the pancreas. (**B**) Patient following pylorus-preserving pancreaticoduodenectomy, with normal remnant body and tail of the pancreas. Fluid and air around the liver related to leak at biliary-enteric anastomosis, managed with percutaneous biliary catheter drainage. (**C**) New desmoid tumor visualized (*arrow* points to cystic component of desmoid mass).

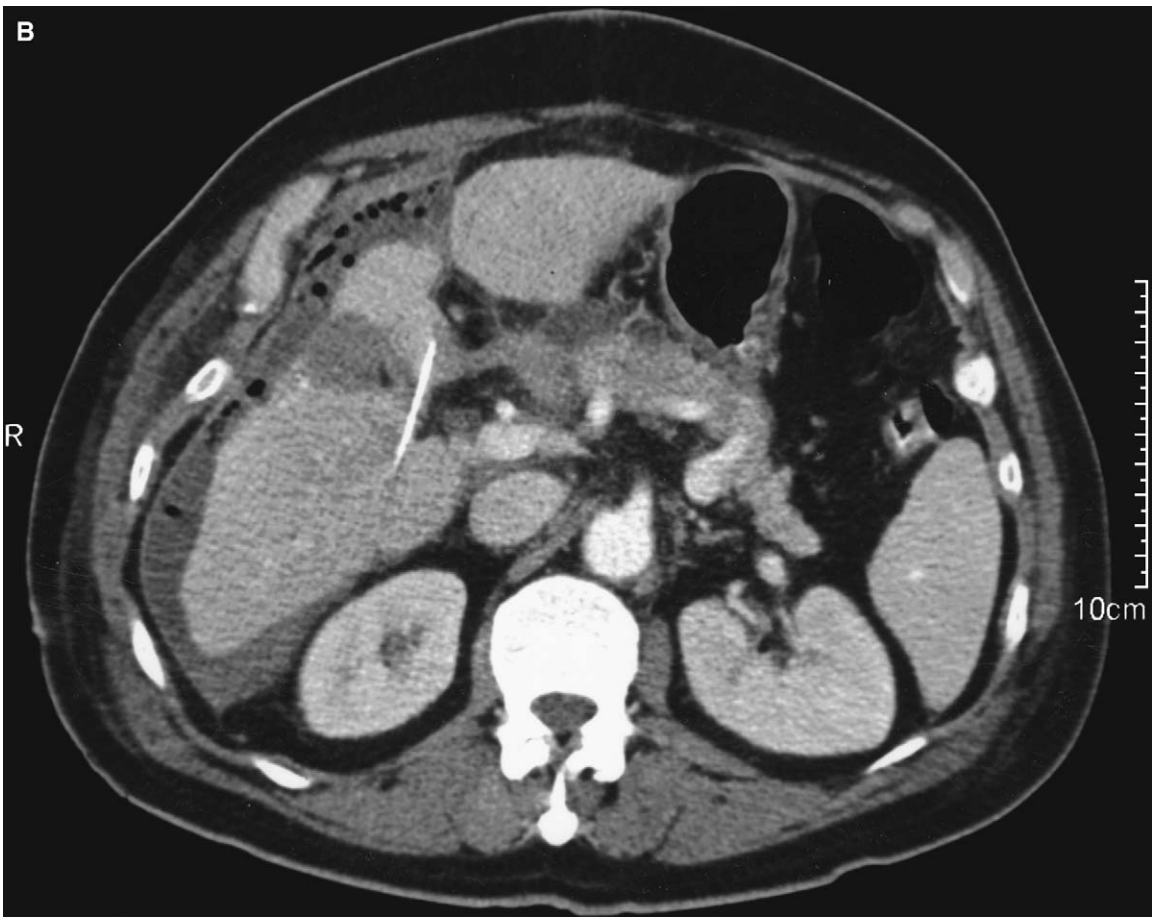

Fig. 1. (*Continued*).

In October 2004, 25 months after his pancreatic resection, the patient developed symptoms of abdominal fullness and epigastric pain. A repeat CT scan revealed a 6.5 × 5.3-cm hypoechoic mass in the remnant pancreatic body and tail, with both cystic and solid components (Fig. 1, *C*). The patient had no symptoms of hypoglycemia at this time, and his serum glucose levels were normal. Various tumor markers were normal including carbohydrate antigen 19-9 (CA 19-9) of <1 U/ml (0-36), chromogranin A of 19.8 ng/ml (6–39), pancreatic polypeptide of 80 pg/nl (100–780), and carcinoembryonic antigen (CEA) of 2.8 ng/ml (0–3).

On November 11, 2004, the patient underwent a distal pancreatectomy with en bloc splenectomy to resect this 6.5-cm mass. This operation removed the caudal most portion of the pancreas, sparing a 6-cm pancreatic remnant attached to the previously constructed pancreaticojejunostomy (Fig. 3, *A*, *B*). Intraoperative frozen section showed dense fibrosis within the mass, with all margins of resection being negative for tumor.

Specimens of the distal pancreas, spleen and multiple lymph nodes (Fig. 4) were routinely processed (10% formalin), paraffin embedded, and stained with hematoxylin and eosin. Microscopically, the lesion was poorly circumscribed and infiltrated the surrounding pancreatic parenchyma. Histopathological examination of the mass demonstrated spindle-shaped cells with hypochromatic nuclei, lack of cellular atypia, and abundant collagen with extensive hyalinization (Fig. 5, *A*). By immunohistochemical staining (Fig. 5, *B*), the lesion was positive for beta-catenin and negative for anaplastic lymphoma kinase, both of which supported the diagnosis of fibromatosis. Fifteen lymph nodes were negative for tumor, and no residual or additional neuroendocrine tumor was identified.

The patient recovered well with no complications and was discharged on postoperative day 6. He is currently doing well, now 9 months after his second resection. His serum glucose levels remain normal, and his epigastric pain has resolved.

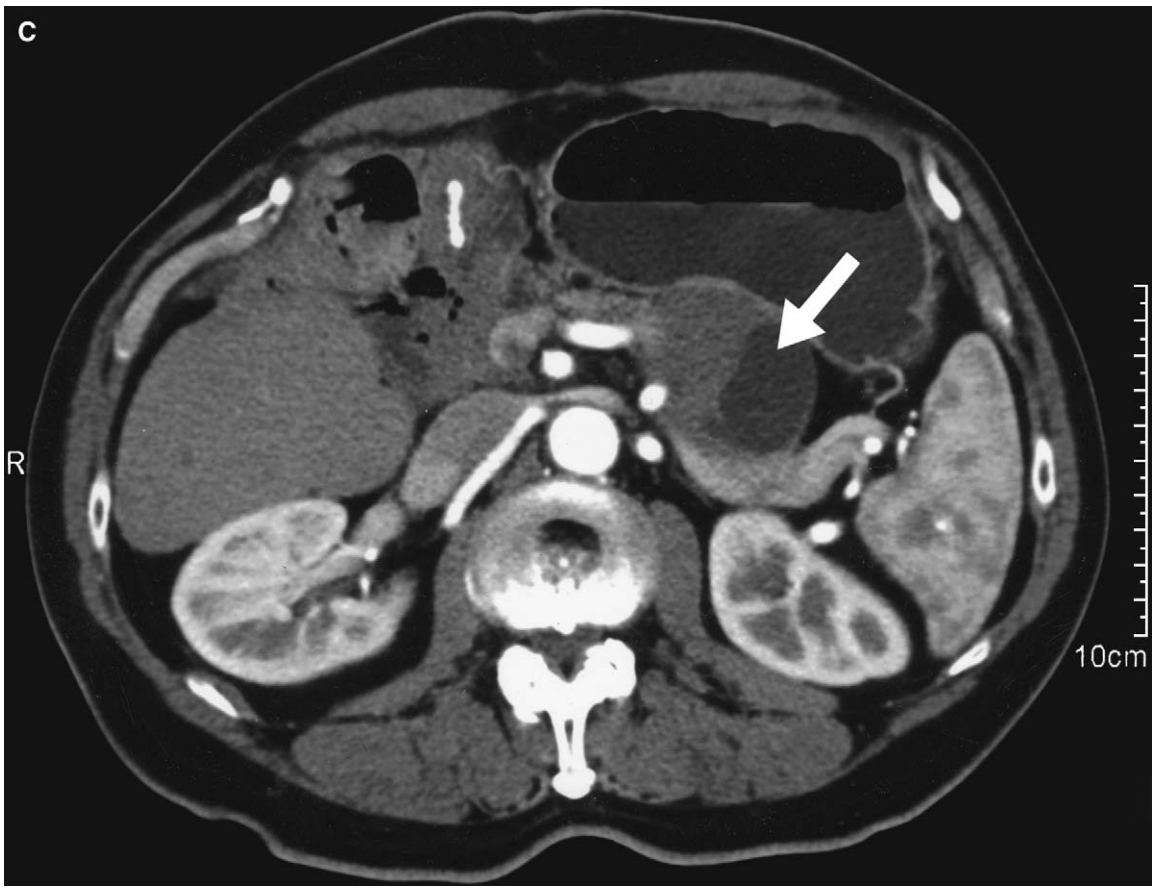

Fig. 1. (*Continued*).

DISCUSSION

Fibromatosis is a rare variety of connective tissue cellular dysplasia. It has classically been dividend into superficial (those involving subcutaneous fascial layers) and deep varieties (those involving muscle and organs). Deep fibromatoses are also known as desmoid tumors and were first described by McFarlane in 1832, when he observed a fibrous tumor in a woman following childbirth.[3] Desmoids were characterized by their noted association with intestinal polyposis and osteomas as part of GS, first described by E. J. Gardner in 1951, and occurring with an incidence of approximately 1:1 million in the general population.[4] FAP, intestinal polyposis without extra-intestinal manifestations, is more common with an incidence of 1:8000 individuals. In patients with both GS and FAP, it is not unusual to identify one or multiple desmoid tumors, as they can occur at a rate that approaches 38% of all patients.[5–7]

When not associated with GS or FAP, desmoids are termed sporadic and are a much rarer entity, occurring at a rate of only 2.4–4.3 cases per million per year.[1] Sporadic intra-abdominal desmoids are even less common, as a review only found 94 reported cases in the English literature.[2]

When desmoids do involve the abdominal cavity, they most often are located in the small bowel mesentery.[8] There have been isolated reports of desmoids involving organs such as the appendix[9] and stomach,[10] but primary involvement of intra-abdominal viscera is quite unusual.

The present case illustrates an example of a sporadic desmoid of the abdominal cavity and more specifically one involving the pancreas. Sporadic desmoids involving the pancreas are quite rare. In our review of the literature, we could only find six previously reported cases of sporadic pancreatic desmoid tumors (Table 1).

These six cases share little in common. Two were among siblings who presented with abdominal pain and were diagnosed by CT scanning.[11] These two individuals did not undergo resection. Two involved pediatric patients, one in a 4-month-old boy with extensive involvement[12] and one in a 15-year-old girl.[10] One case was found incidentally by pathology in association with a resected intraductal papillary

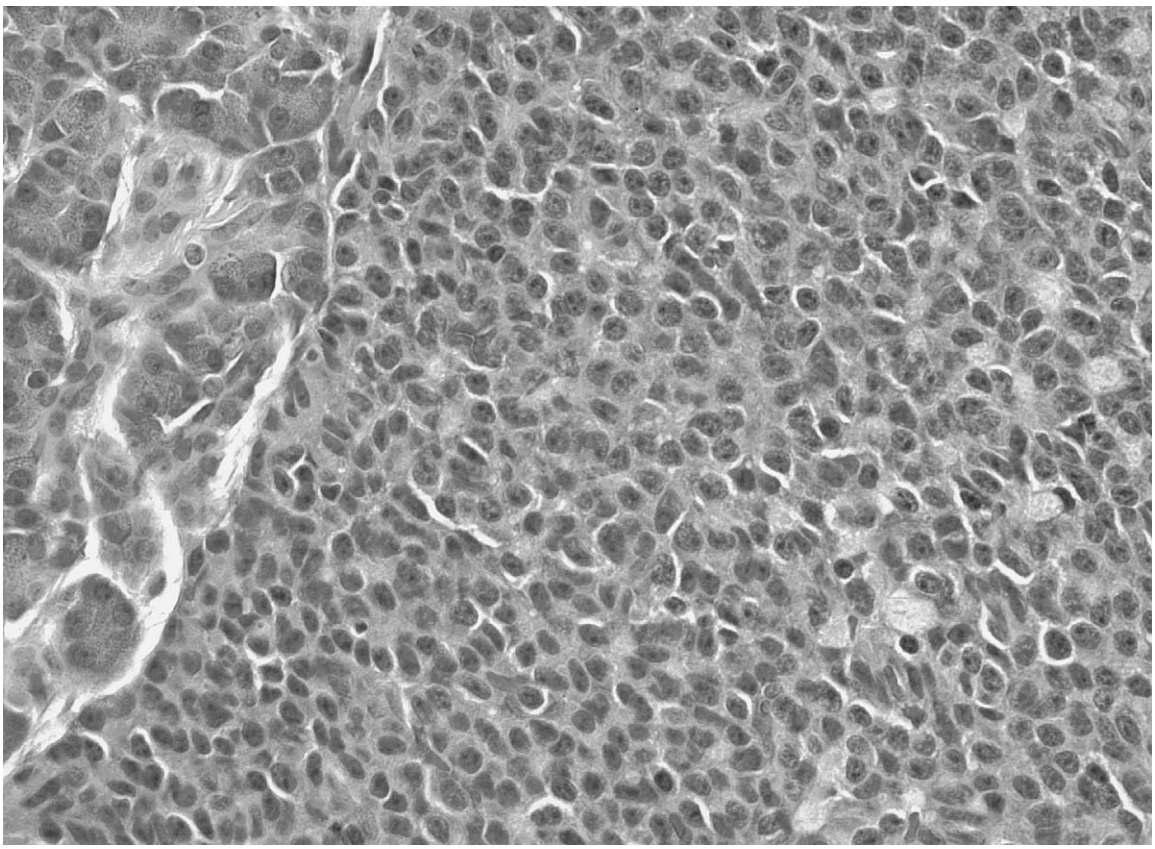

Fig. 2. Hematoxylin and eosin stain of the specimen obtained from the patient's initial operation, demonstrating a well-differentiated neuroendocrine neoplasm of the pancreas (original magnification ×100).

mucinous neoplasm-adenoma in a 68-year-old girl.[13] Finally, one case occurred in a 38-year-old man who had previously undergone a distal pancreatectomy for a neuroendocrine neoplasm.[7] Of these six cases, three of the individuals underwent surgical resection and there was one death. In none of the six cases was there any history of FAP or GS.

Of the previous six cases presented, the report by Bruce et al.[7] of a 38-year-old man who developed his desmoid tumor following distal pancreatic resection for a neuroendocrine neoplasms deserves special mention because of its similarities with the case presented in this review. In both cases, the desmoid mass developed in the remnant pancreas after prior pancreatic resection for a neuroendocrine neoplasm. Additionally, in each case, the mass was identified and characterized by CT scanning. Finally, both cases required repeat pancreatic resection to remove the fibromatosis. The difference between the two cases lies in the specific location of the mass and consequent strategy used for removal. In our case the desmoid occurred in the remnant pancreatic tail after pancreaticoduodenectomy, whereas in the case reported by Bruce et al., the desmoid occurred in the pancreatic head following a distal pancreatectomy. The patient in the latter case thus required a completion total pancreatectomy which spared no pancreas, while we were able to perform a distal pancreatectomy and splenectomy sparing the mid-portion of the pancreas for our patient. This operative strategy will be further discussed below. While it is difficult to draw any meaningful conclusions by examining only two cases, the parallel history and course for these two patients is noteworthy.

From review of these six cases it appears that our own case of fibromatosis is the first following a pancreaticoduodenctomy. In fact, in our institution's experience of 2650 pancreaticoduodenal resections since 1969, there is no other example of a desmoid tumor involving the pancreas either as a preoperative finding leading to resection or as a postoperative finding. This is perhaps surprising, because it has been speculated that desmoids tend to develop following surgical trauma, often localizing to surgical scars.[1]

Intra-abdominal desmoids typically present as fullness or increased girth in the abdominal cavity. A predominance toward women of childbearing age has been reported,[1] and many believe that trauma, either

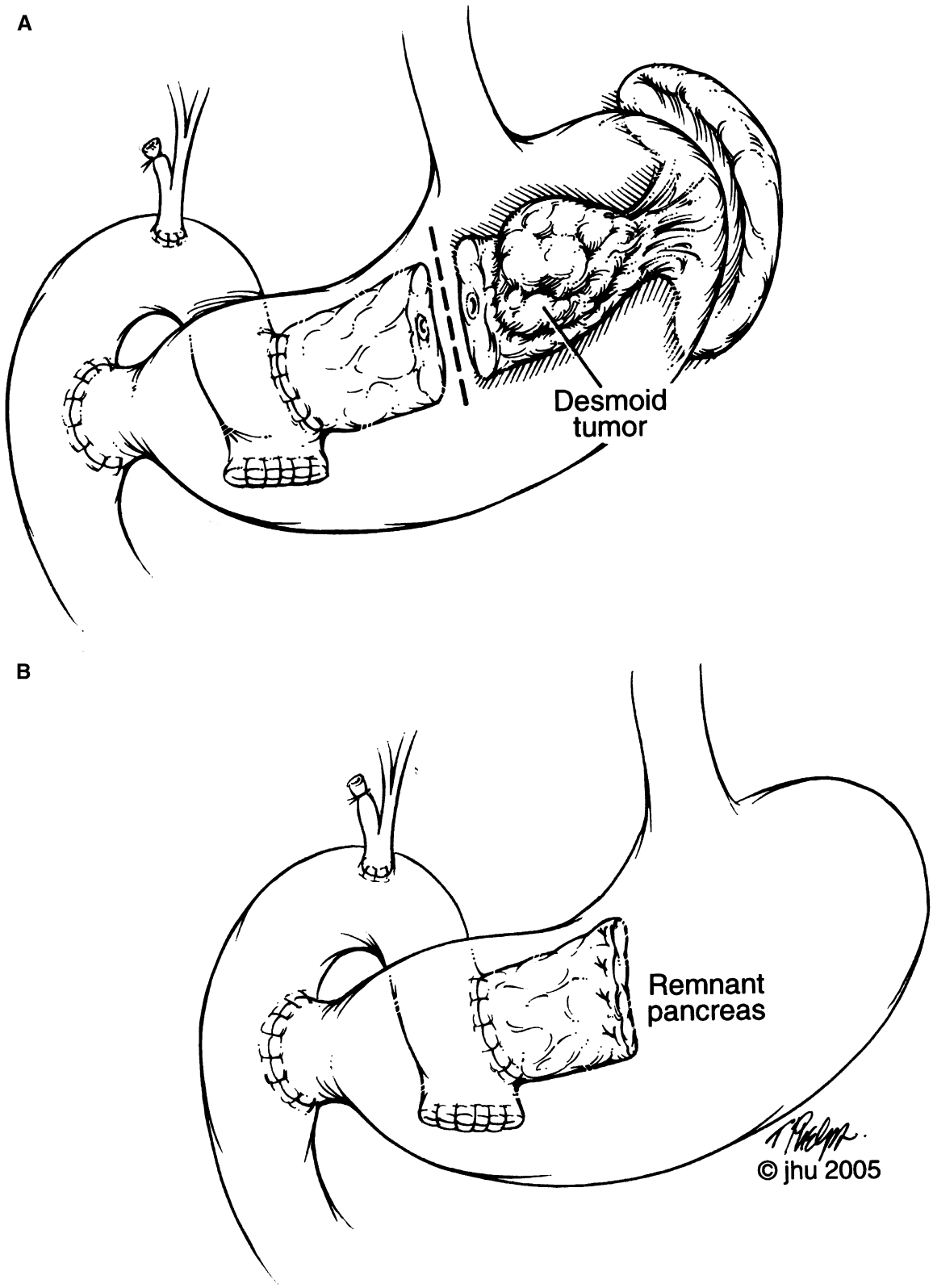

Fig. 3. Diagram depicting the second pancreatic procedure. (**A**) Anatomy after pylorus-preserving pancreaticoduodenectomy with desmoid tumor in pancreatic body and tail. (**B**) Six-centimeter portion of remnant pancreas spared after distal pancreatectomy with en bloc splenectomy. The previous pancreaticojejunostomy was left intact, as the texture of the retained pancreas was normal, suggesting intact pancreatic ductal drainage to the jejunum.

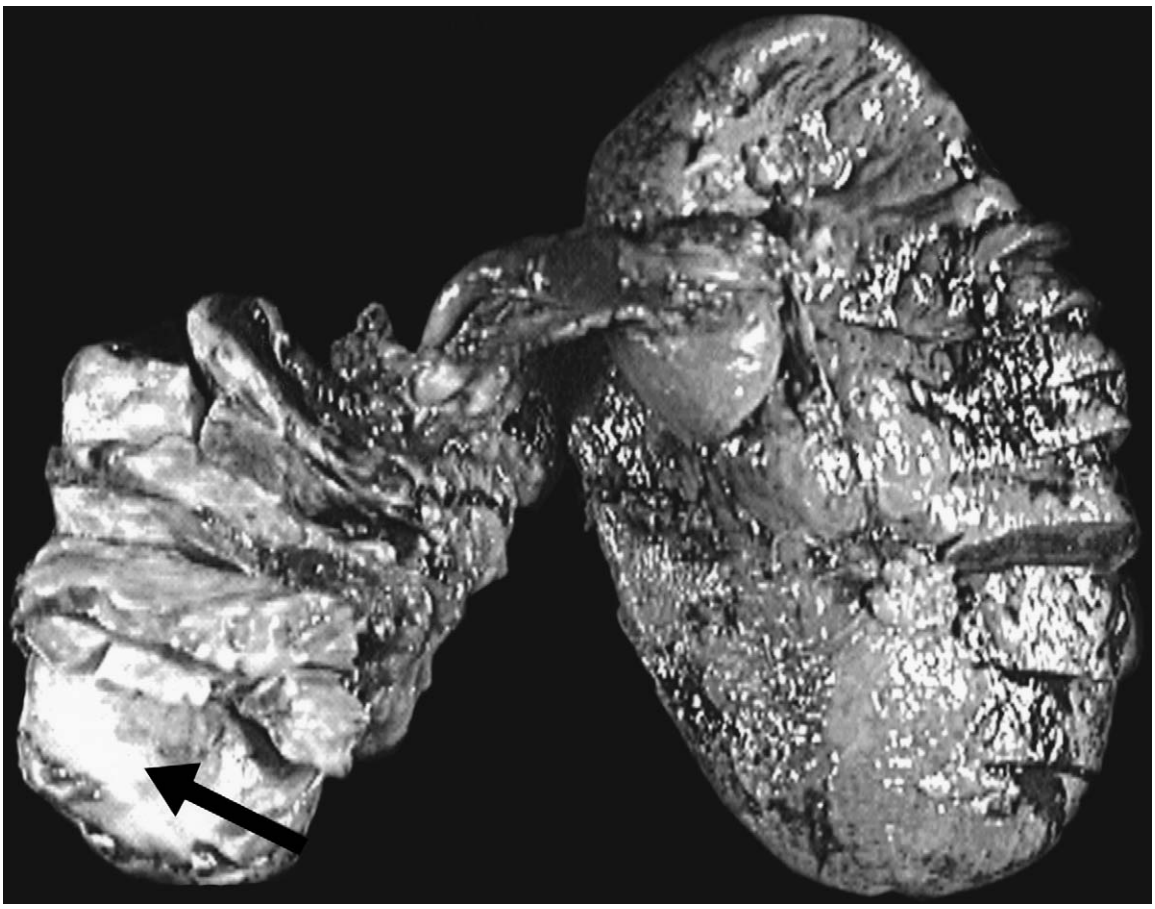

Fig. 4. Gross specimen of the pancreas (*left*) and spleen (*right*) from the second pancreatic operation. Here, both the pancreas and spleen are serially breadloaf sectioned, and the *arrow* points to a portion of the desmoid mass.

surgical or physiologic (pregnancy), can be a predisposing factor in their formation. On CT scan, these lesions appear as large hypoechoic masses, which often displace adjacent structures.[14] The differential diagnosis is broad and includes carcinoma, lymphoma, sarcoma, gastrointestinal stromal tumor (GIST), neuroendocrine tumor, lipoma, and carcinoid tumor, among others. Histologically, desmoids are characterized by proliferation of fibroblasts, abundant collagen, lack of typical malignant cytologic features, and infiltrative growth patterns. In this way, these tumors biologically share features with both benign fibrous lesions and fibrosarcomas, but they never metastasize. Rather, they but tend to invade locally and recur. Our specimen illustrated these features, as minimal cellular atypia and hyperchromasia was visualized with abundant collagen (Fig. 5, *A*).

It is often difficult to distinguish fibromatosis from reactive fibroblastic proliferations or scars on hematoxylin-and-eosin preparations alone, because many cellular features are quite similar. For this reason, immunohistochemical staining with beta-catenin is often used to support the diagnosis of fibromatosis. Both sporadic fibromatosis and fibromatosis associated with GS and FAP demonstrate loss of APC gene function. This loss of function leads to accumulation of beta-catenin in the cytosol and nucleus. Thus, identification of intracellular beta-catenin via special staining strongly supports the diagnosis of fibromatosis.

While fibromatosis is considered a benign lesion that does not metastasize, local control is important as they may aggressively invade surrounding structures. For this reason, treatment is typically surgical resection in selected cases, although other treatment modalities have been explored, in part because of this tumor's high local recurrence rate and in part because of the difficulty of resection in the face of extensive mesenteric involvement.[15] Unfortunately, mixed results have been obtained with the various nonresectional treatments employed. Some desmoids have been observed to be responsive to both doxyrubicin-based chemotherapy and radiation, and some groups are exploring neoadjuvant treatment

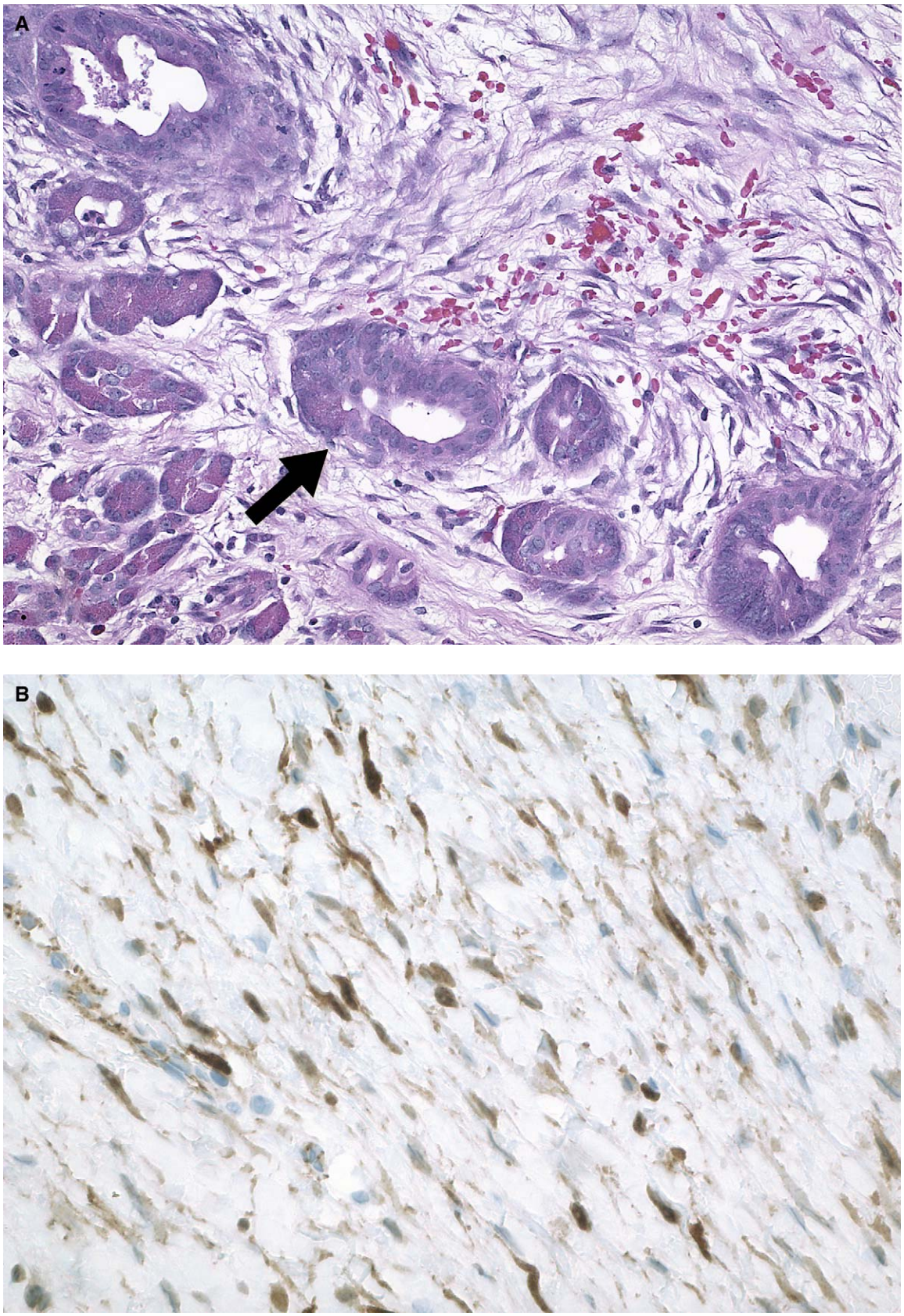

Fig. 5. Histologic images of the desmoid tumor resected during the patient's second operative procedure. (**A**) Microscopically, the lesion is poorly circumscribed and infiltrates the surrounding pancreatic paranchyma. In parts of the tumor (*arrow*), there is extensive hyalinization (hematoxylin-eosin, original magnification ×64). (**B**) Beta-catenin immunostaining was strong and diffuse on paraffin-embedded tissue, confirming the diagnosis of fibromatosis (beta-catenin immunohistochemistry, original magnification ×64).

Table 1. Review of the reported cases of sporadic pancreatic desmoid tumors

Reference	Cases	Presentation	Imaging	Inciting/preceding	Treatment	Outcome
Nursal et al,[11] 2003	2 cases 25-year-old F (1) and 39-year-old M (2) (siblings)	(1) Recurrent epigastric pain (2) Recurrent epigastric and back pain	(1) CT showed 85 × 50 mm mass in pancreatic tail (2) CT showed 75 × 40 mm pancreatic tail mass.	No history of FAP or Gardner's syndrome	Both biopsied with no definitive treatment	Reported as uneventful recovery
Sedivy et al,[13] 2002	68-year-old F	3-month history of weight loss	ERCP revealed cystic dilatation of pancreatic duct US showed 1.3-cm hypoechoic mass Fibromatosis found incidentally in resected IPMN	No history of FAP or Gardner's syndrome	Pancreatico duodenectomy	NA
Bruce et al,[7] 1996	38-year-old M	Mass discovered on follow-up CT scan after distal panc/ splenec	CT scan; 3 times 4cm mass in remnant pancreas	Previous distal panc/splenec for neuroendocine neoplasm No history of FAP or Gardner's syndrome	Total pancreatectomy	No evidence of recurrent disease
Ure et al,[10] 1988 (article in German)	2-month-old F	Pancreatic mass discovered by noting jaundice	Pancreatic mass confirmed by abdominal US	No history of FAP or Gardner's syndrome	NA	NA
Roggli et al,[13] 1980	4-month-old M	Infant with tachycardia, tachypnea, fever, and anorexia	Autopsy demonstrated involved pancreas with lungs, adrenals, bone, and subcutaneous tissue	No history of FAP or Gardner's syndrome	None	Death

M = male; F = female; distal panc/splenec, distal pancreatectomy and splenectomy; CT, computed tomography; ERCP, endoscopic retorgrade choleangiopancreatography; IPMN, intraductal papillary mucinous neoplasm; US, ultrasound; FAP, familial adenomatous polyposis; NA, not available.

as an option prior to surgery.[16] In addition, there has been reported pharmacological treatment with nonsteroidal anti-inflammatory agents (NSAIDs) or antiestrogen therapy with tamoxifen, with modest success.[17] However, these practices are still largely experimental, and currently there exists no proven nonresectional therapies for desmoids. Surgical resection, if possible, remains the treatment of choice for these rare neoplasms.

A further unique aspect of this case is the unusual resection performed. Many series focusing on initial pancreatic resections exist and include analysis of pancreaticoduodenectomies, distal pancreatectomies, total pancreatectomies, and segmental enucleation. By contrast, only occasional reports exist describing repeat pancreatic resections. These are primarily limited to completion or total pancreatectomy after pancreaticduodenectomy or left-side resection.[18,19] The resection performed in this case consisted of a distal pancreatectomy with en bloc splenectomy, sparing a 6-cm mid-portion of the pancreas. In our literature search, we could find no example of this type of repeat pancreatic resection. The rationale to perform this type of re-resection is related to the benign nature of the patient's desmoid mass and the desire to avoid a completion total pancreatectomy, with the attendant obligate insulin-dependant diabetes. It was our desire to attempt to spare uninvolved pancreas, so as to not come full circle with the patient, that is, from symptomatic hypoglycemia due to insulinoma in 2002 to insulin-dependent diabetes mellitus in 2004. If the mass had proved to be recurrent neuroendocrine tumor or a new pancreatic ductal adenocarcinoma, then the indication (or rationale) to perform a mid-pancreas sparing resection would have been less sound.

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Single Center Prospective Randomized Trial of Laparoscopic Nissen Versus Anterior 90° Fundoplication

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Although Nissen fundoplication is a very effective treatment for gastroesophageal reflux, it is associated with a small incidence of troublesome postoperative side effects. To prevent this, progressive modification of surgical techniques has led to the development of an anterior 90° fundoplication. We undertook a prospective randomized trial to compare this procedure with Nissen fundoplication to determine whether it would achieve a better clinical outcome. Patients presenting to a single center for primary laparoscopic antireflux surgery were randomized to undergo either an anterior 90° fundoplication (n = 40) or a Nissen fundoplication without division of the short gastric vessels (n = 39). Clinical questionnaires were used to assess outcome at 1 month, 3–6 months, and 12 months. Both patients and the clinical interviewer were masked as to which procedure was performed. Follow-up with endoscopy, esophageal manometry, and pH monitoring was also undertaken. Operating time was similar for the two procedures (60 minutes for anterior vs. 55 minutes for Nissen fundoplication). Early postoperative complications were more common after Nissen fundoplication (18% vs. 5%). Two patients underwent laparoscopic reoperation for recurrent reflux after anterior 90° fundoplication, and four underwent laparoscopic reoperation after Nissen fundoplication (dysphagia, 3 patients; acute hiatus hernia, 1 patient). One year after surgery, dysphagia and other wind-related side effects were less common after anterior 90° fundoplication. Control of reflux symptoms and satisfaction with the overall outcome was similar for the two procedures. Anterior 90° fundoplication is followed by fewer side effects than Nissen fundoplication. This advantage is offset by a greater likelihood of reflux recurrence. However, this does not diminish patient satisfaction.
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Laparoscopic fundoplication has become the operative modality of choice for the surgical treatment of moderate to severe gastroesophageal reflux.[1] The majority of laparoscopic fundoplications currently constructed are 360° fundal wraps, similar to the procedure originally described by Nissen. Despite achieving excellent control of reflux in the majority of patients, however, the 360° fundoplication can be followed by troublesome postoperative side effects. These include dysphagia and wind-related problems such as abdominal bloating, inability to belch, and flatulence.[2]

To overcome this, Nissen's operation has been progressively modified. Undertaking a laparoscopic anterior partial fundoplication instead of a Nissen procedure has the potential to give good reflux control, but with less side effects. In 1999, we reported the early results of the first prospective randomized trial that compared the outcome of a Nissen fundoplication with an anterior 180° partial fundoplication.[3] This study demonstrated that both procedures achieved satisfactory early control of reflux, but with less side effects after anterior 180° fundoplication. Longer term follow-up has since

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confirmed the durability of the anterior 180° fundoplication procedure beyond 5 years.[4]

Although side effects are less likely after anterior 180° fundoplication compared with Nissen fundoplication, a small risk of persistent dysphagia and wind-related problems remains. This led us to further refine the anterior fundoplication technique, resulting in the development of an anterior 90° fundoplication. Experimental and initial clinical studies have confirmed that anterior 90° fundoplication achieves good short-term reflux control, with a low risk of side effects.[5,6]

In addition, a multicenter prospective double-blind randomized trial of laparoscopic Nissen fundoplication versus anterior 90° fundoplication has recently been published.[7] This study was coordinated by our unit, and we contributed patients to it. The trial demonstrated that overall satisfaction with surgery was better 6 months after anterior 90° fundoplication, although this was offset to some extent by better reflux control in patients who underwent a Nissen fundoplication.[7] In this recently reported study, the laparoscopic Nissen fundoplication procedures included division of the short gastric blood vessels. Four other randomized trials, including one from our unit, have shown that dividing these vessels is unnecessary during Nissen fundoplication,[8–13] and two of these trials have demonstrated an association between division of the vessels and wind-related side effects.[8,10] For this reason, we initiated another randomized trial of laparoscopic anterior 90° versus Nissen fundoplication, in which the short gastric vessels were not divided during Nissen fundoplication. This new trial is a single center experience with a different cohort of patients, rather than the combined experience of a larger group of surgeons.

PATIENTS AND METHODS

The protocol used for this study was similar to that used in other reported randomized trials undertaken by the authors and reported elsewhere.[3,9]

Participant Assignment

Patients undergoing laparoscopic fundoplication for gastroesophageal reflux were randomly assigned to undergo either a total 360° (Nissen) fundoplication without division of the short gastric blood vessels or an anterior 90° partial fundoplication. Informed consent was obtained from all participants, and randomization was undertaken in the operating theater by opening one of 100 previously sealed opaque envelopes after surgery commenced.

Patient Selection and Preoperative Investigation

All patients with reflux who presented for laparoscopic antireflux surgery were considered for enrollment. Patients were excluded if they had a severe esophageal motility disorder that precluded the performance of a Nissen fundoplication, if they required a contemporaneous abdominal procedure (e.g., cholecystectomy), or had previously undergone any type of gastric surgery. All patients underwent preoperative investigation with esophageal manometry and endoscopy. Twenty-four-hour pH monitoring was performed to confirm reflux in patients who did not have unequivocal reflux disease demonstrated by endoscopy.

Operative Technique and Postoperative Care

Laparoscopic Nissen fundoplication was performed using a technique described previously.[14] This comprised preservation of the hepatic branch of the vagus nerve, routine posterior hiatal repair, and the construction of a short, loose Nissen fundoplication around a 52 Fr intraesophageal bougie. The short gastric vessels were not divided in any patients. The technique for anterior 90° fundoplication has also been described previously.[6] The initial steps are similar to those undertaken for the Nissen procedure—mobilization of the esophagus, preservation of the hepatic branch of the vagus nerve, and posterior hiatal repair. The anterior 90° fundoplication was fashioned by first placing an esophagopexy suture between the posterolateral aspect of the right side of the distal esophagus and the posterior aspect of either the right pillar or both pillars of the esophageal hiatus. Two sutures were next placed between the left side of the esophagus and the adjacent gastric fundus to accentuate the angle of His, and the gastric fundus was then sutured loosely over the left side of the front of the esophagus by using an apical suture that anchored the fundus to the anterior esophagus and the apex of the hiatus. Finally, the inferior edge of the fundal fold lying in front of the esophagus was sutured to the esophagogastric junction in the midline. The short gastric vessels were not divided, and an intraesophageal bougie was not used.

Patients were allowed oral fluids postoperatively on return to the ward, and soft solid food was commenced on the first postoperative day. Patients were instructed to remain on a soft diet for the first 3–4 weeks after surgery and then to gradually increase the consistency of their food intake thereafter.

Masking

The type of fundoplication performed was concealed from the patients during follow-up. Follow-up was undertaken by a research assistant who was masked to the randomization of each patient. Final data analysis for this paper was performed in late 2004 by a surgeon investigator (G.M.S) who was not involved in the original surgery.

Clinical Follow-up

Preoperative and postoperative data were collected using a standard form. Follow-up data at 1 month, 3–6 months, and 1 year after surgery were obtained by telephone interview. Longer-term follow-up will be obtained in due course. The presence or absence of the following symptoms was sought: heartburn, epigastric pain, regurgitation, dysphagia for solids, dysphagia for liquids, odynophagia, early satiety, epigastric bloating, anorexia, nausea, vomiting, wheezing, coughing, and increased flatulence. The ability to relieve bloating and whether a normal diet was being consumed were also determined. Heartburn was also scored using a visual analogue scale (0 = no heartburn, 10 = severe heartburn). Dysphagia was scored by several methods. Visual analogue scales (0 = no dysphagia, 10 = total dysphagia) were applied separately for solids and liquids; a previously validated score (0 = no dysphagia, 45 = severe dysphagia) that combines information about difficulty swallowing nine types of liquids and solids was used as well.[9,15]

Overall outcome was determined using three further scales and a question. Patients were asked to assess the outcome of surgery by using a modified Visick grading (Table 1) and were asked to score the outcome as excellent, good, fair, or poor (Table 2). An overall assessment of satisfaction with the operative outcome was also determined using a further visual analogue scale (0 = dissatisfied, 10 = satisfied). In addition, patients were asked whether they thought that their initial decision to have a laparoscopic fundoplication was correct or not. The occurrence of any complications and the need for further surgery, whether early (within 6 weeks of the initial surgery) or late, was also recorded.

Table 1. Modified Visick grading system

1	No symptoms
2	Mild symptoms easily controlled by simple care such as avoiding certain foods or eating small meals, etc.
3	Moderate symptoms not controlled by simple care but not interfering with social or economic life
4	Moderate symptoms interfering with social or economic life
5	Symptoms as bad worse than preoperatively

Table 2. Outcome assessment

Excellent	Complete recovery
Good	Major improvement with minor problems
Fair	Major improvement with still significant problems or adverse effects
Poor	Minor or no improvement or deterioration

Objective Follow-up

Three to six months after surgery, patients were invited to undergo esophageal manometry, 24-hour-ambulatory pH monitoring, and endoscopy. These investigations sought to obtain an objective assessment of lower esophageal sphincter function, postsurgical anatomy, and the degree to which reflux was controlled.

Statistical Analysis

The primary clinical outcomes that the trial was designed to evaluate were postoperative dysphagia and control of reflux symptoms. It was determined that 80 patients (40 in each group) would be needed to demonstrate a 15% difference in these outcome measures at a statistical significance level of $P < 0.05$ and power of 80%. All analyses and comparisons between the two groups were performed on an intention-to-treat basis.

Data were entered onto a computerized database (Filemaker Pro version 7, Filemaker Corporation, Santa Clara, CA) and analyzed with SPSS version 10 for Windows (SPSS Inc, Chicago, IL). Data are expressed as mean (standard error of the mean; mean [SEM]) or median (interquartile range; median [IQR]). Categorical variables were compared by using the Fisher exact test. Continuous variables that followed a parametric distribution were compared by using the independent samples t test. Nonparametric data were compared using the Mann-Whitney U test. Statistical significance was accepted if $P < 0.05$.

The protocol for this trial was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

RESULTS

Seventy-nine patients who underwent a laparoscopic fundoplication between February 1999 and August 2003 at the Royal Adelaide Hospital were

entered into this trial. Thirty-nine patients were randomized to undergo a Nissen fundoplication and 40 patients an anterior 90° partial fundoplication. Follow-up data was available for 71 (90%) patients at the 1-month follow-up point, 72 (91%) patients at 3–6 months follow-up, and 64 (81%) at 1 year follow-up. Missing data were due to the inability to contact patients at these specific follow-up points. Of the 15 patients who were not contacted at 1-year postsurgery, 14 had 3–6 month follow-up data available, and 10 of these 14 patients had a good or excellent outcome at the point of last review. Data was available for 78 (99%) patients in at least one of the last two follow-up points.

Preoperative Assessment

Both study groups were well matched for preoperative parameters (Tables 3 and 4). The degree of heartburn experienced by each group and scored on a visual analogue scale was also comparable between both groups (Table 5), as was dysphagia (Table 6). Likewise, preoperative esophageal manometric parameters and endoscopic findings were similar for the two groups.

Operation

Operations were carried out under the care of three surgeons. Thirty-one procedures (39%) were performed by a consultant, and 48 (61%) were performed by a trainee under supervision. The seniority of the first operator was different for the two groups, there being a higher representation of trainees as the primary surgeon in the Nissen fundoplication group (74% vs. 48%; $P = 0.02$). There was no deliberate bias for this parameter, as randomization was always undertaken after commencing surgery.

One patient who was randomized to undergo a Nissen fundoplication underwent an anterior 90° fundoplication, when the surgeon could not bring the gastric fundus behind the esophagus. This was due to the combined difficulties of excessive adipose tissue in the region of the cardia and a thickened gastric wall. The operating surgeon thought that this problem would not be solved by dividing the short gastric vessels, and hence, a partial fundoplication was performed. All other patients had a fundoplication constructed according to the randomization schedule. Outcomes were analyzed on an intention-to-treat basis.

The laparoscopic procedure was converted to open surgery for one patient in the anterior 90° fundoplication group. This was because of intra-abdominal adhesions. All other procedures were completed laparoscopically. Operating times were similar for the two groups (median 60 minutes; interquartile range 45–75 minutes for anterior 90° fundoplication vs. median 55 minutes; interquartile range 40–65 minutes for Nissen fundoplication; $P = 0.18$). Operating surgeons were asked to rate the degree of difficulty of the operative procedure by using a scale from 1 to 10. There was no difference in difficulty rating between the two groups (4 [3–7] for anterior 90° fundoplication vs. 4 [3–7] for Nissen fundoplication; $P = 0.92$).

Table 3. Preoperative patient characteristics

Variable	Type of fundoplication		
	Anterior (n = 40)	Nissen (n = 39)	*P* value
Age, y	46 (2)	47 (2)	0.62*
Sex, M/F	24/16	19/20	0.37‡
Height, cm	171 (3)	169 (2)	0.51*
Weight, kg	84 (3)	86 (3)	0.59*
Previous upper abdominal surgery	6 (15%)	6 (15%)	0.99†
Duration of symptoms (y)	7 [4–12]	6 [3–20]	0.81‡

Data are given as mean (standard error of mean), or median [interquartile range].
*Student's *t* test.
†Fisher exact test.
‡Mann-Whitney *U* test.

Early Hospital Outcome

The time interval between surgery and the commencement of oral fluids as well as the duration of postoperative hospital stay were not influenced by the type of fundoplication. Time to commencement of solids was longer in the Nissen fundoplication group (Table 7). The incidence of postoperative complications was higher in the Nissen fundoplication group (18% vs. 5%; $P = 0.09$). However, most complications were minor and did not surgically require intervention, or delay discharge from the hospital. After anterior 90° fundoplication, there was one episode of chest infection and one episode of intraoperative cervical subcutaneous emphysema. After Nissen fundoplication, one patient developed urinary retention, one patient developed an umbilical port-site hernia, one patient suffered from excessive retching in the early postoperative period, which settled spontaneously, and three patients developed an intraoperative pneumothorax (none of which required any specific intervention). In addition, one patient in the Nissen group was found to have an acute paraesophageal hernia on a routine barium

Table 4. Assessment of symptoms

	Preoperative		Postoperative					
			1 month		3–6 months		1 year	
Symptom	Anterior %	Nissen %	Anterior %	Nissen %	Anterior %	Nissen %	Anterior %	Nissen %
Heartburn	100	97	11	14	22	3	16	12
Epigastric pain	56	71	49	39	36	33	29	46
Regurgitation	79	89	11*	39*	15	26	3*	27*
Odynophagia	15	24	20	33	18	15	7	18
Early satiety	35	53	60	61	49	59	26*	67*
Epigastric bloating	50	61	37	47	55	56	32	39
Anorexia	9	16	26	31	9	10	3	12
Nausea	29	50	23	19	27	26	7*	30*
Vomiting	35	34	3	17	9	8	7	6
Cough	35	34	20	25	21	13	26	15
Wheeze	24	26	9	11	3	13	0	0
Can relieve bloat	55	53	38	56	50	61	69	50
Eats normal diet	70	70	47	27	89	74	90	83
Increased flatus	NA	NA	54	44	46	67	42*	79*

*$P < 0.05$ (Nissen vs. anterior fundoplication, Fisher exact test).

swallow X-ray carried out on the day after surgery. This was repaired laparoscopically on the second postoperative day, and the patient then made an uneventful recovery.

Clinical Outcome at 1 Month to 1 Year After Operation

A detailed analysis of the clinical outcome at 1 month, 3–6 months, and 1 year are summarized in Tables 4, 5, 6, and 8. At 1 and 3–6 months, there were significant differences between the two groups for the symptoms of regurgitation at 1 month (less after anterior 90° fundoplication) and heartburn at 3–6 months (less after Nissen fundoplication). At 1 year, there were significant differences in the incidence of regurgitation, early satiety, nausea, and flatulence (all less after anterior 90° fundoplication). There was no significant difference between the two groups for the assessment of heartburn by the yes/no question at 1 year (Table 4). With regard to the assessment of heartburn by using the visual analogue scale, the findings were similar to the findings determined by the yes/no question. A statistically significant difference was found in the heartburn scores at 3–6 months (less after Nissen fundoplication), but this was not found at 1 year (Table 5).

Table 5. Assessment of heartburn by visual analogue scale

	Types of fundoplication		
	Anterior	Nissen	*P* value
Preoperative	7 [2.8–9.1]	5 [3–8]	0.31
Postoperative			
1 month	0 [0–0]	0 [0–0]	0.99
3–6 months	0 [0–0.5]	0 [0–0]	0.01*
1 year	0 [0–2]	0 [0–0]	0.08

Data are expressed as median [interquartile range].
*$P < 0.05$ (Nissen vs. anterior fundoplication, Mann Whitney *U* test).

With regard to the clinical assessment of dysphagia, there were significant differences between the two study groups, with less dysphagia experienced after anterior 90° fundoplication (Table 6). At 1 year, the incidence of dysphagia for solid foods, the visual analogue scores for dysphagia (for both liquids and solids), and the 0–45 dysphagia score all concurred.

The satisfaction score, outcome profile, and modified Visick grading all failed to reveal a statistically significant advantage for either type of the fundoplication (Table 8). In both groups, most patients were satisfied with the outcome of their surgery. At both 3–6 months and 1 year postprocedure, more patients in the anterior 90° fundoplication group expressed the view that they had made the correct decision to undergo surgery (86% vs. 77% at 3–6 months, 87% vs. 76% at 1 year). However, these differences were not statistically significant (Table 8).

Postoperative Investigations

Patient compliance with scheduled objective postoperative investigations was low. Twenty-five (32%) patients underwent postoperative upper gastrointestinal endoscopy, 23 (29%) underwent 24-hour-pH

Table 6. Assessment of dysphagia

Symptom	Preoperative		Postoperative					
			1 month		3–6 months		1 year	
	Anterior	Nissen	Anterior	Nissen	Anterior	Nissen	Anterior	Nissen
Dysphagia for:								
Solids, %	32	21	63	69	30	49	13*	49*
Liquids, %	6	8	3	14	0*	21*	0	3
Visual Analogue Scale								
Solids	0 [0–3.3]	0 [0–5]	3 [0–6.8]*	5 [3.3–7.8]*	0 [0–2.5]*	2.5 [0–6.3]*	0 [0–2]*	2 [0–6]*
Liquids	0 [0–0]	0 [0–2.5]	0 [0–0]*	0 [0–4.3]	0 [0–0]	0 [0–1]	0 [0–0]*	0 [0–3]*
Dysphagia score								
Overall result†	1.7 [0–19.5]	8.2 [0–15.9]	16 [0–25.5]*	24 [17.7–29.9]*	0 [0–12]*	9.5 [0–23.5]*	0 [0–8.7]*	12 [3.5–19.5]*
Scored 0 only, %	50	44	27	11	66*	33*	56*	18*

*$P < 0.05$.
†Data are expressed as % or median [interquartile range].

Table 7. Early hospital outcomes

Variable	Types of fundoplication		
	Anterior	Nissen	*P* value
Postoperative stay (days)	2 [2–3]	2 [2–3]	0.42
Days to taking oral fluids	1 [1–1]	1 [1–1]	0.52
Days to taking solid foods	1.5 [1–2]*	2 [1.5–2]*	0.03

Data expressed as median [interquartile range].
*$P < 0.05$.

monitoring, and 25 (32%) underwent esophageal manometry. Upper gastrointestinal endoscopy revealed an intact fundoplication and satisfactory repair of hiatus hernia in all patients studied. With regards to Savary-Miller grading of esophagitis, one of eight patients was scored as Savary-Miller grade 1 after anterior 90° fundoplication, and 1 of 16 patients had grade 3 esophagitis after Nissen fundoplication. Esophagitis was not present in any other patient.

Twenty-four-hour pH monitoring demonstrated normalization of acid exposure times in all but one of the 23 patients studied. This patient had undergone a Nissen fundoplication. The percentage time with pH less than 4 over the 24-hour study period was significantly less in the Nissen fundoplication group (0% [0%–0.6%] vs. 0.7% [0.3%–2.5%]; $P = 0.02$). The postoperative lower esophageal sphincter resting pressure measured at esophageal manometry was similar for the two groups (anterior 14 mmHg [10–24] vs.

Table 8. Postoperative Visick grading, outcome grading, and satisfaction scores

Variable	Postoperative status			
	3–6 months		1 year	
	Anterior	Nissen	Anterior	Nissen
Modified Visick grade α				
1	25%	21%	32%	16%
2	47%	54%	48%	52%
3	6%	3%	8%	13%
4	8%	18%	0	19%
5	14%	5%	12%	0
Outcome				
Excellent	43%	28%	40%	21%
Good	30%	41%	33%	50%
Fair	11%	23%	13%	29%
Poor	16%	8%	13%	0%
Satisfaction score*	9 [7.5–10]	9 [7–10]	9 [6.1–10]	9 [6–10]
"Made correct decision"	86%	77%	87%	76%

*Data are given as %, or median [interquartile range].

Nissen 18 [14–29]; $P = 0.22$). Lower esophageal sphincter residual relaxation pressure was, however, significantly higher after Nissen fundoplication (7 mm Hg [3–13] vs. 3 [0–5]; $P = 0.02$).

Late Reoperation

A reoperative procedure was performed between 4 and 10 months after surgery in five patients—two after anterior 90° fundoplication, and three after Nissen fundoplication. All of these procedures were undertaken and completed laparoscopically. The two reoperations in the anterior 90° fundoplication group were undertaken at 7 and 10 months postoperatively, and entailed conversion to a Nissen fundoplication for recurrent reflux. In the Nissen fundoplication group, all three reoperations were for dysphagia. They were performed at 4, 6, and 9 months after the original procedure. In two of these operations, the hiatus was tight and it was widened. In these patients, the fundoplication was thought to be loose, and therefore it was left intact. In the other operation, the hiatus was widened and the Nissen fundoplication was converted to a posterior partial fundoplication.

DISCUSSION

Controversy remains as to which fundoplication technique offers the best outcome for patients. Although uncontrolled studies have reported good results for Nissen, anterior partial, and posterior partial fundoplication variants,[6,14,16] these studies should not be used to determine which technique is best. In recent years, there has been an increase in the number of prospective randomized trials that compare the short-term[3,17,18] and long-term[4,19] outcomes of various laparoscopic partial fundoplication techniques with the "gold-standard" Nissen 360° fundoplication. Hence, better evidence is becoming available that can help to determine the relative merits of the different types of laparoscopic fundoplication currently undertaken.

We have evaluated progressive modifications to Nissen's original procedure as part of a program to develop a fundoplication technique that achieves effective control of gastroesophageal reflux, but with minimal side effects and excellent patient acceptance. We have reported longer-term outcomes from a previous trial of anterior 180° partial fundoplication, which demonstrates that this approach achieves an excellent outcome compared with the Nissen procedure.[4] Similar results have also been reported by Baigrie et al.[20] Unfortunately, anterior 180° fundoplication is still followed by some side effects, and for this reason we developed the lesser anterior 90° fundoplication. Its antireflux efficacy has been demonstrated in previous laboratory and clinical studies. More recently, we reported the outcome from a larger multicenter randomized trial of Nissen fundoplication versus anterior 90° partial fundoplication[7] and demonstrated the short-term efficacy of this procedure and its potential to significantly reduce the risk of side effects.

We undertook the current prospective randomized trial independently of the recently reported multicenter study to further evaluate the anterior 90° technique in a single center against a Nissen procedure at which the short gastric vessels were not divided. Overall, the results from our new trial broadly concur with the findings from the multicenter study, that is, the anterior 90° technique is followed by fewer postoperative adverse effects.

It could be argued that the increased wind-related problems associated with Nissen fundoplication might be attributable to division of short gastric vessels, and this step was integral to the design of the multicenter study protocol.[8] Short gastric vessel division at Nissen fundoplication has previously been shown by our group, and others, to be associated with an increased risk of long-term wind-related problems without improving any outcome.[8,10] In our current study, division of the short gastric vessels was not undertaken in any patients, suggesting that differences in wind-related symptoms in this trial are a function of the type of fundoplication, and not division of the short gastric vessels.

In addition to any differences inherent in division of the short gastric vessels during Nissen fundoplication, the fact that our current study was undertaken at a single center also differentiates it from the previously reported multicenter study. The restriction of the current trial to a single unit, with all procedures undertaken or supervised by one of three surgeons, guaranteed the standardization of the technical aspects of the surgical procedures. This is particularly important when one is comparing a novel technique with a technique that is already established. It is possible that bias can be introduced in a multicenter setting, because surgeons in some of the centers may not be familiar with the newer of the techniques under scrutiny, leading to it being performed less well relative to the more conventional treatment. The fact that the results for the two trials are similar, however, also suggests that the anterior 90° fundoplication can be reliably performed by a wide range of surgeons.

Our current trial, like all other trials including an anterior fundoplication variant, has demonstrated a lower incidence of postoperative dysphagia. Disparity in dysphagia profiles between the two procedures was evident from assessment at the end of the first postoperative month, continuing through

to assessment at 1 year. Statistical significance was reached for most measures of dysphagia at 1 year. However, it should also be noted that the better adverse effect profile of the anterior 90° fundoplication group is, to some extent, counterbalanced by less effective control of reflux, and this is a similar outcome to the results from the other trial of anterior 90° fundoplication.[7] Hence, there seems to be a trade-off between the risk of adverse effects and risk of recurrent reflux when comparing partial versus total fundoplication procedures. This premise is also strengthened by the indications for reoperation in the two groups in the present study. This outcome is also similar to that of other trials.

A possible criticism of our current study is the asymmetrical distribution of operator level between the two groups, with a higher proportion of trainees undertaking the surgery in the Nissen group. Although this is a potential confounder, we have previously shown that outcome after laparoscopic fundoplication is not affected by the seniority of the principal operator.[21] A further criticism could be the low rate of patients undergoing objective postoperative investigation with upper gastrointestinal endoscopy, 24-hour-pH monitoring, and esophageal manometry. However, overall satisfaction with the clinical outcome was similar after both types of fundoplication.

In summary, our current study confirms that anterior 90° fundoplication is followed by fewer side effects than Nissen fundoplication. There is a trade off between this benefit and a greater likelihood of recurrent or incompletely controlled reflux, although overall satisfaction is at least as good after anterior 90° fundoplication. This outcome is similar to that reported in a previous trial, and it supports continued evaluation of anterior 90° fundoplication. However, longer-term follow-up is needed to determine the durability of this antireflux procedure.

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Role of Glucocorticoid Receptor in Serosa-Involved Gastric Carcinoma After Gastrectomy

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Glucocorticoid receptor (GR) was first found in the cytosol of gastric cancer tissue more than 15 years ago. At present, most gastric cancers are diagnosed at the advanced stage. To elucidate the role of GR in gastric cancer, the GR levels of the cancer tissue of 75 consecutive patients with grossly serosa-involved gastric carcinoma were determined by the dextran-coated charcoal method. The clinicopathologic characteristics and long-term survival duration were compared in patients with GR-positive and GR-negative cancer cells. We found that GR could be detected in the cytosol of cancer cells in 31 (41.3%) of the gastric cancer patients with a median concentration of 18.5 (range, 1.03–73.9) fmol/mg protein. No significant differences could be found in any clinicopathologic characteristic between the patients with GR-positive and GR-negative cancers. After multivariate analysis, gross Borrmann's type, metastatic lymph node number, and GR positivity were the independent prognostic factors after gastrectomy for serosa-involved gastric carcinoma. GR-positive gastric cancer had a worse survival rate than GR-negative gastric cancer. Multimodality adjuvant therapies should be considered in patients with GR-positive serosa-involved gastric carcinoma. (J GASTROINTEST SURG 2006;10:706–711)

KEY WORDS: Serosa-involved gastric carcinoma, glucocorticoid receptor, prognosis, gastrectomy

Although in declining incidence, gastric carcinoma still ranks as the fourth leading cause of cancer death in Taiwan,[1] and most patients present with an advanced stage of cancer.[2] The prognosis of such patients is usually dismal even after radical resection.[2–4] The prognostic factors of gastric carcinoma after resection have been extensively studied, and most researchers agree that the depth of invasion, nodal metastatic status, and distant metastasis are important prognostic factors for gastric carcinoma.[2–5]

On the other hand, glucocorticoid has been claimed to enhance or limit the progression of various cancers.[6–13] The biologic effects have been reported to be through the glucocorticoid receptor (GR) in the cancer cell.[10–13] More than 15 years ago, GR was also found in the cytosol of gastric carcinoma.[12] However, the role of GR in advanced gastric carcinoma has not yet been clarified. Herein, we measured the GR level in cancer cells of 75 consecutive patients with serosa-involved gastric carcinoma. Thus, the aim of this study was to elucidate the role of GR in serosa-involved gastric cancer patients.

PATIENTS AND METHODS

Seventy-five consecutive patients with grossly serosa-involved gastric carcinoma who underwent a potentially curative gastrectomy with systematic lymphadenectomy (D3 gastrectomy based on Japanese classification[5]) between 1997 and 1999 were included in this study. Before resection of the stomach, cytologic peritoneal washing was performed in all patients, and only those whose cytological washings were negative for malignant cells were considered for systematic lymphadenectomy.[2] The procedures for intra-abdominal systematic lymphadenectomy included dissection of lymph nodes around the paraaortic area, in the hepatoduodenal ligament, around

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the common hepatic artery, and splenic artery. The right and left gastric arteries were divided and ligated at their root.[2,14] For cancer located at the distal half of the stomach, distal subtotal (resection of distal 80%–85% of the stomach) was carried out. For tumors involving the upper half of the stomach, a total gastrectomy with pancreas-sparing splenectomy[15] was performed if pancreas showed no cancer involvement. The grossly involved neighboring organs were also resected en bloc.[2] The gallbladder was simultaneously removed to prevent postoperative cholecystitis.[16] Those patients who did not undergo D3 gastrectomy or whose tumor had not invaded the serosa were not included in the study. After pathological examination, the degree of cancer differentiation was determined according to the World Health Organization classification.[17] The histological depth of cancer invasion (pT3 or pT4) was classified according to the UICC-TNM (Union International Contra la Cancrum tumour-node-metastasis) classification.[18] The metastatic status of lymph nodes in each station in systematic lymphadenectomy was based on the criteria used by the Japanese Gastric Cancer Research Society, and the positivity of metastatic nodes level was also according to the Japanese classification.[5] The number of metastatic nodes was also counted.

MEASUREMENT OF GR

The GR was measured by the dextran-coated charcoal (DCC) method used in previous reports.[6,12,13,19] Briefly, about 2 g of gastric cancer tissue was removed immediately after the stomach was resected, and the specimen was macroscopically examined by a senior pathologist (W.-L.H.). The gastric cancer tissue was stored in liquid nitrogen at −80° C until assay of GR. The assay of GR was usually performed within 2 weeks after gastrectomy. During assay, the frozen specimens were weighed and melted in 6 volumes of TEDG buffer (10.0 mmol/L Tris, 1.5 mmol/L EDTA, 0.5 mmol/L dithiothreitol, and 10% glycerol, pH 7.4). Samples were homogenized using a PST-10 Polytron homogenizer (Brinkmann Instruments, Westbury, NY). The cytosol was obtained by centrifuging the homogenates at 105,000*g* at 4° C for 60 minutes. Endogenous steroids in the cytosol were removed by adding 0.2 volumes of DCC solution (5% Norit A charcoal, 0.5% dextran in TEDG buffer) to the cytosol and centrifuging at 1800*g* for 10 minutes. The clear supernatant was incubated in the presence of increasing amounts of tritiated triamcinolone, with a 500-fold excess of unlabeled triamcinolone acetonide, at 4° C for 4 hours. After incubation, free steroid was removed by adding 1 volume of DCC solution to 4 volumes of cytosol. The cytosol was then centrifuged at 2500*g* for 10 minutes after incubation at 4° C for 15 minutes. Radioactivity in the supernatant was measured with a liquid scintillation counter. The results were analyzed using Scatchard's method.[20] The cytosol protein was determined by the methods described by Lowry and colleagues.[21]

PATIENT FOLLOW-UP AND STATISTICAL METHODS

After discharge from the hospital, all patients were followed-up at the outpatient clinic every 3 months in the first 3 years and every 6 months thereafter until December 2004. Adjuvant chemotherapy was not used in all patients.

The data regarding continuous variables are presented as median (range) and were compared by the Mann-Whitney *U* test. The frequencies were compared by Pearson's χ^2 test. The survival data was calculated using the Kaplan-Meier life table method and compared by the generalized Wilcoxon test. A statistically significant level was defined as $P < 0.05$. The prognoses of varied clinicopathologic factors, including gender, age, tumor size, tumor location, gross Borrmann's type, cancer cell differentiation, histological depth of invasion, location of metastatic lymph nodes (Japanese classification[5]), number of metastatic lymph nodes, and GR positivity, were compared. The significant prognostic factors were included in a multivariate analysis by the Cox regression hazard model to determine the independent factors that influenced the prognosis after radical gastrectomy for serosa-involved gastric carcinoma patients.

RESULTS

Positive GR Rates and Patient Characteristics

GR could be detected in the cytosol of gastric cancer in 31 patients (41.3%), with median (range) concentration of 18.5 (range, 1.03–73.9) fmol/mg protein. The clinicopathologic characteristics of the two groups are shown in Table 1. The differences in variables between GR-positive and GR-negative cancer patients were not statistically significant.

Significant Prognostic Factors for Serosa-Involved Gastric Cancer Patients

There was no significant difference of the prognosis regarding the sex (male vs. female; $P = 0.6914$),

Table 1. Clinicopathologic characteristics of patients with serosa-involved gastric carcinoma who have undergone radical gastrectomy

	GR positive (n = 31)	GR negative (n = 44)	*P*
Sex, M:F	25:6	33:11	0.78
Age (yr)	62 (32–83)	64 (38–80)	0.40
Tumor size (cm)	6.1 (2.3–10.4)	5.8 (2.6–9.8)	0.76
Type of gastrectomy			
Total : subtotal	16:15	17:27	0.35
Tumor location			
Upper third	9	11	0.49
Middle third	6	7	
Lower third	12	23	
Whole stomach	4	3	
Borrmann's type			
I:II:III:IV:V*	0:6:13:10:2	2:12:22:7:1	0.28
Tumor differentiation			
Well differentiated	0	1	0.67
Moderately differentiated	10	16	
Poorly differentiated	21	27	
Depth of invasion			
Serosa (pT3)	17	22	0.82
Adjacent organ (pT4)	14	22	
Lymph node metastatic status†			
N0	3	3	0.40
N1	8	13	
N2	6	15	
N3	14	13	
Number of metastatic lymph node			
0	3	3	0.45
1–6	9	17	
7–15	8	15	
⩾16	11	9	

*Borrmann's type V means unclassified type.[5]
†Japanese classification.[5]

age (greater than 70 years vs. less than 70 years; $P = 0.9280$), tumor location (upper third vs. middle third vs. lower third vs. whole stomach; $P = 0.0907$), cancer cell differentiation (well differentiated vs. moderately differentiated vs. poorly differentiated; $P = 0.0662$), and histological depth of invasion (pT3 vs. pT4; $P = 0.3343$). Table 2 shows factors that significantly influenced the prognosis of the patients after gastrectomy and survival rates. Multivariate analysis using the Cox regression hazard model was performed; the independent prognostic factors that influenced the prognosis were Borrmann's gross tumor type, number of metastatic nodes, and GR positivity (Table 3). Patients whose gastric cancer contained GR had a significantly worse prognosis than patients whose cancer did not contain GR Fig. 1.

DISCUSSION

GR was firstly found in hepatoma-cultured cells by Baxter and Tomkins in 1971.[22] Thereafter, GR was found in leukemia, melanoma cells, and various types of cancer cells.[6–13,19] However, the clinical significance of GR in various malignancies differs. In human hepatocellular carcinoma, we found that the prognosis of GR-positive patients was poorer than that of GR-negative patients.[19] In 1989, Wu et al.[12] also found GR in 7 of 16 gastric cancer tissues. However, the clinicopathologic role of GR in gastric cancer has not yet been elucidated.[13]

GR has three domains: steroid-binding, DNA-binding, and N-terminal.[10–12] The glucocorticoid binds with cytosol GR. After passive diffusion, the steroid-GR complex translocates into intracellular nuclei and binds with DNA to influence the cellular function and growth. GR may act at the presynthetic gap (G1 phase)/DNA synthesis phase (S phase) cell cycle.[6,10,11]

Due to the lack of a screening system in our institution, most of our gastric cancer patients were in the advanced stage.[2,14,16] Most patients with advanced gastric cancer with serosal involvement (pT3 and pT4 in TNM staging system[23]) will die of peritoneal cancer recurrence, even after a radical resection.[2–4,14,16] Because adequate gastric cancer tissue should be obtained for the DCC method, we only selected the grossly serosa-involved gastric cancer patients for this study to avoid interference of the subsequent pathological examination of actual histological depth of tumor invasion. From our analysis, we found that no differences could be found in any of the clinicopathologic factors between patients with positive-GR and negative-GR cancer cells. However, the presence of GR in gastric cancer cell cytosol significantly influenced the prognosis after univariate and multivariate analyses.

Searching for the prognostic factors could lead to the appropriate managements for cancer.[18,23] Recently, multimodality adjuvant therapies have been effective for advanced gastric cancer.[24,25] In contrast, surgery alone may be adequate for cancer at early stage.[25] Multivariate analysis using the Cox hazard model is usually conducted to determine the independent factors that are more important and pertinent for identifying patients with a poorer prognosis. It is well-known that the Borrmann's tumor type, especially Borrmann's type IV, had a very poor prognosis after surgery.[4,5,26] Moreover, the presence of a large number of metastatic lymph nodes is usually associated with a poor prognosis.[2–4] Because of this phenomenon, the "N-category" in UICC-TNM classification was changed from the

Table 2. Univariate analysis of prognostic factors in serosa-involved gastric carcinoma survival rate

	1 year	3 year	5 year	*P*
Tumor size < 6 cm (n = 38)	73.9%	57.0%	48.9%	0.0135
⩾ 6 cm (n = 37)	54.9%	28.3%	28.3%	
Borrmann's type				
Type I (n = 2)	100%	100%	100%	0.0062
Type II (n = 18)	82.4%	43.9%	22.0%	
Type III (n = 35)	70.7%	52.1%	52.1%	
Type IV (n = 17)	32.3%	16.2%	4.9%	
Type V (n = 3)	100%	60.0%	60.0%	
Lymph node metastatic status*				
N0 (n = 6)	100%	100%	75.5%	0.0085
N1 positive (n = 21)	94.4%	71.5%	61.5%	
N2 positive (n = 17)	56.1%	42.1%	25.3%	
N3 positive (n = 27)	43.2%	25.4%	6.6%	
Metastatic lymph node number				
0 (n = 6)	100%	100%	75.5%	0.0043
1–6 (n = 26)	87.5%	63.2%	50.4%	
7–15 (n = 23)	49.1%	32.7%	24.5%	
⩾ 16 (n = 20)	41.1%	17.8%	17.8%	
GR positivity				0.0465
Positive (n = 31)	51.5%	27.8%	22.3%	
Negative (n = 44)	74.4%	65.0%	56.7%	

*According to Japanese classification.[5]

"location" of metastatic lymph nodes to the "number" of metastatic lymph nodes in 1997.[3,18]

The cause of poorer prognosis in patients with GR-positive cancer was unclear in this study. In animal experiments, Kanemasa et al.[27] found that the GR immunoreactivity was diminished in the nuclei of parietal cells in the gastric mucosa in adrenalectomized rats. Therefore, the growth rate of gastric mucosa may be regulated by circulating glucocorticoid through GR. Based on the results of this study, we believe that the reproductive activity of GR-positive gastric cancer cells may be greater than that of GR-negative cancer cells, which is in line with the findings of a previous study on hepatocellular carcinoma.[18] We speculate that the presence of GR in gastric cancer cells may be caused by the malfunction of regulatory control of the gastric cancer cells. Thus, although all cancer cells were grossly removed after radical surgery, the indolent cancer cells may regenerate earlier in patients with positive GR under

Table 3. Independent prognostic factors of serosa-involved gastric cancer after multivariate analysis using the Cox proportional hazard model

	β	SE	Odds ratio (95% CI)	*df*	*P*
Borrmann type				4	0.0462
Type I					
Type II	−13.02	1240.4	2.21×10^{-6} (3×10^{-7}–10^{-4})		
Type III	−0.62	1.13	0.54 (0.06–4.87)		
Type IV	−0.44	1.11	0.65 (0.07–5.68)		
Type V	0.74	1.12	2.09 (0.23–18.7)		
GR positive	−0.9333	0.3916	0.39 (0.18–0.85)	1	0.0371
Metastatic lymph node number				4	0.0072
0					
1–6	−15.22	676.96	2.46×10^{-7} (10^{-7}–10^{-4})		
7–15	−1.70	0.58	0.18 (0.06–0.56)		
⩾ 16	−0.25	0.46	1.24 (0.32–1.90)		

df = degrees of freedom; SE = standard error.

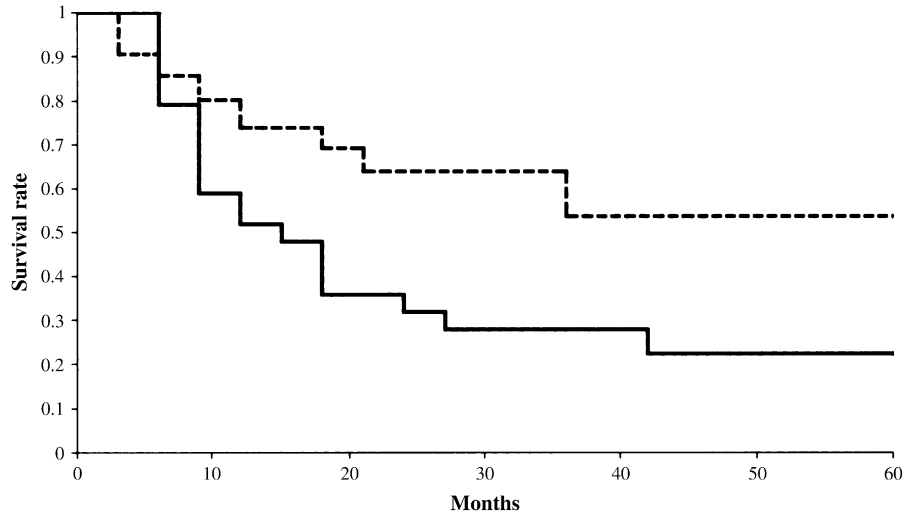

Fig. 1. Actuarial survival rates in patients with serosa-involved gastric cancer. Solid line = GR positive; dotted line = GR negative. GR-positive versus GR negative; $P = 0.0465$.

the influence of a normal circulating glucocorticoid hormone.

Corticosteroid has been widely used to treat various malignancies such as leukemia, lymphoma, and solid organ cancers.[6–13] Although the action of glucocorticoid on the cancer cells is through GR, its effects differ in different cancers. For example, in human adult acute lymphoblastic leukemia, the prognosis of the patients whose leukemic cellular GR level can be reduced by administration of glucocorticoid is better than those whose leukemic cellular GR level cannot be reduced by glucocorticoid.[8] However, in childhood acute lymphoblastic leukemia, this phenomenon has not been observed.[9] In an in vitro study on human hepatoma HepG2 cell lines, administration of progestin (a glucocorticoid antagonist) may reduce the cancer cell activity by blocking the expression of α-fetoprotein.[6] In contrast, in another in vitro study on gastric cancer, administration of glucocorticoid increased the production of arginase in gastric cancer cell lines. The induction of arginase production by corticosteroid can be inhibited by RU 38486, another glucocorticoid antagonist.[13] Arginase may promote cancer growth by depressing cellular immunity in gastric cancer patients.[12]

Based on this study, we think that postoperative multimodality adjuvant therapies[24,25] should be recommended in GR-positive serosa-involved gastric cancer. Moreover, we speculate that antiglucocorticoid therapy may help some patients with GR-positive gastric cancer. However, clinical application of this strategy requires further randomized trials until this modality of therapy can be proven to be effective for such patients.

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Diagnosing Regenerative Nodular Hyperplasia, the "Great Masquerader" of Liver Tumors

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Distinguishing benign tumors and pseudotumors of the liver from malignant tumors is a common clinical problem. Regenerative nodular hyperplasia (RNH) represents one of the more challenging pseudotumors to diagnose, because they can appear clinically indistinguishable from either a primary or a secondary liver malignancy. Even after comprehensive radiologic evaluation and image-guided percutaneous biopsy, the diagnosis of RNH can remain elusive. We reviewed the pathophysiology of RNH and present five cases illustrating the limitations of percutaneous biopsy and the utility of laparoscopic wedge biopsy in establishing the diagnosis. All patients underwent a complete workup that included percutaneous biopsy. Patients with a nondiagnostic percutaneous biopsy underwent a laparoscopic wedge biopsy or anatomical resection. H&E, vimentin, trichrome, and reticulin staining as well as CD34 immunostaining were performed. Five patients were diagnosed with RNH between May 2002 and April 2004. Three had focal nodular disease, whereas the other two had a diffuse multinodular presentation. Percutaneous biopsy definitively made the diagnosis in only one out of the five cases. Laparoscopic wedge biopsy was necessary to accurately make the diagnosis in three cases, whereas the fifth diagnosis was established after an anatomical resection. RNH is a unique pseudotumor of the liver that can present either as a solitary nodule or as a multinodular process. Percutaneous biopsy is associated with limitations in diagnosing RNH, and a more definitive surgical biopsy may be required. When RNH is considered, laparoscopic wedge biopsy is a safe and efficient way to obtain enough tissue to preserve the hepatic architecture required for diagnosis, while avoiding the morbidity of an unnecessary open resection. (J GASTROINTEST SURG 2006;10:727–733)

KEY WORDS: Liver masses, biopsy, regenerative nodular hyperplasia, laparoscopy

Regenerative nodular hyperplasia has historically been a condition recognized at autopsy, having been found in up to 2.6% of the autopsy case series.[1,2] It was first described by Ranstrom[3] in 1953 and labeled miliary hepatocellular hyperplasia. Steiner[4] changed the nomenclature in 1959 to nodular regenerative hyperplasia to distinguish this condition of nodule formation from the process of cirrhosis where fibrosis is pathognomonic.

The development of regenerative nodular hyperplasia (RNH) seems to center around alterations in hepatic blood flow. It is well recognized that hepatic artery blood flow can often be heterogeneous in nature. These observed alterations in hepatic blood flow have been shown to induce regional hypertrophy of the overperfused area and atrophy of the adjacent areas receiving standard or suboptimal perfusion. Specifically in RNH, there seems to be focal augmentation of arterial flow in some hepatic lobules, which can compress neighboring lobules and portal vessels, resulting in adjacent lobule atrophy and portal vein thrombosis.[5–7] The theory of a vascular etiology for RNH is additionally supported by the fact that up to 80% of the reported cases of RNH are associated with systemic diseases that cause vascular alterations or vasculitis, as well as the presence of portal vein thrombosis (Table 1).[5,6,8–11] Histologically, RHN is seen as hypertropic, hyperplastic nodular formation in the high-flow areas and atrophy in the low-flow areas. Recently, Shimamatsu and Wanless[12] observed that the low-flow areas have increased apoptotic rate, possibly representing the mechanism responsible for the cirrhosis and hepatic insufficiency observed in patients with RNH.

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Table 1. Conditions associated with RNH

Immunological disorders
Rheumatoid arthritis
Systemic lupus
Polyarteritis nodosa
CREST syndrome
Cryoglobulinemia
Myeloproliferative disorders
Myeloid metaplasia
Polycythemia vera
CML
Primary thrombocythemia
Monoclonal gammopathies
Multiple myeloma
Waldenstrom's macroglobulinemia
Renal transplantation
Bone marrow transplantation
Primary pulmonary hypertension
Malignant neoplasms
Hodgkin's disease
NHL
Metastatic carcinomas
Drug & Toxins
Corticosteroids
Androgenic steroids
Oral contraceptives
Immunosuppressants
Cytotoxic agents
Toxic oil syndrome

Benign liver conditions are very common, occurring in up to 20% of the population in autopsy series. With the increased utilization of abdominal CT scanning and the concomitant improvement in image quality, benign tumors and pseudotumors are identified more frequently and are sometimes difficult to distinguish from malignant lesions. These patients are often referred to a hepatobiliary specialist, who must safely distinguish the more common benign processes of the liver from potentially malignant conditions. This can be challenging when only 1–2 out of every 20 liver masses are malignant.[13]

Although the majority of benign liver tumors present as a solitary lesion, the pseudotumors often present as a diffuse multinodular process indistinguishable from a metastatic process. Most benign liver tumors and pseudotumors can be diagnosed with a history and physical exam, serological tests, radiologic imaging, and image-guided percutaneous biopsy. RNH is a unique pseudotumor that can present either as a focal nodular or a diffuse multinodular process throughout the liver. Percutaneous biopsy is often nondiagnostic, and a wedge biopsy of the liver may be required.[14–16] In this paper, we review our recent experience in the diagnostic evaluation of five cases of RNH.

METHODS

This is a retrospective, institutional review board–approved analysis of five cases of RNH that presented between May 2002 and April 2004 to the hepatobiliary service at Roswell Park Cancer Institute. Four female patients and one male presented at an average age of 44 years (range, 25–69).

Laboratory studies included complete blood cell count, electrolytes, liver function tests, coagulation profile, hepatitis B and C serologies, and alpha-fetal protein (AFP). Imaging studies included ultrasound (n = 1), CT scan (n = 4), and magnetic resonance imaging (n = 2). All patients underwent percutaneous biopsy. Intraoperative ultrasound was performed in four out of the five cases during laparoscopy or laparotomy.

All cases were reviewed by an experienced pathologist (M.I.). The specimens were fixed in formalin and embedded in paraffin blocks. The stains performed included hematoxylin-eosin, reticulin, vimentin, trichrome, and CD34. Histological diagnosis was ultimately made based on percutaneous biopsy (n = 1), laparoscopic wedge biopsies (n = 3), or resection (n = 1).

RESULTS

During the 24-month period of our review, five patients were identified who had a final diagnosis of regenerative nodular hyperplasia. The presenting characteristics are listed in Table 2. All patients were referred from outside physicians who were concerned that these lesions represented malignant neoplasms of the liver.

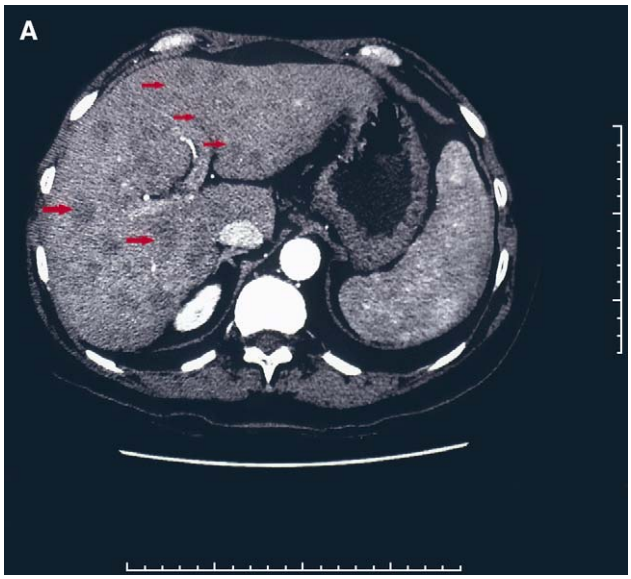
Case 1

A 69-year-old woman presented to her primary care physician with complaints of back pain. An abdominal CT scan revealed multiple liver nodules best visualized during the arterial phase of the examination (Fig. 1). She underwent a workup for an unknown primary that included hepatitis serology, AFP, CEA, bilateral mammograms, upper endoscopy, and lower endoscopy. A magnetic resonance image confirmed the presence of multiple lesions in the liver. Two percutaneous biopsies (ultrasound and CT-guided) were performed that showed only normal liver tissue and inflammatory changes. The patient then underwent a diagnostic laparoscopy, where grossly the liver showed multiple grey-brown-tan nodules (Fig. 2). Laparoscopic ultrasound revealed multiple hypoechoic nodules, and a wedge biopsy was performed. The diagnosis of RNH was made histologically by H&E, trichrome, vimentin,

Table 2. Patient characteristics

Patients	Symptoms	Nodule Type	RGB	Wedge blopsy	Follow-up
Case 1	Back pain	Multinodular	Nondiag	Y	Alive and well
Case 2	Abd pain	Focal (single)	Nondiag	Y	Alive and well
Case 3	Abd pain	Focal (two)	Nondiag	Y*	Alive and well
Case 4	Nausea/bloating	Multinodular	Diag	N	Alive and well
Case 5	Abd pain	Focal (single)	Nondiag	Y	Alive and well

RGB = radiologic guided biopsy; nondiag = nondiagnosed; abd = abdominal; diag = diagnosed.
*Anatomical resection.



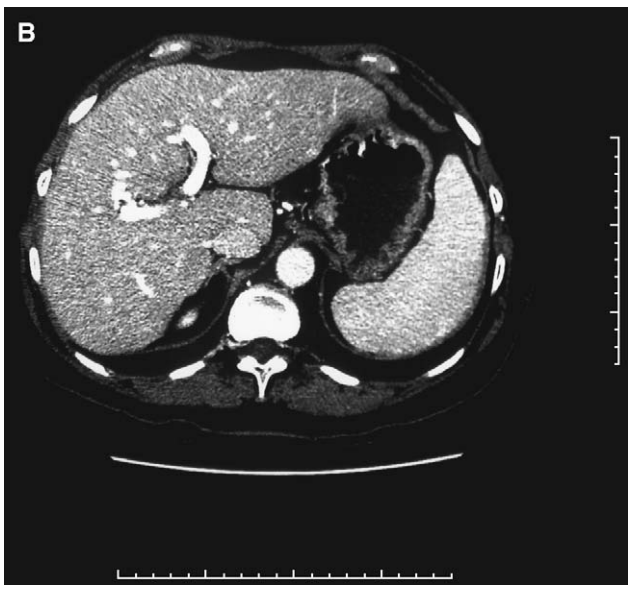


Fig. 1. This CT scan illustrates multiple hypodense nodules (*red arrows*) with peripheral enhancement during hepatic arterial phase (**A**) that become isodense during portal venous phase (**B**).

and reticulin stain, together with CD34 immunostaining (Fig. 3). The patient was discharged on postoperative day 1 and is doing well in follow-up.

Case 2

A 49-year-old woman presented to her primary care physician because of nausea and vague abdominal pains. Abdominal ultrasound revealed gallstones and an 11 × 10.5 × 5 cm mass in the left lobe of the liver. A CT scan confirmed the presence of an enhancing solitary mass (Fig. 4). Standard laboratory studies and serologic tests were normal. A laparoscopy was performed that showed a grey-tan mass in the left hepatic lobe. Laparoscopic ultrasound found the mass to be hyperechoic, abutting the middle hepatic vein. A liver wedge biopsy and ultrasound-guided core biopsies of the mass and adjacent normal-appearing liver were obtained. The diagnosis of RNH was made, and the patient continues to do well in annual follow-up.

Case 3

A 40-year-old woman with history of alcohol use and oral birth control use developed transient abdominal pain. A CT scan revealed two lesions in the right lobe, one 5 cm mass and a 2 cm lesion. A percutaneous biopsy was performed and felt to be consistent with a hepatic adenoma by the outside pathologist. The pathology was reviewed at Roswell Park Cancer Institute and found consistent with steatosis. Given the size of the lesion and radiological characteristics, there was still clinical suspicion for hepatic adenoma or HCC. These findings, together with the patient's profound anxiety, led to a surgical exploration. Intraoperative ultrasound revealed no other lesions, and a right hepatectomy was performed. The final diagnosis was RNH, and the patient is currently doing well.

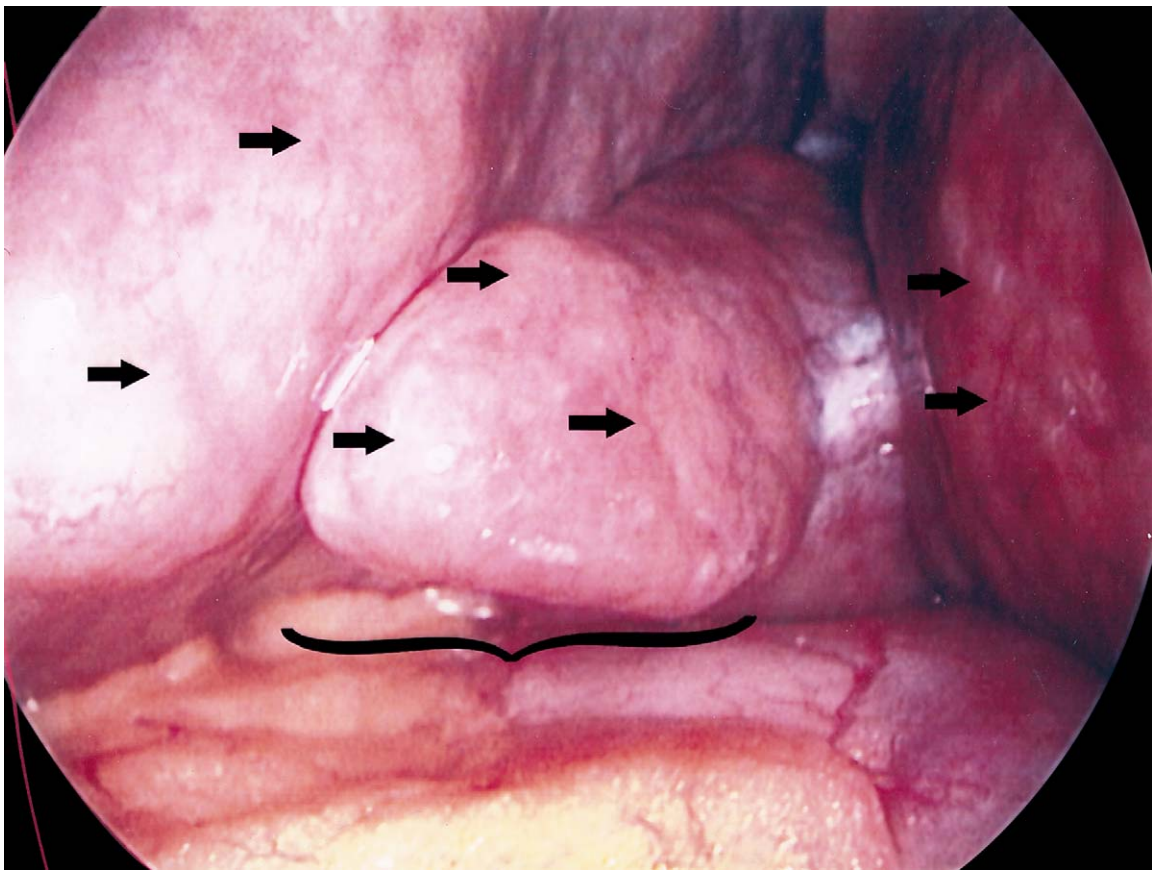


Fig. 2. In this photo taken during laparoscopy, multiple nodules with a whitish/grayish appearance can be seen diffusely involving the liver (*black arrows*). There is a prominent caudate lobe (bracket) that has significant nodular change.

Case 4

A 39-year-old woman with a 4-year history of benign liver nodules developed bloating and nausea. Standard blood tests, bilateral mammograms, and upper and lower endoscopies were normal. Repeat abdominal CT scans revealed an increased number of lesions. A percutaneous biopsy was performed that provided the diagnosis of RNH. The patient is doing relatively well with only some mild bloating and occasional nausea.

Case 5

A 25-year-old man who presented with vague abdominal pain had an abdominal ultrasound that identified a 1 cm gallbladder polyp that was monitored by annual ultrasounds. At his first follow-up ultrasound, the polyp was unchanged, but a 5 cm mass was identified in the left lateral segment. Abdominal CT scan characterized the mass as a 6 cm enhancing lesion within the liver. LFTs, viral serology, and AFP were all normal, and a percutaneous biopsy could not conclusively determine if this lesion was an adenoma or cirrhosis. Laparoscopy was performed with removal of the gallbladder and wedge biopsy of the lesion and adjacent normal liver. Histologically the mass and adjacent normal liver both had evidence of RNH, and the patient is currently doing well.

DISCUSSION

This series describes our use of laparoscopy in the management of an uncommon liver disorder, RNH, referred to our hepatobiliary service. Most cases of RNH in the literature are primarily autopsy series with an incidence ranging from 0.1% to 2.6%.[1,2] We speculate that the increased use of body imaging for vague abdominal and back pain may make this a more commonly encountered condition. The etiology of RNH is still very obscure. Many studies and case reports have linked it with a number of conditions associated with vascular abnormalities, immunodeficiency, neoplasia, and medications (Table 1), but there are no proven risk factors.[5,6,8–10,14,15] None of the patients in our series had any of the

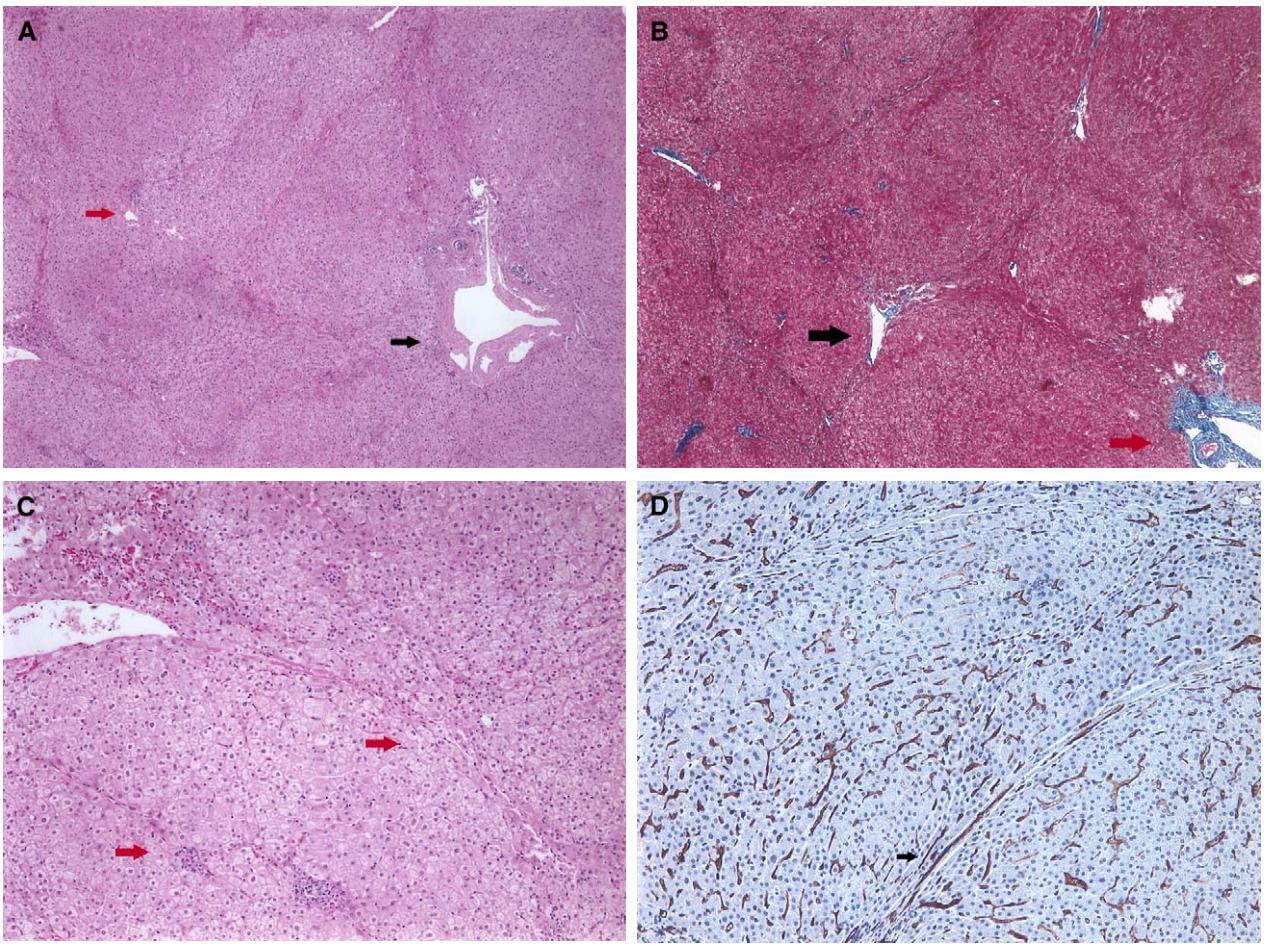


Fig. 3. Case 1: (**A**) 40× H&E stain demonstrating the nodules but maintained portal triad (*black arrow*) and hepatic vein (*red arrow*) architecture (no evidence of fibrosis). (**B**) 40× trichome stain for collagen shows collagen staining around the portal triads (*red arrow*)and central veins (*black arrow*) but no evidence of fibrosis around the nodules. (**C**) 100× H&E illustrates that the nodules formed are encased by compressed hepatocytes (*red arrows*), not fibrosis. (**D**) 100× H&E CD34 immunostain is specific for the bile canaliculi demonstrating that the hepatocytes forming the nodule can be 2 to 3 cell plates in thickness, and this sinusoidal staining illustrates the compressed hepatocytes encasing the regenerative nodules (*black arrow*).

associated conditions found in the literature, but one did use oral birth control.

Reported long-term sequelae of RNH include ascites, splenomegaly, hepatomegaly, portal hypertension, esophageal varices, cirrhosis, hepatic failure, and hepatic rupture.[2,17,18] The exact incidence of each varies in the literature, but the most common sequelae are cirrhosis and portal hypertension, with estimates of 30%–50%.[17] In the autopsy series of Wanless,[2] cirrhotic changes were found to be present in all livers with RNH, but extensive fibrosis was seen only in 47%. Evidence of portal hypertension was present in only 5% of these patients. A more recent retrospective clinical series out of Belgium with 14 patients reported nine patients with cirrhosis (60%) and 10 patients (71%) with varices secondary to portal hypertension.[18] Interestingly, the rate of varices in this series was significantly higher than that found from the autopsy series of Wanless,[2] but this may be due to the small sample size. Even though patients with RNH may develop cirrhosis, the prognosis of RNH-induced cirrhosis is better than other common causes of cirrhosis.[2,17,18] We recommend that these patients be monitored for the development of liver dysfunction and varices.

There is no known evidence that RNH is associated with any benign or malignant masses of the liver. However, the potential of malignant transformation of RNH is an area of debate, and the exact risk is unknown. Pathologically, these cells exhibit hyperplastic growth features and can manifest dysplastic changes, suggesting at least a potential biological mechanism for transformation.[19] However, there is no prospective or retrospective data to support any predisposition to hepatocellular carcinoma. RNH patients at potential risk for primary hepatic

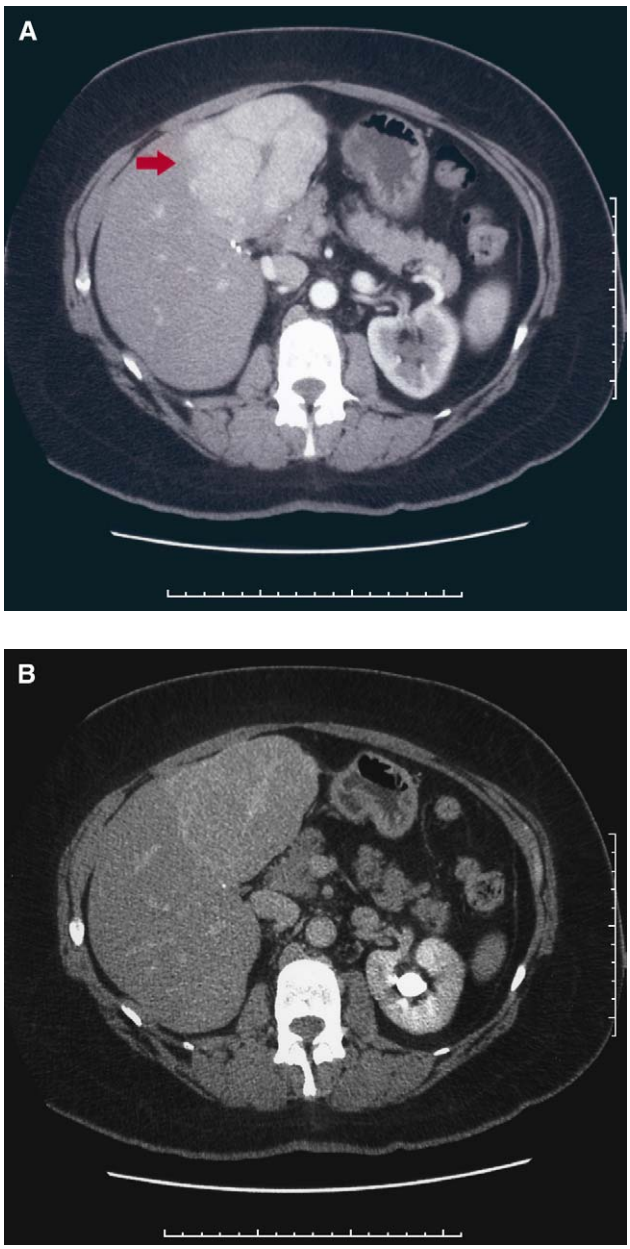


Fig. 4. This CT scan reveals a large solitary RNH nodule in the left lobe of the liver that is hypervascular during hepatic arterial phase (**A**) with central scar (*red arrow*). This lesion is isodense during the delayed phase (**B**).

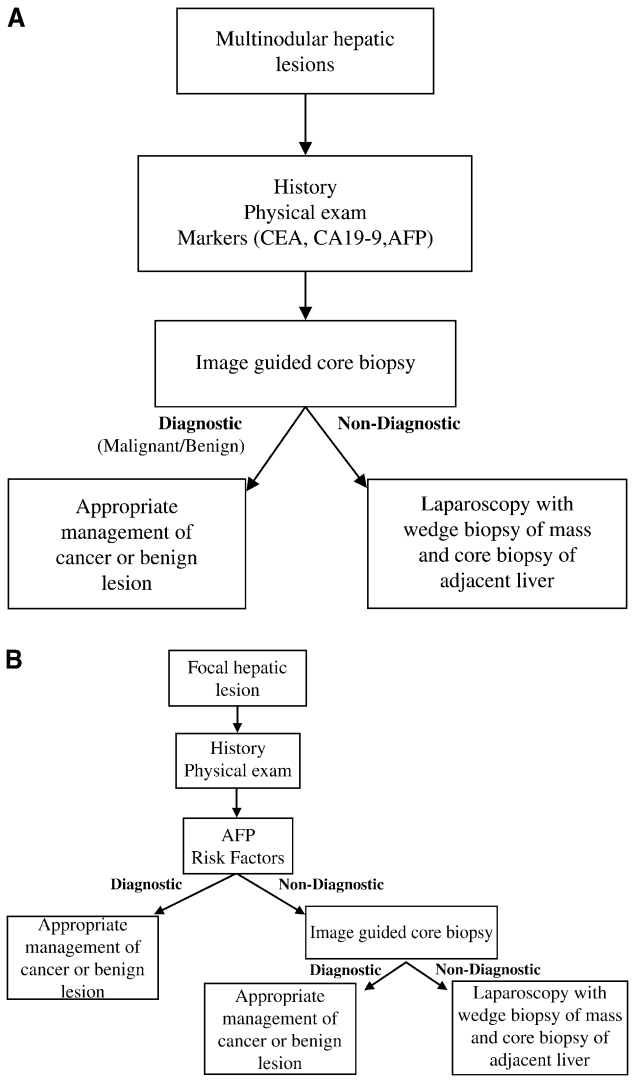


Fig. 5. Management strategy.

malignancy are those who have cirrhosis from another etiology or subsequently developed cirrhosis secondary to the RNH. Although it would be difficult to attribute malignant risk to RNH alone, it may synergize with other conditions known to lead to malignant transformation.

RNH should be viewed as a chameleon pseudotumor of the liver. It classically presents with diffuse parenchymal involvement, but can coalesce to form focal nodules. Pathologically, focal nodule formation has been observed in some of the larger series, such as Stromeyer's review from the AFIP where 3 out of 30 patients with RNH had solitary nodules.[16] Radiographically, RNH is manifested by the different spectrums of presentations, both solitary (Fig. 4) and multinodular (Fig. 1) liver masses. This is important because the radiologic presentation modifies the clinical evaluation of these patients (Fig. 5). One radiologic clue to the diagnosis of RNH is the presence of isolated arterial phase enhancement and an isodense appearance on the portal venous or delayed phase (Fig. 4).[17,20,21] This finding is more commonly observed in the diffuse type of RNH; however, we found this in our solitary nodule patients. Radiologically, these nodules can also present as hypodense lesions during arterial phase that become isodense on portal vein and delayed phase imaging (Fig. 1).

Percutaneous biopsy of these lesions can be nondiagnostic because the cells obtained appear as

normal hepatocytes. Thus, a wedge liver biopsy that provides an adequate tissue sample and best preserves the architecture of the liver is often required to diagnose RNH.[14–17] Because RNH is known to be a diffuse process, core biopsy of the adjacent normal appearing liver is necessary to illustrate the pervasive hepatic involvement and solidify the diagnosis. By obtaining these biopsies laparoscopically, the liver can be evaluated by visualization, tactile compression, and ultrasound to identify any gross stigmata of a malignant process, which may alter the management.

On pathologic evaluation of the biopsies, the maintenance of the portal tract architecture distinguishes it from other benign and malignant processes such as focal nodular hyperplasia, adenoma, or hepatoma. The presence of compressed liver plate(s) encasing the nodule instead of fibrosis is pathognomonic for RNH, distinguishing it from the regenerative nodules of cirrhosis.[2–4] Staining with reticulin, trichome, and vimentin aid in the diagnosis by enhancing the collagen surrounding the portal tracts, not the nodules as seen in cirrhosis. CD34 staining delineates the normal compressed liver plates surrounding the nodules by staining the sinusoids (Fig. 3).

Although RNH is a benign condition with no direct malignant association, it is a progressive process that may result in a number of liver sequelae, including the development of cirrhosis and portal hypertension. Accurate diagnosis of this liver condition is paramount to facilitate proper management of these patients. We advocate the use of laparoscopy with intraoperative ultrasound to define the lesion(s) and facilitate wedge and large core biopsies for suspected RNH (Fig. 5).

In conclusion, RNH is a benign condition that should be considered in patients with solitary or multinodular liver lesions, particularly after percutaneous biopsy fails to make the diagnosis. Given the benign nature of RNH and the risk for cirrhotic sequelae, accurate diagnosis and avoidance of liver resection are prudent. There is no known indication for liver resection, and it should only be considered in cases were there is a persistent diagnostic dilemma. In general, the prognosis is good for RNH patients, with the majority of the patients never developing cirrhosis and the ones that do typically having a better prognosis than with other causes of cirrhosis.

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Postoperative Recurrence in Hepatic Hydatid Disease

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Recurrence of hepatic hydatid disease is still a serious problem in endemic areas like our country. In this study, we present the causes and management of recurrences after surgical therapy of the hepatic hydatid cysts. Hepatic hydatid cyst patients treated surgically and followed afterward at Istanbul University, Cerrahpasa Medical Faculty, Department of General Surgery between January 1998 and January 2003 were evaluated retrospectively. During this period, 172 primary patients with hepatic hydatid disease were attended to at our clinic. Morbidity and mortality rates for this series were 5.8% and 0.58%, respectively. Recurrence rate was 4.65% during the follow-up period of 60.5 months (range, 25–84 months). Primary causes of recurrence were thought to be unnoticed cysts with exophytic development due to inadequate incision and exposition and spreading of the disease during conservative operative interventions. It is concluded that selection of the proper incision allowing complete exposition, and performance of pericystectomy in solitary, peripherally located cysts prevent recurrence. (J GASTROINTEST SURG 2006;10:734–739)

KEY WORDS: Hepatic hydatid disease, echinococcosis, postoperative recurrence

Recurrence is seen in approximately 10% of patients treated for hepatic hydatid disease.[1] This is still a serious problem in endemic areas like our country.[2] Although the recurrence is merely an important problem, morbidity and mortality rates of secondary surgical procedures are significantly higher when compared with primary interventions.[3] In this study, patients with hepatic hydatid cysts treated surgically and followed afterward in our clinic were evaluated retrospectively to detect preventable causes of recurrence development, technical problems associated with secondary operations, cautions for prevention of recurrence, and management of recurrence.

MATERIAL AND METHODS

In this study, patients with hepatic hydatid cysts treated surgically and followed afterward at Istanbul University, Cerrahpasa Medical Faculty, Department of General Surgery between January 1998 and January 2003 were evaluated retrospectively. Patients who underwent surgery elsewhere for hepatic hydatid disease and referred to our clinic for recurrence were excluded from the study. Preoperative diagnosis of hydatidosis was confirmed by abdominal ultrasonography (US), computerized tomography (CT), and enzyme-linked immunosorbent assay-indirect hemagglutination (ELISA-IHA) tests. Main parameters were age, sex, mean hospital stay, morbidity and mortality, localization and size of the cyst, complication of the cyst, type of surgical intervention, complications resulting from surgical interventions, postoperative medical therapy, and follow-up periods. Routine follow-ups included the ELISA-IHA test for echinococcosis in the third postoperative month, and ELISA-IHA and abdominal US in the sixth postoperative month. After 6 months, annual ELISA-IHA and US were performed. Patients with any suspect of recurrence on US are confirmed with CT. Routine albendazole treatment was given to 165 of the patients. Albendazole treatment protocol was 10 days of albendazole administration 10mg/kg preoperatively followed by an initial treatment of 14 days postoperatively, and according to the hepatic function and full blood count tests, medical therapy was continued for 6 months with 2-week intervals between each month. Time of recurrence, localization of the new cyst, complication due to the new cyst,

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type of surgical intervention, and complications resulting from surgical interventions were also evaluated in patients with recurrence.

The comparable parameters were evaluated by one-way ANOVA and chi-square (Fisher exact test) tests, and $P \leqslant 0.05$ was accepted to be statistically significant.

RESULTS

Two hundred twenty-five interventions were performed for hepatic hydatid disease and related reasons on 208 patients. Thirty-six patients with recurrent cysts referred to our clinic from other hospitals were not included in the study. The female to male ratio of 172 patients with primary disease who underwent surgery in our clinic was 109/63, with a mean age of 42.38 ± 1.19 (mean ± standard error; range, 17–78). Of these 172 patients, 45 were treated by laparoscopic approach, and conventional open surgery was performed on the remaining 127 patients. Types of surgical interventions are summarized in Table 1. Mean hospital stay was 9.50 ± 0.53 (range, 2–51) days. The postoperative morbidity rate was 5.8% (10 patients). Postoperative complications are summarized in Table 2. In the patient with subphrenic abscess, reoperation for drainage was performed on the seventh postoperative day. Postoperative endoscopic retrograde cholangiography and endoscopic sphincterotomy was performed on all of the patients with prolonged bile drainage. The only mortality was the patient with pulmonary embolism who died on the sixth postoperative day (0.58%). Albendazole treatment was given to 165 of the patients. In the remaining seven patients, albendazole treatment could not be administered due to impaired hepatic function tests. The mean follow-up period was 60.52 ± 1.32 (range, 25–84) months.

During the follow-up period, eight patients suffered recurrence (recurrence rate, 4.65%). The mean period of recurrence development was 23.37 ± 5.31 (range, 8–48) months. Routine albendazole treatment was given to all of these patients with recurrence.

When the size and the localizations of the previous cysts were investigated in patients suffering recurrence, it was shown that in four of these patients (50%) previous cysts were multiple. Mean diameter of the previous cysts was 9.36 ± 1.76 cm. In six of the patients (75%), primary cysts were localized in the posterior segment of the right hepatic lobe. The mean diameter of the recurrent cysts was 8.7 ± 0.63 cm. Recurrences were in the same localizations of the primary cysts. Additional intrapelvic recurrence was observed in one of the patients.

Previous operation was cystotomy plus partial cystectomy plus drainage in all patients with recurrence, and four of them were treated laparoscopically. The rate of recurrence was 3.15% and 8.89% in the open surgery group and laparoscopic-treated patients, respectively; however, there was no statistically significant difference between these groups ($P = 0.209$).

In the open surgery group, the choice of incision was supraumbilical median in one patient and right subcostal incision in the remaining patients. Laparoscopic intervention was again preferred in one of the patients with recurrence previously operated laparoscopically, but in the rest of the patients open surgery was performed. Except for one patient who

Table 1. Surgical interventions performed in our patients

		Type of operation	No. of patients
Laparoscopic	Conservative (n = 44)	Cystotomy, cyst evacuation, partial cystectomy, and drainage	29
		+ omentoplasty	7
		+ cholecystectomy	4
		+ cholecystectomy, choledochotomy, T-tube drainage	1
		+ total abdominal hysterectomy-bilateral salphingo-oopherectomy	1
		+ totally extraperitoneal hernia repair	2
	Radical (n = 1)	Pericystectomy	1
Open	Conservative (n = 121)	Cystotomy, cyst evacuation, partial cystectomy, and drainage	79
		+ omentoplasty	10
		+ introflexion	10
		+ cholecystectomy	14
		+ cholecystectomy, choledochotomy, T-tube drainage	5
		+ cholecystectomy, choledochotomy, and choledochoduodenostomy	2
		+ appendectomy	1
	Radical (n = 6)	Pericystectomy	6
Total			172

Table 2. Postoperative complications

Complication	No. of patients
Wound infection	2
Atelectasis	1
Subphrenic abscess	1
Pulmonary embolism	1
Prolonged bile leakage	5
Total	10

previously underwent surgery through a supraumbilical median incision, all of the patients were reoperated through a right subcostal incision extending to the left. A suprainfraumbilical median incision was preferred in the above-mentioned patient, who had intrapelvic recurrence. In all of the patients, cystotomy plus partial cystectomy and drainage procedure were performed, and total cystectomy was performed for the intrapelvic recurrence. In all of the patients, dense intra-abdominal adhesions were detected during exploration, resulting in preoperative iatrogenic abdominal organ injuries (small bowel injury and diaphragmatic injury) in 25%; however no preoperative complication occurred in the operations of the primary patients. On the contrary, the postoperative complication rate was 5.8% in primary patients, whereas prolonged bile leakage postoperatively was observed in only one patient with recurrence. This patient was treated by endoscopic retrograde cholangiography and endoscopic sphincterotomy on the 25th postoperative day. The mean period of hospital stay was 16.43 $\pm$ 3.80 (range, 6–35) days in these patients with recurrence. When the mean hospital stay of patients with recurrence and primary patients were compared, patients with recurrence had a statistically significant longer time of hospital stay than did the primary patients (16.4 vs. 9.5 days, P = 0.018). Albendazole treatment was administered to all of these patients postoperatively.

DISCUSSION

Human infection with *Echinococcus granulosus* typically results in a slowly growing parasitic disease most frequently seen in the liver. The infection may cause fatal complications and is therefore one of the most dangerous helminthic diseases in humans. The goals of therapy are to treat associated complications, eliminate local disease, and avoid recurrence while minimizing morbidity and mortality of the treatment itself. There is a wide spectrum of treatment ranging from radical surgical resections, operative conservative interventions, medical therapy with antihelmintic agents, and drainage under US.[1–5]

Recurrence is one of the major problems in the management of hepatic hydatid disease. It is defined as the appearance of new active cysts after therapy of intrahepatic or extrahepatic disease. The failure to achieve permanent control of the primary treated cyst is considered to be the cause of the local recurrence. Local recurrence occurs after surgical or radiological intervention and manifests as reappearance of live cysts at the site of a previously treated cyst or the appearance of new extrahepatic disease resulting from procedure-related spillage. The rate of recurrence is reported to be ranging from 10%–20% in different series in the literature.[1,6] The rate of recurrence was reported as 0% and 12% in patients with radical surgical interventions and in patients who underwent operative conservative interventions, respectively, in a study performed by Chautems et al.[7] Sielaff et al.[1] reported the recurrence rate as 10% and suggested that complete excision of the cyst decreased the recurrence rate below 10%. The rate of recurrence in our series was 4.65%, independent from the type of intervention.

It should be kept in mind that besides being a primary problem, recurrence increases the rate of preoperative complications in the secondary operations leading to a mortality rate of 10%.[3,6] According to Mottaghian and Saidi,[8] each intervention performed for intra-abdominal recurrences makes the technique more difficult due to adhesions resulting from previous operations and/or spilt hydatid fluid. Our results are similar to these reports, despite the primary operations without any preoperative complications; dense intra-abdominal adhesions were the primary problem in the operations performed for recurrences. In 25% of these patients, intraoperative complications such as injuries of small bowel and diaphragma occurred. Mean hospital stay was also more statistically significantly prolonged in the patients with recurrence than in the primary patients.

Regarding the factors leading to recurrence, many opinions are suggested in the literature. Mottaghian and Saidi[8] emphasized in 1978 that the main cause of the recurrence was spillage during surgical removal. Haddad et al.[9] suggested that the most important cause of the recurrence was incomplete excision of the endocyst with inaccessible or difficult locations for surgery. They also emphasized that inability to kill or evacuate all of the living cysts and protoscolexes during the first operation was the primary cause of the local recurrences and suggested that full attention to not cause intraperitoneal spillage and mechanical clearance of whole alive cystic material was necessary during the operative conservative interventions. The type of the surgical intervention,

either as radical or conservative, was reported to be directly associated with the incidence of recurrence in another study.[3] Although all of these approaches seem to be acceptable, we do not suggest such radical excisions with higher mortality rates for such non-malignant disease, regardless of the characteristic of the patient and the cysts; however, in selected patients without any comorbid diseases, and especially patients with solitary cysts located peripherally, such radical interventions—either by conventional methods or by totally laparoscopic pericystectomy—are preferred in our clinic as well. No recurrence occurred in those patients treated by radical interventions in our clinic. Radical interventions decrease the recurrence rates while increasing the mortality rates associated with the procedure.[1,7,8,10,11]

In our study, we detected an important aspect that was not strongly emphasized in the literature: the rate of recurrence in patients treated by laparoscopic conservative interventions was higher than the open conservative interventions (8.89% vs. 3.15%), but there was no statistically significant difference between the two groups.

Another problem of the operative conservative interventions for hydatid disease is intra-abdominal contamination due to leakage of the cystic contents. The main principle is to avoid spillage of living cystic content into the abdomen or wound edges. In eight patients with recurrence in our series, only one intra-abdominal contamination accompanied by local recurrence was detected. After the sterilization of the pericystic area and the wound edges with towels soaked with povidone iodine, injection of povidone iodine 10% or hypertonic saline 20% is performed after the detection of the clear fluid aspirated from the cyst during the open operative conservative interventions. Leaving the solution in the cystic cavity for 5 minutes, the cyst is aspirated through a laparoscopic port inserted directly into the cavity. After the complete evacuation and irrigation of the cyst with povidone iodine solution, laparoscopic port is extracted and cystotomy and partial cystectomy are performed. Similar procedures are performed in the laparoscopic conservative interventions.[12,13]

Although there are not any reports showing the association of recurrence and the choice of incision, older cysts have an increased risk of exogenous daughter cyst formation, which is an important factor for recurrence of disease after surgery. Therefore, it is suggested that there is a risk of leaving viable material behind during the operative conservative interventions.[1,7] From our point of view, one of the main causes of recurrence is that risk. Significant exophytic cyst development is shown on CT image in Fig. 1. However, exophytic developments are not usually seen as significant on CT images as that in our study, and minor intraparenchymal penetrations through the pericyst or a small exophytic formation can easily go unnoticed. In patients where operative radical interventions are not planned, careful exploration should be done in these long-standing, huge, multiple cysts, and the cystic cavity should be examined thoroughly. In our series, the majority of the recurrences were in the previous localization of posterior segments of the right hepatic lobe, and in 50% of these patients, primary cysts were multiple. Moreover, the preferred incision was a standard right subcostal incision in most of these patients. The choice of incision is so important in cysts with a difficult location for surgery. We suggest using for primary patients, especially those with cysts located in the posterior segments of the right hepatic lobe and the patients with recurrence, a right subcostal incision extending to the left or an oblique thoracoabdominal incision extending to the 11th rib bed, with the patient lying at a 45° angle.[14] Athanassiadi et al.[15] also surgically treated 31 patients, with hydatid cysts located in the posterior segment of the right hepatic lobe, through a transthoracic approach. They also suggested that right posterolateral low thoracotomy was a good alternative in hardly exposed patients.

Another important factor is the use of the intraoperative US in patients with long-standing huge and multiple cysts after the evacuation of the cyst and partial cystectomy procedure. We have been using intraoperative US in multiple, large cysts with inaccessible or difficult locations for surgery in recent years. By this method, any exophytic development can be clearly detected either through the cavity or from the outer portion of the cyst ultrasonographically. The use of intraoperative US has changed the course of the procedure in 8 of the 34 latest patients in our practice by showing the exophytic development previously unnoticed in the preoperative diagnostics.

There is not a consensus about the type and duration of the follow-up period after primary surgical intervention. In the literature, it is suggested that the postoperative follow-up period should not be shorter than 3 years and should be continued as long as possible. In our series, the mean period of recurrence development was detected as 23.37 months. Therefore, we agree that the follow-up period should be as short as 3 years and with rarer intervals, depending on the necessities of the patient thereafter.[1] Blood titers do not return to normal values soon after the operation; therefore, positive serological tests are not significant for the follow-up period, and recurrence should be additionally confirmed by

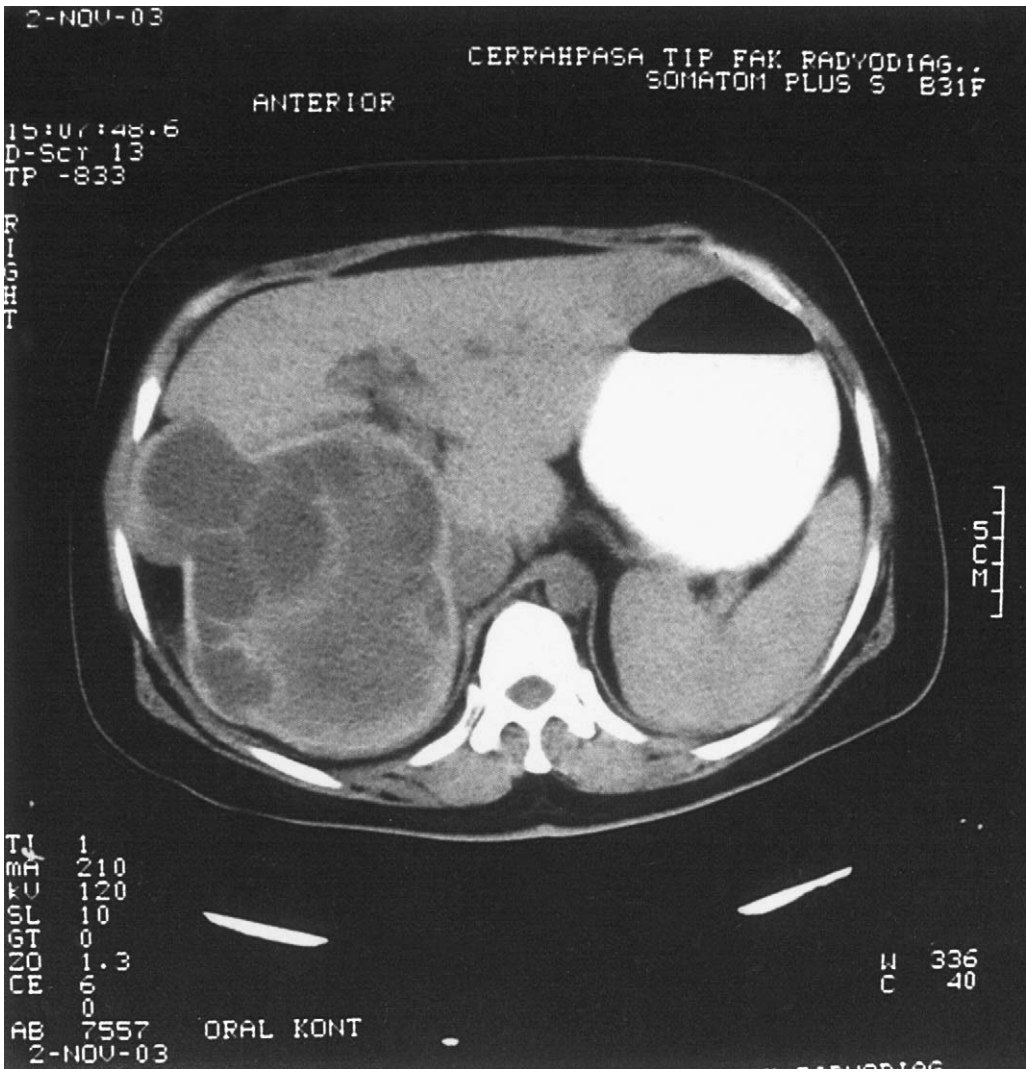

Fig. 1. Compute tomographic appearance of an hepatic cyst with significant exophytic development.

US or CT. CT should be performed routinely for patients in which a second operation is planned, due to the superiority of CT in showing nature of the cyst, association with the biliary system, vascular structures, and related organs.[1,3,16] Radiographic appearance of postoperative cysts may vary significantly and is frequently time-dependent. Cystlike structures are usually seen in the surgical evacuation area, but differential diagnosis of these structures—whether as persistent changes or as newly formed parasites—is always difficult. The best marker suggesting recurrence is accepted to be "the increase in the diameter of the cyst."[1,17]

It seems to be rational to give medical therapy after the operation. Albendazole alone is highly unsuccessful in treating primary patients, and recurrence rate is high after the cessation of medical therapy. In a study from the literature, regardless of the surgical method, recurrence rate was 6.7% and 23.3% in patients who were given perioperative medical therapy and in patients who were not, respectively.[3,7,16] Although the administration of albendazole postoperatively is routinely performed in our clinic, we think that it alone is not adequate in preventing recurrences.

Also, there is not a consensus on the management of the diagnosed recurrence in the literature. Patients of advanced age with local recurrence and serious comorbid diseases, and asymptomatic patients, should be treated medically when complications development.[1] Haddad et al.[9] suggested that in patients with recurrences smaller than 5 cm in diameter, antihelmintic therapy for 3–6 months was the ideal treatment, and the cysts with difficult location for surgery should be drained percutaneously. On the contrary, there are also reports suggesting that in patients for

whom albendazole treatment for the primary disease failed, treatment of recurrence would also fail. In fact, treatment options for local recurrence are similar to those for the primary disease; however, radical interventions are also suggested in patients with recurrence who previously underwent surgery conservatively.[1] Nevertheless, these radical operations are technically more difficult, and reoperations have higher morbidity and mortality rates. Therefore, we performed operative conservative interventions in all patients in our series. No recurrence was observed in the follow-up of these patients. We also prefer to continue albendazole treatment after the second operation, even when the patients were given albendazole treatment before the operation.

CONCLUSION

As a result, we can say that recurrence is a serious problem in hepatic hydatid disease. Spillage during removal of the cysts, incomplete excision of the endocyst, and type of surgical intervention are main factors reported in the literature for causing recurrence. Moreover, we observed that factors such as choice of incision and exogenous daughter cyst formation occurring in older cysts are also important in the development of recurrence. Maximum surgical care to avoid intra-abdominal contamination of the cystic contents during operative conservative interventions should be undertaken. The choice of incision should be good enough to achieve the best exposition in patients with long-standing, huge, multiple cysts, especially those located in the seventh or eighth segments of the liver. Routine albendazole therapy postoperatively should be continued; however, albendazole therapy alone cannot prevent recurrence. Due to the decreased rates of recurrence after radical operations, pericystectomy could be performed with lower morbidity and mortality rates in selected patients with solitary, small, and peripherally located cysts. Moreover, we suggest the use of intraoperative US in long-standing patients so that any exophytic development is not missed. Prospective studies should be done evaluating the use of intraoperative US and recurrence rates after laparoscopic conservative interventions.

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Hepatectomy in Patients With Nonuremic Minimal Renal Failure

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In this study, the perioperative management and short-term outcome of hepatectomy were evaluated in patients with nonuremic minimal renal failure to assess the safety of hepatectomy in such patients. Ninety-one patients who underwent hepatectomy were retrospectively divided into two groups based on their creatinine clearance (Ccr) values: a group with Ccr values ⩾50 but <100 ml/min (group 1; n = 77) and a group with Ccr values of ⩾20 to <50 ml/min (group 2; n = 14). Preoperative patient characteristics, intraoperative parameters (including operation time and blood loss), and postoperative management and complications were evaluated. The preoperative evaluation showed no differences in liver function between the two groups, and there were no statistically significant differences between the two groups in intraoperative blood loss (522 ml in group 1 and 806 ml in group 2) or intraoperative urine volume (1.01 ml/kg per hour in group 1 and 0.75 ml/kg per hour in group 2). The difference between the two groups in postoperative complications was not statistically significant. None of the patients in group 2 required dialysis therapy, and no patients died as a result of hepatectomy or hepatectomy-related causes. Adequate indications, appropriate operative procedures, and perioperative management can enable hepatectomy to be performed safely in patients with nonuremic minimal renal failure. (J GASTROINTEST SURG 2006;10:740–745)

KEY WORDS: Hepatectomy, nonuremic renal failure, hepatocellular carcinoma

Although advances in surgical techniques and management have made it possible to perform hepatectomy safely, renal dysfunction remains a major risk factor for perioperative management of hepatectomy.[1] Renal dysfunction is classified into nonuremic and uremic stages, and since patients in the uremic stage are maintained on artificial kidneys, there is no concern about deterioration of their renal function due to complications of hepatectomy. Patients in the nonuremic stage, on the other hand, have impaired renal function and depend on their own kidneys, and thus they require special attention to prevent deterioration of renal function and avoid the need for dialysis therapy when subjected to hepatectomy. Furthermore, any major surgery, including hepatectomy, is risky in patients with nonuremic renal failure, because they usually have complications, including a compromised immune system, coagulopathy, and systemic atherosclerosis. There have been several reports on hepatectomy in patients with end-stage renal failure or uremic renal failure.[2,3] Although they addressed the risks of hepatectomy in uremic patients, management of preoperative and postoperative dialysis, selection of anticoagulants for dialysis, and intraoperative hemostasis, no reports have been published reports on hepatectomy in patients with nonuremic renal failure. In this study we retrospectively evaluated the results of perioperative, intraoperative, and postoperative management and the short-term outcome of hepatectomy in patients with nonuremic minimal renal failure to assess the safety of hepatectomy in such patients.

PATIENTS AND METHODS

Ninety-one patients who underwent hepatectomy for hepatocellular carcinoma (HCC) or metastatic liver tumors between April 2000 and December 2003 and whose creatinine clearance (Ccr) was precisely recorded in the medical record were included

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in this study. Renal function in all patients was evaluated by a creatinine clearance test, which was usually performed 1 week before the operation. Nonuremic renal failure was defined according to the NHA criteria[4,5] as a creatinine clearance (Ccr) of between ⩾20 and <50 ml/min.

The patients were divided into two groups based on their Ccr: a group with a Ccr of ⩾50 to <100 ml/min (group 1; n = 77) and a group with a Ccr of ⩾20 but <50 ml/min (group 2; n = 14). The patients' characteristics are shown in Table 1.

The extent of liver resection was decided on the basis of criteria reported elsewhere.[6] Briefly, patients who had ascites or a serum bilirubin level above 2.0 mg/dl were not considered candidates for hepatectomy, and the extent of liver resection was decided as follows, based on the indocyanine green retention rate at 15 minutes (ICG R15): R15 ⩾40%, enucleation; R15 ⩾30% but <40%, partial resection; R15 ⩾20% but <30%, subsegmentectomy; R15 ⩾10% but <20%, segmentectomy and left lobectomy; R15 < 10%, right lobectomy and extended lobectomy (Fig. 1). In this study partial resection was defined as nonanatomical resection in which the tumor was resected with at least a 2-cm surgical margin. These criteria were strictly applied to both groups. Details of the hepatectomy procedures are summarized in Table 2, and all hepatectomies were performed by one surgeon (coauthor K.K.), supported by other well-trained surgeons, in a single institution.

Our strategy for patients with nonuremic renal failure was to maintain intraoperative and postoperative urine volume at more than 1 ml/kg per hour. Maintaining urine volume above this level, administering an adequate infusion volume, and use of diuretics were done.

The data are expressed as mean ± SD, except when the value is described as a median. Statistical calculations were performed by applying the two-tailed *t* test to mean ± SD and the Mann-Whitney *U* test to median values.

RESULTS

Preoperative clinical data are shown in Table 1. There were no significant differences between group 1 and group 2 in preoperative liver function values. The percentages of patients with cirrhosis in groups 1 and 2 were 54.5% and 61.5%, respectively. There were no typical manifestations of hepatic viral infections in either group. The ICG R15 value was 17.4 ± 7.8% in group 1 and 18.4 ± 8.8% in group 2.

Higher serum Cr (sCr) and BUN values were observed in group 2 than in group 1, but the differences were not statistically significant ($P = 0.07$ for sCr, $P = 0.06$ for BUN). The Ccr value was significantly

Table 1. Patient characteristics

	Group 1	Group 2
No. of patients	77	14
Gender (M/F)	62/15	10/4
Age (yr)	63.8 ± 1.0	68.9 ± 2.3
Cause of disease		
HCC	77	13
Non-HCC	0	1
Preoperative data		
Virus (B/C/B and C/none)	21/46/2/13	3/8/1/1
Cirrhosis	42 (54.5%)	8 (57.1 %)
Albumin (g/dl)	3.7 ± 0.4	3.6 ± 0.3
Total bilirubin (mg/dl)	0.7 ± 0.3	0.6 ± 0.1
ALT	41.2 ± 17.0	40.8 ± 27.5
AST	39.3 ± 24.4	31.5 ± 25.0
AFP[†]	25.5	73
Indocyanine green retention rate at 15 min (%)	17.4 ± 7.8	18.4 ± 8.8
Blood urea nitrogen (mg/dl)	12.9 ± 3.6	17.2 ± 7.5
Creatinine (mg/dl)	0.6 ± 0.2	0.9 ± 0.5
Creatinine clearance (ml/min)	93.9 ± 43.2	35.3 ± 13.2[††]

HCC = hepatocellular carcinoma; ALT = alanine aminotransferase; AST = aspartate amino transferase; AFP = alpha fetoprotein.
[†]Media value.
[††]Statistically significant.

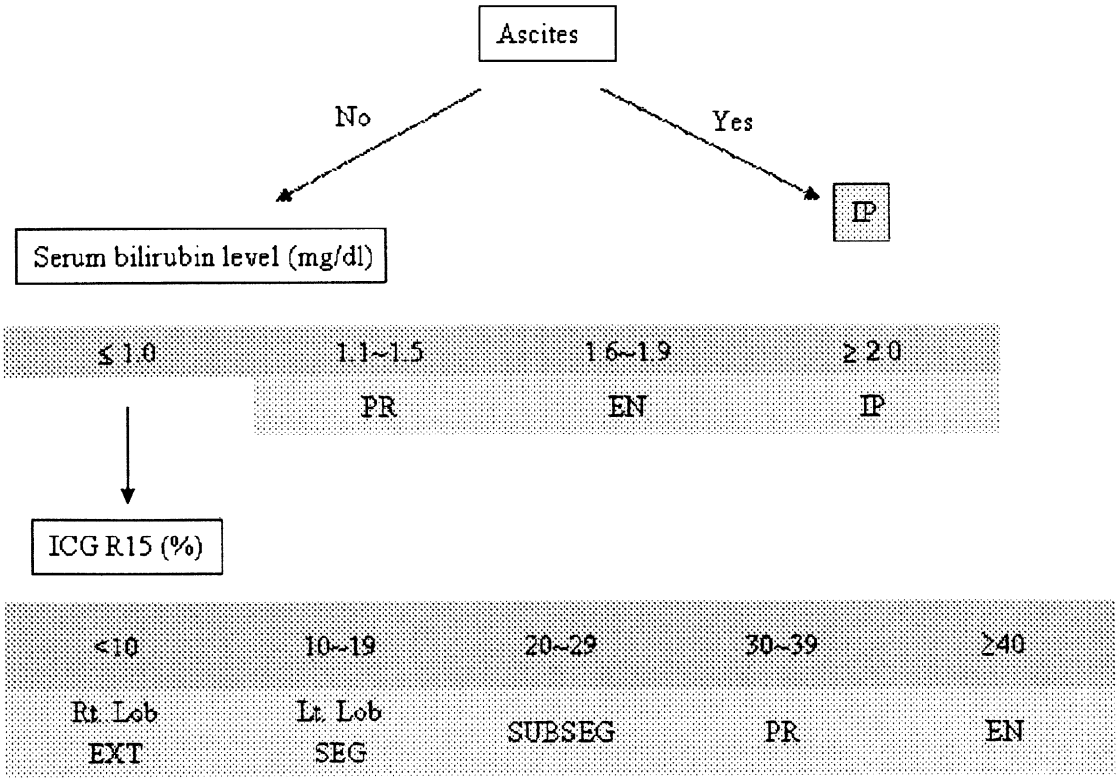

Fig. 1. Algorithm for deciding the extent of liver resection. IP = inoperable, PR = partial resection, EN = enucleation, Rt. Lob = right lobectomy, EXT = extended lobectomy, SEG = segmentectomy, SUBSEG = subsegmentectomy.

lower in group 2 than in group 1 (93.9 ± 43.2 versus 35.3 ± 13.2 ml/min, $P < 0.0001$). No proteinuria was observed in any patients in either group.

Table 2 shows details of the hepatectomy procedures. Operation time was 334.8 ± 104.6 min in group 1 and 389.8 ± 117.9 min in group 2 (Fig. 2, *A*). Blood loss tended to be greater in group 2 than in group 1, but the difference was not statistically significant (Fig. 2, *B*, $P = 0.415$). Intraoperative urine volume did not differ between the two groups (Fig. 2, *C*). Resected liver volume was similar in the two groups (Fig. 2, *D*).

The sCr values before hepatectomy and the highest sCr values after hepatectomy are shown in Figure 3. The median preoperative sCr value was 0.7 mg/dl in group 1 and 0.9 mg/dl in group 2, and the median peak sCr value after hepatectomy was 0.9 mg/dl in group 1 and 1.2 mg/dl in group 2. None of the patients in either group were placed on hemodialysis after hepatectomy.

Table 2. Operative data

	Group 1 (n = 77)	Group 2 (n = 14)	*P*-value
Extent of liver resection			
Enucleation	5	2	
Partial resection	25	1	
Segmentectomy	21	6	
Lobectomy	25	3	
Resection of more than one lobe	11	2	
Operation time (min)	334.8 ± 104.6	389.8 ± 117.9	0.180
Blood loss (ml)*	522 (60–6840)	806 (96–1923)	0.415
Urine volume (ml/kg/h)*, range	1.01 (0.13–5.16)	0.75 (0.64–7.19)	0.476
Resected liver volume (g)*, range	234 (7–1960)	250 (118–810)	0.313

*Median value.

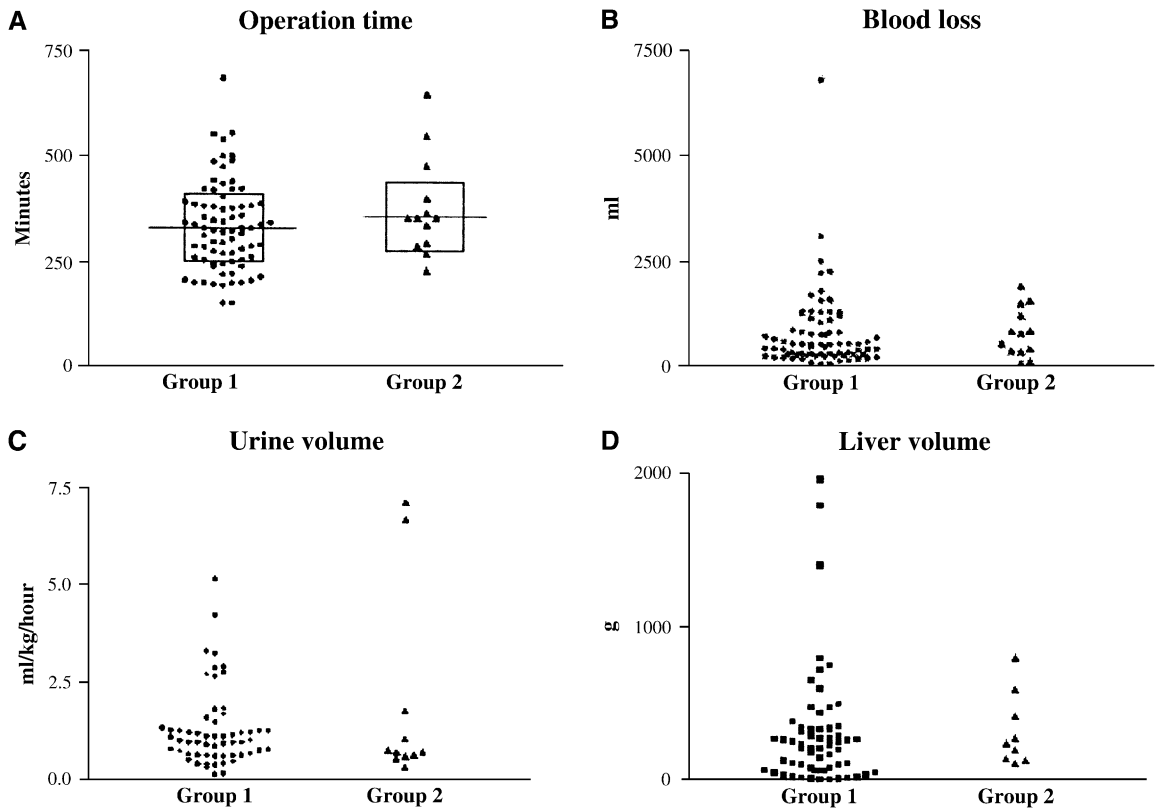

Fig. 2. Intraoperative parameters. Operation time (**A**), blood loss (**B**), urine volume (**C**), and resected liver volume (**D**) were compared between group 1 and group 2. (**D**) Horizontal bar: median value, square: standard deviation. There were no significant differences in any of the parameters showed.

The antibiotics administered to the patients were cefotiam hydrochloride and piperacillin sodium. The dose was 2 g/day in both groups, and the median duration of administration was 7 days, with no statistically significant difference between the groups.

The complications associated with hepatectomy are shown in Table 3. Major complications included bile leakage, pleural effusion, ascites, and wound infection, but their incidences did not differ between the two groups. The postoperative morbidity rate in group 1 and group 2 was 29.9% and 38.5%, respectively. The median postoperative hospital stay was 29 days in both groups, indicating that patients with nonuremic minimal renal failure can be discharged from the hospital in the same way as patients with normal renal function. No patients died as a result the hepatectomy procedure or of hepatectomy-related causes.

DISCUSSION

The critical factor in curative hepatectomy in nonuremic renal failure patients is to perform the procedure safely in order to prevent deterioration of renal function and avoid the need for dialysis therapy. The results of this study demonstrate that hepatectomy can be performed safely without rapid and progressive deterioration of renal function in patients with nonuremic renal failure. In fact, there were no differences between the two groups in terms of operation time, intraoperative blood loss, urine volume, or volume of the resected liver.

The preoperative evaluations were performed by routine methods. Computed tomography with contrast enhancement and angiography were routinely performed in the patients with nonuremic renal failure in the same manner as in patients with normal renal function, and no deterioration of renal function was observed in this series. As expected, there were no differences in preoperative sCr and BUN values, which should not be used to detect renal failure.

Patients with nonuremic renal failure have impaired blood-coagulation function.[7] The impaired blood coagulation system and platelet dysfunction may increase perioperative bleeding, which is the main cause of deterioration of perioperative renal function and often results in other postoperative

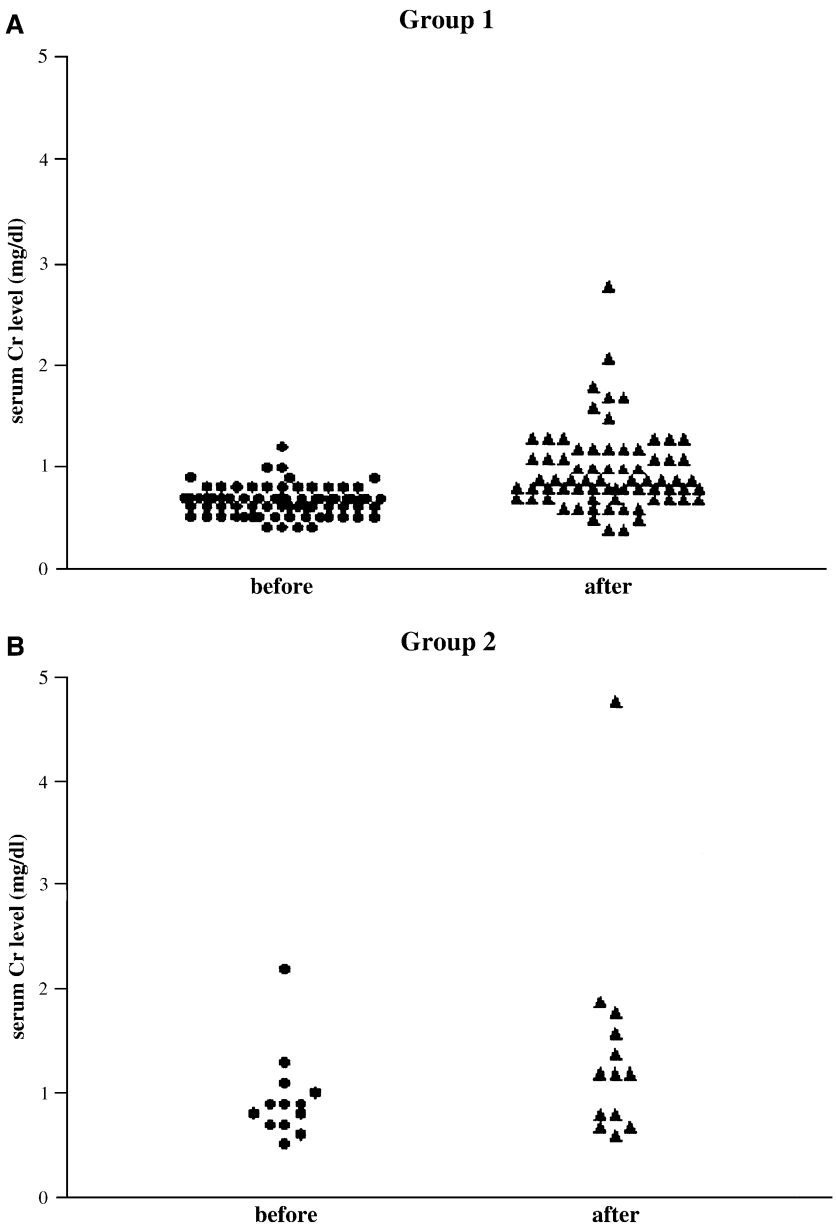

Fig. 3. Preoperative serum creatinine (sCr) and the peak postoperative sCr. Neither group 1 (**A**) nor group 2 (**B**) showed statistically significant increases in sCr values after hepatectomy.

complications, such as gastrointestinal bleeding and wound infection. Thus, proper intraoperative hemostasis is essential to performing hepatectomy safely in patients with nonuremic renal failure. Our results indicated that careful hemostasis ensured there was no difference in perioperative blood loss between the patients with normal and impaired renal function.

The complications of hepatectomy included bile leakage, uncontrollable pleural effusion and ascites, pneumonia, and wound infection, but none of these complications were unique to the patients with nonuremic renal failure. The median postoperative hospital stay was 29 days in both groups, and there was no statistically significant difference between them ($P = 0.601$). No patients with nonuremic renal failure were placed on dialysis.

It is well known that patients with renal failure are immunocompromised, and the occurrence of perioperative infection is higher than in the normal population,[8] but no opportunistic infection or higher rate of infection was observed in the patients with

Table 3. Postoperative data

	Group 1 (n = 77)	Group 2 (n = 13)	*P*-value
Complications			
Bile leak	3	1	
Pleural effusion	8	1	
Ascites	4	2	
Pneumonia	2	0	
Wound infection	6	1	
Morbidity rare (%)	29.9	38.5	
Postoperative hospital stay, days,* range	29 (14–149)	29 (13–197)	0.601
Hemodialysis	No	No	

*Median value.

nonuremic renal failure in this study. The dose of antibiotics was not reduced because of the impaired renal function, and no cases of drug-induced deterioration in renal function were observed. Administration of suitable antibiotics for an appropriate period made it possible to avoid infection and further impairment of renal function.

In conclusion, patients with nonuremic minimal renal failure can undergo hepatectomy safely, based on reasonable decisions as to the indications and for extent of liver resection, appropriate operative procedures, and accurate perioperative management.

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Abdominal Lymphangiomas in Adults

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Abdominal lymphangiomas are rare benign cystic tumors that can become locally invasive and often require resection. They arise in all ages and have a variable presentation. We performed a retrospective review of a single institution surgical experience with this lesion in adults. The pathology prospective database was reviewed to identify patients with surgically resected abdominal lymphangiomas from January 1986 to May 2004. Retrospective review and follow-up was performed for each patient. The six patients with abdominal lymphangiomas ranged in age from 38 to 66 years. They presented with a variety of signs and symptoms. All underwent CT scan that demonstrated a cystic lesion, but in only one third was the diagnosis made preoperatively. Tumors were located in the retroperitoneum, small bowel mesentery, liver, and pancreas. Five of the six tumors were completely resected. Two of the six required resection of adjacent or involved organs. Follow-up ranged between 6 months and 18 years. All had symptomatic relief after resection, and no patient showed evidence of recurrence in this time period. Abdominal lymphangiomas are rare. The correct diagnosis often remains elusive until tissue is obtained. The treatment of choice is complete surgical resection. When completely resected, these lesions seem not to recur, and the overall prognosis is excellent. (J GASTROINTEST SURG 2006;10:746–751)

KEY WORDS: Lymphangioma, resection, cystic, intra-abdominal

Abdominal lymphangiomas are a group of benign cystic tumors. They are extremely rare in the adult population, with reported frequencies of less than 1 in 20,000 to 1 in 250,000 hospital admissions.[1,2] Although the etiology remains unclear, lymphangiomas are thought to result from a developmental failure of the lymphatic system.[3,4] Another possibility includes inflammation in the lymphatic channels leading to obstruction and subsequent development of lymphangiomas.[5] They are often confused with mesenteric cysts that arise from mesothelial, not lymphatic, tissue. This differentiation is important because lymphangiomas often behave in an invasive and aggressive manner, whereas mesothelial cysts do not. Despite being difficult to differentiate on imaging studies, they are histologically distinct from one another. Lymphangiomas have an endothelial lining, foam cells, and a wall that contains lymphatic spaces, lymphoid tissue, and smooth muscle.[3] Mesenteric cysts either have no lining or are lined with cuboidal or columnar epithelium.[1,2]

Most reports demonstrate a female predominance and low incidence among African Americans.[1,3] Abdominal lymphangiomas can occur at any age and present with a wide range of signs and symptoms, making the correct diagnosis difficult.[6,7] On one end of the spectrum, they can be found incidentally on computed tomographic (CT) scan obtained for other reasons. When patients are symptomatic, signs and symptoms include abdominal or back pain, nausea, vomiting, palpable abdominal mass, ascites, change in bowel habits, and fever. In the adult population, these symptoms are rarely acute in onset, but develop insidiously over time. Acute presentations can occur from traumatic rupture, hemorrhage into the lesion or into the peritoneal cavity, bowel obstruction, or infection.[1–3]

Plain abdominal films have little diagnostic value in patients with abdominal lymphangiomas. They are, however, able to detect complications arising as a result of these lesions, such as bowel obstruction or bowel displacement.[6] Ultrasonography is sensitive

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and specific for abdominal cystic masses but cannot provide important information regarding exact anatomical location, involvement of adjacent organs, and cyst size.[6–8] CT or magnetic resonance imaging (MRI) provide the best anatomic imaging and are most useful in surgical planning.[1]

Although benign, abdominal lymphangiomas can behave aggressively, invading surrounding structures, necessitating large and potentially hazardous resections.[3,9] Complete resection is possible when the lymphangioma invades resectable abdominal organs including the liver, small bowel, colon, spleen, or pancreas.[2–4] However, adhesion to vital structures (i.e., root of the mesentery) can render these lesions unresectable.[10]

This report summarizes the experience of The Johns Hopkins Hospital with abdominal lymphangiomas in adult patients. The details of six patient cases are reviewed, including the demographics, clinical presentation, intraoperative course, postoperative course, pathology, and long-term follow-up.

METHODS

After obtaining approval from the Institutional Review Board, the Johns Hopkins Hospital Pathology prospective database was reviewed to identify patients with surgically resected abdominal lymphangiomas. Between January 1986 and May 2004 six adult patients underwent surgical resection for such lesions. A retrospective chart review was performed to assess the demographic characteristics, presenting signs and symptoms, laboratory data, pathology, surgical treatment, and long-term outcomes of these patients.

All lymphangioma specimens were reviewed by a single pathologist (F.B.A). The diagnosis of cystic lymphangioma was confirmed using three standard histological criteria: (1) cyst lined by a flat endothelial epithelium, (2) small lymphatic spaces, and (3) abundant lymphoid tissue. Two additional features were often present, but not considered requisite for the diagnosis: (1) smooth muscle present in the cyst wall and (2) foam cells containing lipoid material present in varying numbers (Fig. 1). Although there are two histochemical markers, CD31 and factor VIII-related antigen, that have demonstrated the possibility of specificity in the diagnosis of lymphangiomas in one small study, these markers are not commonly in use. The diagnosis of a lymphangioma is most commonly founded upon the standard histological criteria above.[11]

All means are presented as mean + standard deviation. Follow-up included a review of medical

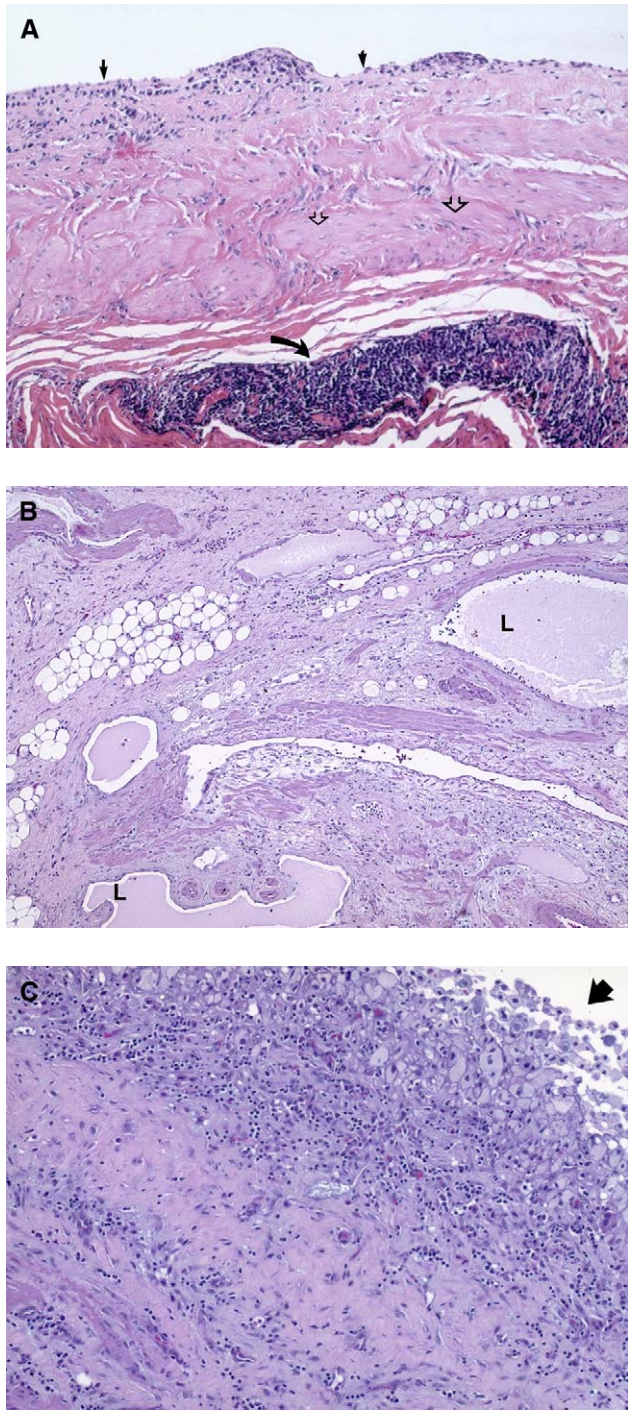

Fig. 1. (**A**) Medium power (20×) photomicrograph showing the wall of the lymphangioma, composed of smooth muscle bundles (*open arrowheads*) and prominent lymphoid tissue (*curved arrow*). The interior wall of the lymphangioma is lined by flattened endothelium (*solid arrowhead*). (**B**) Low power (10×) photomicrograph of the lymphangioma showing dilated spaces filled with lymph (L). In addition, there are multiple bundles of smooth muscle, areas of fibrous tissue, and fat. (**C**) High power (40×) photomicrograph showing foamy macrophages (*solid arrowhead*) filling the lumen of the lymphangioma and attached to its inner wall. A few smooth muscle bundles can be seen at the lower left.

records from the operating surgeon/hospital and individual patient contact, when possible.

RESULTS

Six patients underwent resection for abdominal lymphangioma between January 1986 and June 2004. Patients were generally healthy with a mean American Society of Anesthesiologists (ASA) risk score of 2.2 + 0.4 and a mean body mass index of 25 + 5. The patient's demographics, presentations, and tumor characteristics are summarized in Table 1. All patients were female and ranged in age from 38 years to 66 years. The majority of patients in this study presented with the gradual onset of pain or unrelated complaints for weeks to months, prompting an imaging study that ultimately revealed a cystic, intra-abdominal lesion. All patients underwent elective resection. One patient presented acutely with fever and abdominal pain that, given her findings of a cystic lesion on CT and lack of concomitant pathology, was consistent with an infected lymphangioma. Her symptoms resolved with antibiotic therapy, and she was electively resected.

All patients in this series underwent abdominal CT scan to obtain the diagnosis of a cystic intra-abdominal lesion (Fig. 2). Three underwent abdominal ultrasounds and two had MRI scans. Despite this, only one third of patients were correctly diagnosed with a lymphangioma preoperatively. Both of these patients had undergone ultrasound-guided percutaneous biopsy, and the diagnosis was made from the pathological specimen obtained.

All resected lymphangiomas were of the cystic type. None of the patients were found to have ascites at the time of resection. Two of the six patients required resection of adjacent organs secondary to lymphangioma involvement, including the pancreas and small bowel.

Because each patient in the series had a unique presentation and postoperative course, the next several paragraphs detail their individual presentation and clinical course. Patient 1 is a 60-year-old white woman with a history of multiple abdominal surgeries (appendectomy, total abdominal hysterectomy/bilateral salingoophovento, and abdominal hernia repair), arthritis, and smoking, who presented to an outside hospital complaining of 3 weeks of constipation and a 25-pound weight loss over the previous year. CT scan revealed a large cystic lesion emanating from the liver and extending into the pelvis. She was referred to Johns Hopkins, where exploratory laparotomy revealed a 10 × 14 × 9 cm multiloculated cystic lesion. This lesion involved segment IV of the liver as well as the retroperitoneum. It was the only lesion in our study group that was not completely resected, as a small piece of cyst was left on the underside of segment IV of the liver. The mucosal lining of the remaining cyst was cauterized.

Patient 2 is a 40-year-old white woman with a history of smoking, who presented to her primary care physician with 1 week of left-sided flank pain and fever. Her symptoms resolved with antibiotics, but prompted a CT scan to rule out nephrolithiasis. This scan demonstrated a 7 cm cystic lesion thought to arise from the tail of the pancreas. Further workup included an MRI that characterized the lesion as either a pancreatic pseudocyst or a simple pancreatic cyst. She too was referred to Johns Hopkins, where exploratory laparotomy uncovered a single 6 × 6 × 6 cm cystic lesion arising from the

Table 1. Characteristics of six patients and their lymphangiomas

Patient	Age (yr)	Sex	Race	Symptoms	Clinical Signs	Duration of symptoms	BMI	ASA	Location	Size (cm)	Multiplicity
1	60	F	W	Constipation*	None	Weeks	23.6	2	Retroperitoneum/	10 × 14 × 9	One, ML
2	47	F	W	R flank pain*	Fever*	1 week	25.1	2	Liver (seg IV)	6 × 6 × 6	One
3	66	F	W	RLQ & scapular pain	None	Months	22.5	2	Retroperitoneum	10 × 8 × 8	One
4	38	F	W	N/V, fever, RUQ pain	Fever	Days	19.4	2	Retroperitoneum SB Mesentery	10 × 9 × 9 3.5 × 3.5 × 3.5	Two
5	51	F	W	Back pain	None	Months	35.2	3	Retroperitoneum/ root of mesentery	7 × 6 × 7	One, ML
6	38	F	AA	Inc abd girth	Mass in LUQ	Months	23	2	Retroperitoneum tail of pancreas	17 × 12 × 25 (3.5 × 3 × 3) × 2	Three

BMI = body mass index; ML = multiloculated; SB = small bowel; W = white; AA = African American; ASA = American Society of Anesthesiologists; R = right; N/V = nausea/vomiting; RUQ = Right upper quadrant; Inc abd = increased abdominal; LUQ = left upper quadrant.
*Signs/symptoms attributed to a source other than the lesion, hence lesion was discovered incidentally on imaging.

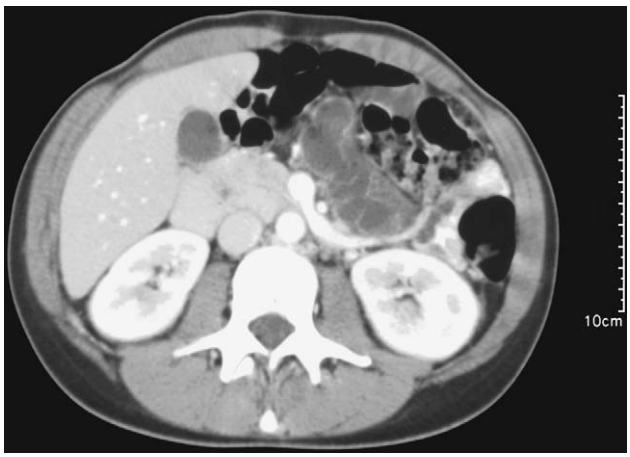

Fig. 2. CT scan of a large retroperitoneal cystic mass. This abdominal lymphangioma was resected with a small segment of jejunum.

retroperitoneum. It was completely resected without complications (Fig. 3).

Patient 3 is a 66-year-old white woman with a history of cystic breast disease, hypertension, and smoking, who presented to an outside hospital with 2 months of right lower quadrant pain that radiated to her right scapula. Abdominal ultrasound showed a cystic lesion near the head of the pancreas. MRI and CT yielded similar findings. The cyst was percutaneously aspirated on multiple occasions with no evidence of malignancy, and each time, it recurred. She was referred to Johns Hopkins, where exploratory laparotomy revealed a single 10 × 8 × 8 cm cystic lesion behind the head of the pancreas and duodenum, originating from the suprarenal aortocaval groove. After a difficult dissection, the lesion was completely resected.

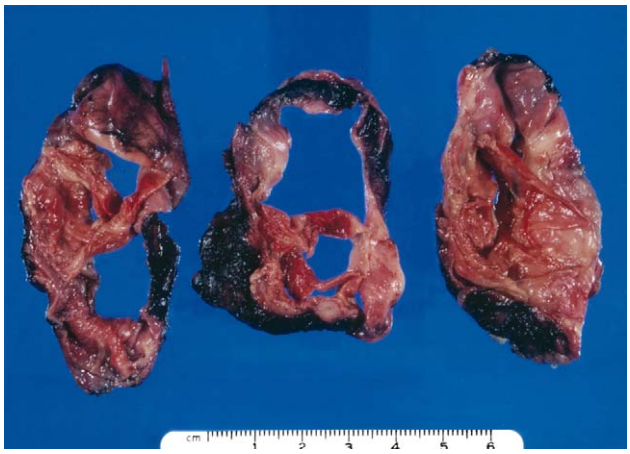

Fig. 3. Cut section of a multiloculated cystic lymphangioma with trabeculated lining. The lymphangioma was filled with cloudy yellow-grey fluid.

Patient 4 was a 38-year-old white woman with active hepatitis C being treated with Pegylated interferon and ribavirin, who presented to Johns Hopkins Hospital with 2 days of fever, nausea, vomiting, and right upper quadrant/epigastric pain that radiated to her back. Abdominal CT demonstrated a large retroperitoneal/mesenteric cystic mass. She underwent ultrasound-guided percutaneous aspiration of the mass, providing the diagnosis of infected lymphangioma. She was treated with antibiotics and discharged home. Her symptoms resolved and she was electively resected. Exploratory laparotomy revealed two cystic masses emanating from the small bowel mesentery and invading the proximal jejunum. These were resected en bloc with a 12-inch loop of jejunum, and a primary anastomosis was performed.

Patient 5 was a 51-year-old white woman with a history of obesity, osteoarthritis, and chronic back pain, who underwent an MRI of her lumber spine to evaluate her back pain. Incidentally, she was found to have a 3 cm retroperitoneal mass on the right side of her aortic bifurcation. This prompted a CT scan that confirmed the size and location. The lesion was considered suspicious for paraganglioma. She had no history of symptoms indicative of a catecholamine-secreting tumor, but her 24-hour urinary norepinephrine was found to be slightly elevated. She was referred to Johns Hopkins, where she was preoperatively alpha-blocked with phenoxybenzamine. Exploratory laparotomy revealed a 5 × 5 × 7 cm cystic mass at the root of the cecal mesentery, which was completely resected without removal of any adjacent organs.

Patient 6 was a 37-year-old African American woman with a history of hypertension, who presented to Johns Hopkins Hospital with 1 week of indigestion, increasing abdominal girth, and a 15-pound weight gain over the previous 3 months. Physical exam was remarkable for a left-sided abdominal mass palpated from the costal margin to the pelvis, as well as a palpable mass on pelvic exam. Abdominal CT demonstrated a 25 ×17 × 11 cm multiloculated, cystic mass. Ultrasound exam confirmed this and suggested this mass was ovarian in origin. She was taken to the operating room by the gynecology service for a presumed ovarian tumor. However, on exploration, she was found to have multiple, large cystic masses arising from the tail of her pancreas with extension into the base of the colonic mesentery. General Surgery was consulted intraoperatively and proceeded to perform a distal pancreatectomy with a jejunal Roux-en-Y reconstruction to the remnant pancreas, with complete resection of all cystic masses.

There was no evidence of recurrence in any patient at a mean follow-up of 6 years. Five of the six patients were contacted directly and all had resolution of their initial symptoms. Both the surgical treatment and follow-up are summarized in Table 2.

DISCUSSION

Cystic lymphangiomas are slow growing benign soft tissue tumors most commonly found in children.[12] They are usually found in the neck (75%, also called cystic hygromas) and axilla (20%).[1] However, cases have been reported originating from any portion of the gastrointestinal tract,[13–17] most abdominal organs,[18–21] and some areas of the chest.[22–25] Less than 1% of lesions affect the mesentery and retroperitoneum.[9,26] The fact that only six cases were diagnosed and treated at our large tertiary care center over the last 18 years is a tribute to their rarity.

The distinction between mesenteric/retroperitoneal lymphangioma and mesenteric cysts has not always been adequately detailed in the literature, leading to the unintentional inclusion of both entities in previous case series. To avoid this problem, a histological characterization of the five standard criteria for diagnosis of a cystic lymphangioma was carefully performed by a single pathologist, and the lesion of each patient was found to meet these criteria.

The present series is among the largest characterizing abdominal lymphangiomas in adult patients. It confirms past reports of a white and female predominance of these tumors, with 100% of the current patients being female and 5 of 6 being white. However, this stands in contrast to most studies of these lesions in children, which suggest a closer to 1:1 female to male distribution.[4–6,12] This could suggest a difference in the presentation, diagnosis, or biology of these lesions in female versus male children, leading to a persistence of the lesion into adulthood in females.

Our series did not reveal any patients presenting with ascites. This is in contrast to studies and reviews indicating that upward of 50% of patients diagnosed with lymphangiomas presented with ascites.[1,2] However, as in previous series, some of these cystic lesions were large enough to mimic ascites on physical exam.[5]

Abdominal lymphangiomas are notoriously difficult to diagnose given their failure to produce characteristic signs or symptoms. Forty percent of the lesions in this series were asymptomatic and were discovered incidentally on an imaging study. Even when CT and ultrasound are used, the differential diagnosis of a cystic lesion in the abdomen is extensive. In patients whose lesions were not biopsied preoperatively, lymphangioma was not entertained as a likely diagnosis. Another series of lymphangioma cases reported that, after imaging studies, the diagnosis of lymphangioma was suspected in less than 25% of cases.[5]

The treatment of choice is complete resection, if possible (including involved loops of bowel and/or solid organs), yielding a cure for this benign lesion. However, a subtotal resection can yield disease-free survival. In cases of infected lymphangioma, the patient should be stabilized if possible with supportive treatment and antibiotics before resection. Although no recurrence was observed in this small series; recurrence of cystic lymphangiomas have been reported at rates of 0% to 27% for complete resection and 10% to 100% for incomplete resection.[26] Alternatives to surgery for unresectable disease have been cited in the recent literature. These include the percutaneous administration of ablative injected agents such as alcohol[27,28] and OK432.[29]

In conclusion, abdominal lymphangiomas are rare tumors that present a difficult diagnostic challenge. In adults, these lesions are predominant in whites and females, and the correct diagnosis often remains elusive until tissue is obtained. CT and ultrasound imaging are useful in the diagnosis of a cystic mass; however, narrowing the differential can be difficult.

Table 2. Treatment, outcomes, and follow-up

Patient	Surgery	Outcome	Length of follow-up	Adjuvant therapy
1	98% excision, liver biopsy	No evidence of recurrence*	7.5 yr	None
2	Complete resection	No evidence of recurrence	3.75 yr	None
3	Complete resection	No evidence of recurrence	3 yr	None
4	Complete resection, SB reaction	No evidence of recurrence	6 mo	None
5	Complete resection	No evidence of recurrence	3.85 yr	None
6	Distal pancreatectomy, Roux-en-Y	No evidence of recurrence	18 yr	None

SB = small bowel.
*Unable to contact patient directly.

The treatment of choice is complete surgical resection, which provides an excellent prognosis.

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Laparoscopic Strategies for Resection of Insulinomas

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Sporadic insulinomas are suitable for the laparoscopic approach because they are solitary, resectable, and not metastatic. Laparoscopy and laparoscopic ultrasonography (LapUS) can identify lesions that are undetectable by preoperative imaging techniques. However, it is still worthwhile to attempt preoperative imaging by endoscopic ultrasonography to provide useful information for patient positioning and port placement. Laparoscopic pancreatic resection and laparoscopic enucleation are feasible and safe techniques. Conversion to the open approach should be considered for tumors that cannot be identified accurately by LapUS. In patients with insulinomas in the setting of multiple endocrine neoplasia 1, the laparoscopic approach is slightly different. Laparoscopic subtotal distal pancreatectomy preserving the spleen combined with laparoscopic enucleation of any tumors identified in the pancreatic head should be the standard operation. The advantages of laparoscopic pancreatic procedures should be those of all laparoscopic procedures, which obviously reduce the parietal damage in the abdomen. This may be associated with reductions in postoperative pain and hospital stay and an earlier return to previous activity. A cosmetic advantage is also clear because of the absence of long abdominal incision, and this should be taken into account, especially in young women. (J GASTROINTEST SURG 2006;10:752–760)

KEY WORDS: Laparoscopic enucleation, laparoscopic resection, laparoscopic sporadic insulinoma, laparoscopic MEN 1 insulinoma

Sporadic insulinomas are suitable for the laparoscopic approach because they are solitary, resectable, and not metastatic. The size of the tumor is variable, but many are small, being 1–2 cm in diameter. Only occasionally (10%) are they multicentric. However, when insulinomas are multiple, multiple endocrine neoplasia Type I (MEN-I) should be suspected.

Once the diagnosis of an insulinoma has been confirmed from serum glucose and insulin levels, most surgeons prefer that the localization studies be performed. Detection rates of transabdominal US and CT are lower than 50%–60%. However, spiral CT and magnetic resonance imaging have improved this sensitivity considerably. Endoscopic ultrasonography seems to be more sensitive with preoperative detection rates of 86%–93%.[1,2]

Other surgeons will explore the pancreas, with the suspected diagnosis of an insulinoma, without knowing its exact location but by using intraoperative ultrasonography (IOUS). Ultrasonography islet cell tumors are typically hypoechoic and easy to differentiate from the surrounding pancreatic parenchyma (Fig. 1).[3] IOUS can be also used to define the relationship between the tumor and the Wirsung duct to facilitate safe resection. Laparoscopy and laparoscopic ultrasonography (LapUS) provide information similar to that obtained by means of open IOUS and can identify lesions that are undetectable by preoperative imaging techniques. However, despite the advantages of LapUS, it is still worthwhile to attempt preoperative imaging. Endoscopic ultrasonography is the most sensitive modality, as it provides useful information for patient positioning and port placement (Fig. 2).[4,5] In addition, preoperative knowledge of tumor localization helps focus IOUS localization and limits mobilization and exposure of the pancreas.

The surgical strategy in patients with solitary insulinoma should be restricted to removing the solitary tumor in about 90% of cases. Enucleation or

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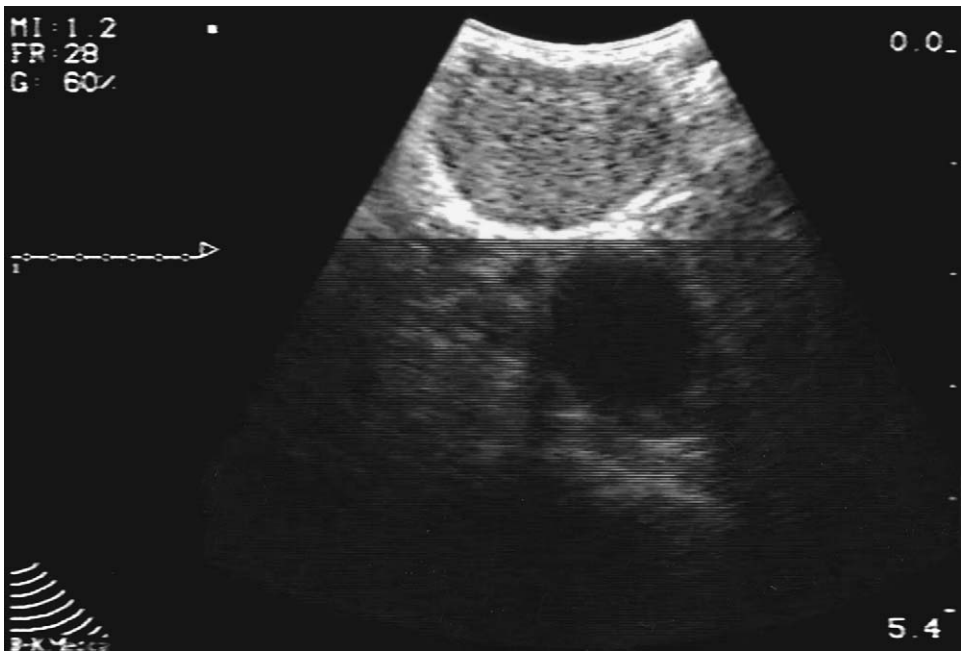

Fig. 1. Intraoperative laparoscopic ultrasonography. Hypoechoic tumor and a plane of separation from the splenic vein.

pancreas resection has been advocated to manage these tumors. The clear indications for enucleation are tumors located at the periphery of the gland and tumors on the surface of the pancreatic parenchyma totally or partially covered by a thin layer of pancreatic tissue. However, when the tumor is in close proximity to the Wirsung duct, resection should be indicated to avoid pancreatic fistula.

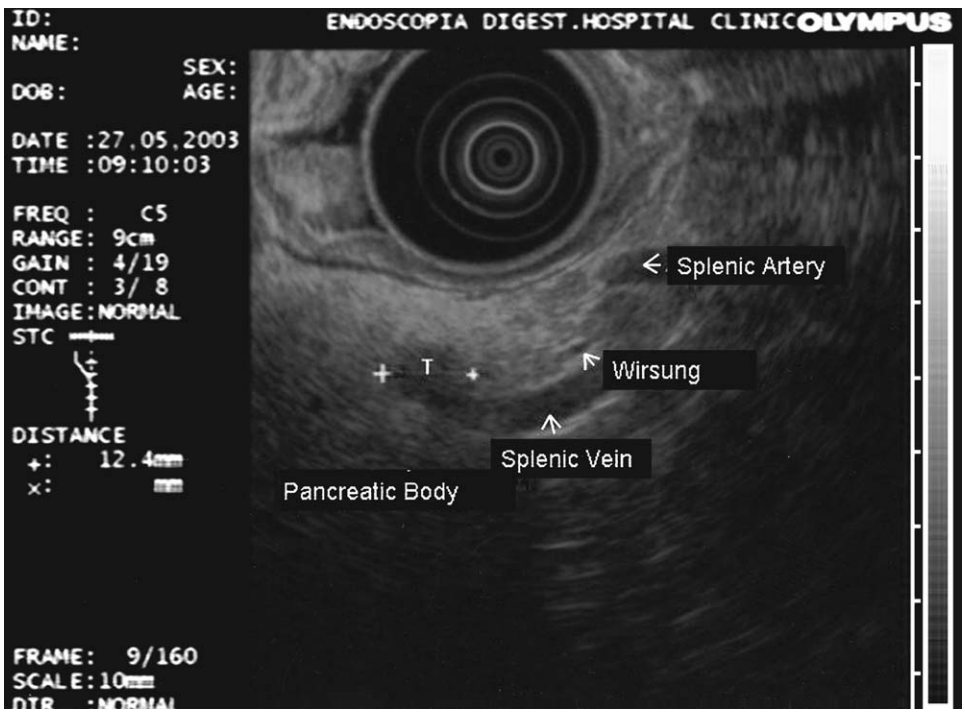

Fig. 2. Endoscopic ultrasonography showing 1 cm tumor (T) in close proximity to the splenic vein and Wirsung duct.

Multiple tumors of varying size are found in about 10 % of patients. When located in the body and tail of the pancreas, the tumors are probably better treated by distal pancreatectomy. Very rarely is a Whipple type pancreaticoduodenectomy with pyloric preservation justified for multiple tumors in the head of the pancreas or for deeply situated tumors that cannot be safely enucleated.

Patients with insulinomas associated with MEN 1 need a different surgical approach than that required for patients with sporadic insulinoma.[6] According to Gauger and Thompson,[7] the surgical approach is based on the premise that patients with MEN 1 and neuroendocrine disease of the pancreas can potentially be cured of their syndrome or nonfunctioning tumors provided the tumor has not metastasized to the liver and the operation is sufficiently extensive to excise all sites of disease. In addition, the picture of pancreatic lesions in MEN 1 is one of diffuse microadenomatosis with one or more macro tumors. In most reports, enucleation or limited resection did not result in the development of recurrent hyperinsulinism up to 15 years.[8,9] However, others reported recurrence rates of 40% at 10 years after enucleation.[6] Distal pancreatectomy with the enucleation of any tumors residing in the head of the pancreas may be offered to selected patients.

The reported success rates for laparoscopic resection of insulinomas range from 60% to 100%.[4,5,10–18] In most reports, the reason for conversion was a failure of LapUS to localize the tumor intraoperatively or the tumor location was in a difficult-to-access site. In our series, the success rate of laparoscopic resection of insulinomas was 93% (Table 1).

PATIENT POSITION AND PORT PLACEMENT

With our approach, the patient is placed in half-lateral position with the left-side up for tumors located in the body or tail of the pancreas, or with the right-side up for tumors in the head of the gland, and in the reverse Trendelenburg position. When tumors are localized in the left side of the pancreas, the surgeon and assistant stand on the left of the patient while the cameraperson and the scrub nurse stand on the opposite side. Four 10–12 mm trocars are inserted in the abdominal wall: 3–4 cm above the umbilicus, in the xiphoid area, subcostal on the midaxillary line, and in the subcostal midclavicular line. Two television monitors are used. CO2 pneumoperitoneum is used. Abdominal pressure is monitored and maintained at less than 14 mm Hg. A 300 laparoscope is used, and the liver is explored visually and with LapUS (7.5-MHz probe, 10 mm in diameter; B-K Medical, Gentolfe, Denmark).

INSULINOMA IN THE PANCREATIC HEAD

Step One: Exploration and Identification

The gastrocolic omentum on the pancreatic head is divided up to the level of the body-tail of the pancreas. The avascular attachments between the antro-pyloric region of the stomach and the anterior pancreatic head are incised. It allows a wide exposition of the anterior pancreatic head. The pancreatic head is the thickest portion of the gland, and the tumor may be embedded in this particular area of the pancreas. Detection of an insulinoma during a laparoscopic procedure depends solely on visualization or the use of LapUS. The use of LapUS is therefore essential in providing crucial information on the proximity of the tumor on the anterior or posterior wall of the head of the pancreas and on the location of the tumor at the superior or inferior margin (uncinate process) of the pancreas.

Tumor localization dictates different strategies: (1) When the tumor is localized on the superior border of the pancreatic head, the hepatic artery should be identified and separated from the margin of the pancreas. (2) When the tumor is localized on the inferior border of the pancreatic head, the superior mesenteric vein should be identified. In this location, the inferior border of the pancreatic head is widely separated from the mesenteric-portal vein axis by dividing the collateral veins (by using clips) at the entry of the mesenteric vein in the pancreatic groove. This exposure allows a complete separation, by blunt

Table 1. Laparoscopic resection of insulinomas

	Gagner et al.	Gramatioo et al.	Berends et al.	Iihara and Obaro	Fernández-Cruz et al.
No. of patients	5	9	10	7	15
Laparoscopic procedures enucleation	1	4	5	4	9
Distal pancreatectomy	3	5	1	2	5
Converted to open surgery	1	-	4	1	1
Success rate (%)	80	100	60	86	93

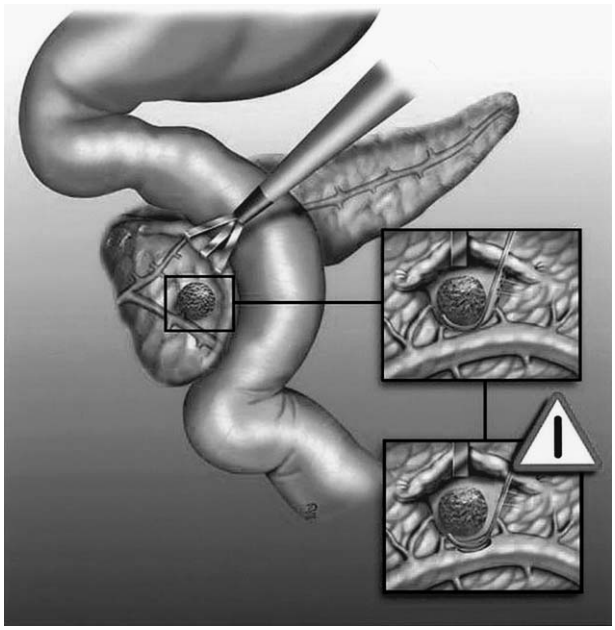

Fig. 3. Insulinoma in the posterior head of the pancreas. Adequate examination after an extensive Kocher maneuver. The dissection starts by using the cautery in the plane surrounding the tumor. It will usually appear to have a bluish coloration. The tumor is enucleated by blunt dissection, usually with the blunt end of the hook coagulator. LapUS may demonstrate the location of the duct of Wirsung, and this permits its protection during this enucleation. Bleeding is best controlled by the careful placement of clips or cautery. The danger is the injury of the Wirsung duct. Once the lesion is removed, the bed of the tumor should be carefully examined.

dissection of the mesenteric-portal axis from the pancreas, creating a tunnel behind the pancreatic neck. (3) In case of tumors localized posteriorly in the pancreatic head, the duodenum is extensively kocherized. A division of the avascular attachments between the posterior head of the pancreas and the retroperitoneum allows a wide exposition of this area. The duodenum and head of the pancreas are extensively mobilized and separated from the retroperitoneal bed and medially rotated away from the inferior vena cava and the aorta (Fig. 3).

Step Two: Resection

LapUS will define the exact location of the tumor where the incision will be made. In cases of tumors localized anteriorly or posteriorly in the pancreatic head, electrocautery with the hook coagulator will penetrate in the pancreatic parenchyma until tumor visualization. An adequate hemostasis is important, provided that LapUS may be repeated to identify the trajectory of the pancreatic duct and the proximity of the superior mesenteric vein (Fig. 3). The main danger is to injure the Wirsung duct; pancreatic fistula will result.

For tumors localized at the inferior border of the head-neck area, the plane between the pancreas and the tumor is incised by using the LigaSure device (Tyco, US Surgical Volleylab, Boulder, Co). This instrument is particularly valuable to ensure hemostasis along the lateral margins of the tumor. This dissection allows a combination of enucleation and limited resection of the pancreatic parenchyma. In all circumstances, a Jackson-Pratt drain is left on the cavity from which the tumor has been enucleated.

INSULINOMAS IN THE BODY-TAIL OF THE PANCREAS

Step One: Exploration and Identification

With the LigaSure device, the gastrocolic omentum is divided throughout its length, and the entire pancreas is widely exposed by retracting the stomach upwards. The avascular attachments between the stomach and the anterior pancreatic capsule are sectioned to allow a complete visualization of the superior margin of the pancreas. The spleno-colic ligament is divided, and the peritoneum along the inferior pancreatic margin is incised from left to right so that the body-tail of the gland can be lifted from its bed. In this region, most insulinomas are spherical, and often a portion of the neoplasm will be evident underneath the capsule of the pancreas. However, other insulinomas may be embedded in the pancreatic parenchyma. Exploration of the pancreas by using LapUS allows defining the relationship between the tumor and the Wirsung duct and the splenic vessels. The laparoscopic resection strategies will vary depending on the location of the tumor in the left pancreas.

Step Two: Resection

For tumors localized on the anterior pancreatic wall, LapUS provides information on the extension and depth of the tumor in the pancreas. Then, the capsule of the pancreas is incised with the cautery. This incision should be long enough to visualize the lateral borders of the tumor. The dissection starts in one border of the tumor to find a plane of cleavage between the capsule of the tumor and the surrounding pancreas (Fig. 4). A small pancreatic portion of the pancreas attached to the tumor is seized by a blunt grasper. Then, the tumor is lifted from its bed, facilitating the dissection on its deeper aspect. At this point, laparoscopic ultrasound may

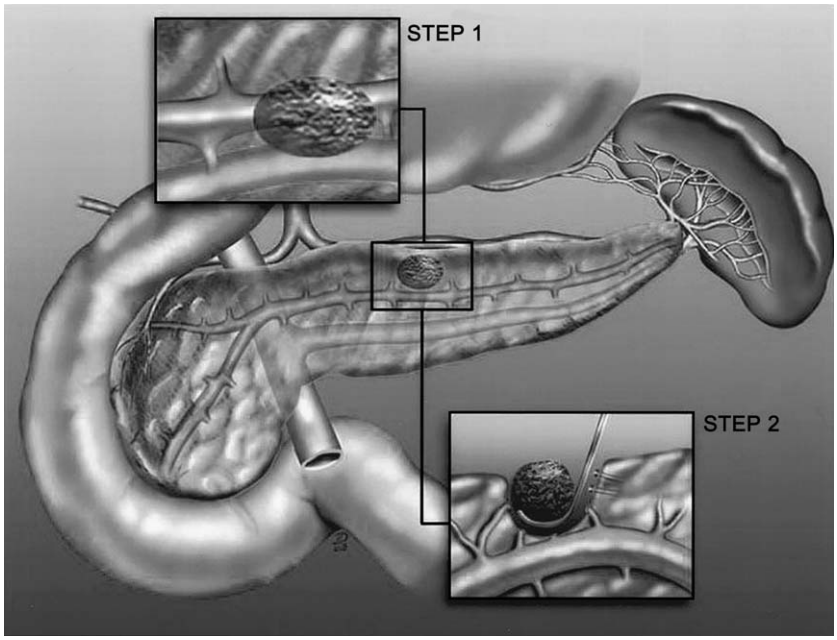

Fig. 4. Insulinoma in the body of the pancreas. An incision with the cautery is made around the area (defined by LapUS) of the adenoma. The lesion is usually shelled out with a blunt dissection, placing clips on the pancreas side and cauterizing toward the insulinoma side. The bed of the tumor should be examined to be certain there is no evidence of a major pancreatic duct injury that occurred during the dissection.

demonstrate the location of the duct of Wirsung and thus permit its protection during the enucleation. Bleeding is best controlled by cautery or clipping. Finally, tumor removal is completed by enucleation.

When the tumor is located at the inferior border of the body-tail of the pancreas, the plane between the pancreas and the tumor is opened by using the LigaSure device (Fig. 5). This bloodless mobilization of the tumor facilitates shelling out of the tumor when deep-seated in the pancreas.

When the tumor is localized posteriorly and partially covered by the splenic vein, the inferior border of the pancreas is lifted upwards allowing visualization of the splenic vein. A curve dissector is used to isolate the segment of splenic vein in close contact with the tumor; at this point, the vein is divided between 7 mm clips (two on each side; Fig. 6). The tumor is then shelled out, but care should be taken to avoid injury to the splenic artery, easily identified by its pulsation. During the dissection, great attention is needed to keep the main pancreatic duct intact. The little hollow space from which the tumor has been removed should be carefully inspected. In all circumstances, a Jackson-Pratt drain is left in the cavity.

When the tumor is localized in the tail of the pancreas, enucleation is usually not possible because of the proximity of the tumor to the Wirsung duct. A limited pancreatic resection is advisable unless the tumor is superficially visible, allowing a safe enucleation.

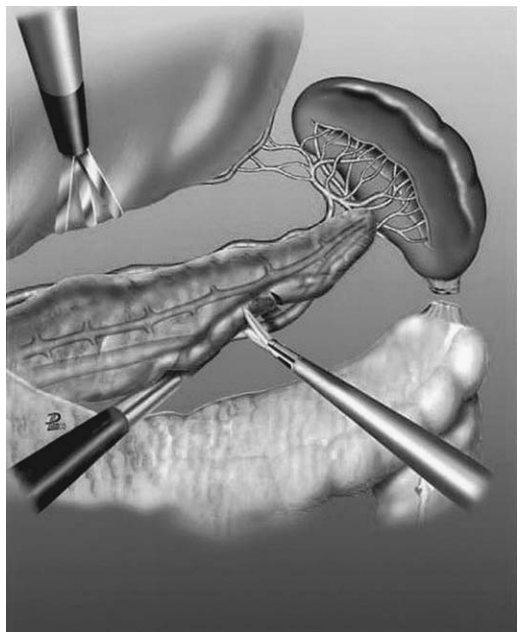

Fig. 5. A combination of small pancreatic resection and enucleation for tumors localized at the periphery of the gland.

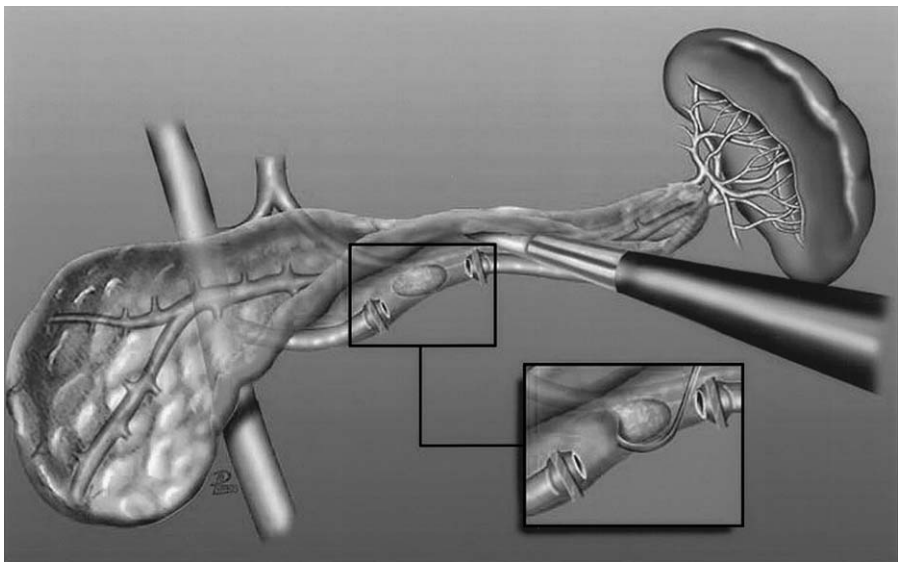

Fig. 6. Dissection of the inferior border of the pancreas and mobilization of its posterior surface. The pancreas is elevated by gentle retraction, and dissection is continued until the splenic vein is identified. The fascial layer covering the vein is divided, and the vein is separated from the pancreas; the splenic vein is divided between clips. The tumor is enucleated by blunt dissection.

INSULINOMAS IN MEN 1 PATIENTS

The surgical treatment of pancreatic insulinomas in the setting of MEN 1 is slightly different. Enucleation alone of an insulinoma in patients with MEN 1 would likely lead to missed tumors and failed operation. More than 75% of patients with insulinoma and MEN 1 had multiple tumors. During the operation, intraoperative LapUS may recognize other tumors not seen in preoperative localization studies. It seems that subtotal distal pancreatectomy,

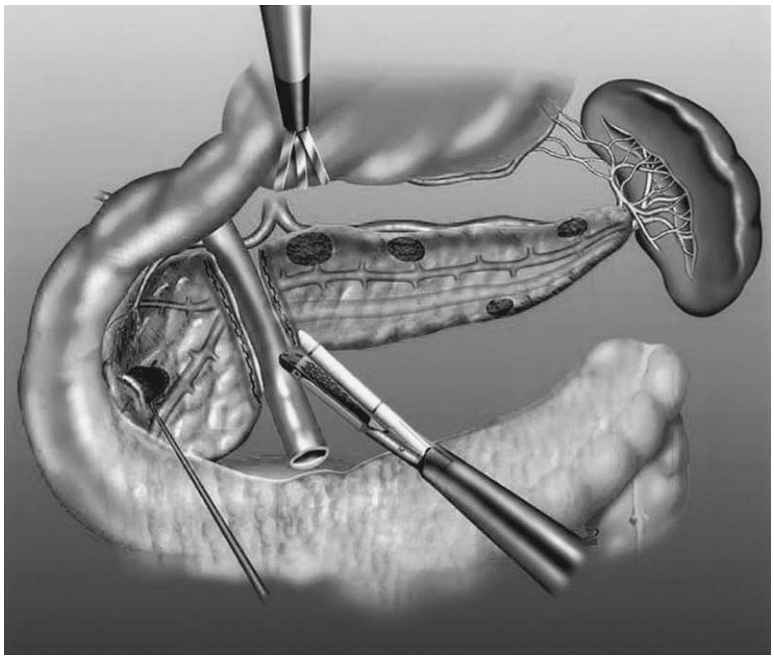

Fig. 7. Eighty percent distal pancreatic resection and insulinoma enucleation from the head of the pancreas.

preserving the spleen, combined with enucleation of any tumors identified in the pancreatic head should be the standard operation. Spleen-preserving 70%–80% distal pancreatectomy may be performed with or without splenic vessel preservation (Fig. 7). In the latter technique, it is mandatory to preserve the short gastric vessels, and if possible, the left gastroepiploic vessels.

Spleen-Preserving Distal Pancreatectomy with Splenic Vessel Preservation

The first step is to start with sectioning the lienorenal ligament and dissecting the subjacent fascia lateral to the spleen. The splenocolic ligament is divided using the LigaSure device. The splenic flexure of the colon is mobilized downward. The gastrocolic omentum is widely opened, up to the level of the mesenteric vessels, and the body-tail of the pancreas is then visualized. The anterior aspect of the pancreas is exposed by dividing the adhesions between the posterior surface of the stomach and the pancreas. Care must be taken to preserve the short gastric and the left gastroepiploic vessels. The inferior border of the pancreas is dissected and the body and tail of the pancreas are completely detached from the retroperitoneum. This mobilization of the pancreas allows us to visualize the posterior wall of the gland, where the splenic vein entering the superior mesenteric vein is easily identified. The splenic vein is pushed away from the posterior pancreatic wall with gentle blunt dissection. Visual magnification through the laparoscope permits excellent control of the small pancreatic veins, which are coagulated using the LigaSure device, the harmonic scalpel, or are clipped with titanium clips. A tunnel is created between the splenic vein–superior mesenteric vein junction and the pancreas. The splenic artery is identified through this space by using blunt careful dissection with a curve dissector. The pancreas is then transected with a 30 mm endoscopic linear stapler. Usually, two stapler applications are necessary. The body-tail of the pancreas is then grasped and retracted anteriorly with a 5 mm forceps, and traction is applied to expose the small branches of the splenic artery and vein, which are coagulated by using the LigaSure device or are clipped. The dissection is continued laterally until the splenic hilum (Fig. 8). A silicon drain is left in the pancreas bed close to the pancreatic stump.

Spleen-Preserving Distal Pancreatectomy Without Splenic Vessel Preservation

This technique follows the same surgical steps as described above, until the plane behind the neck-body of the pancreas and in front of the superior mesenteric and portal veins. At this point, the splenic

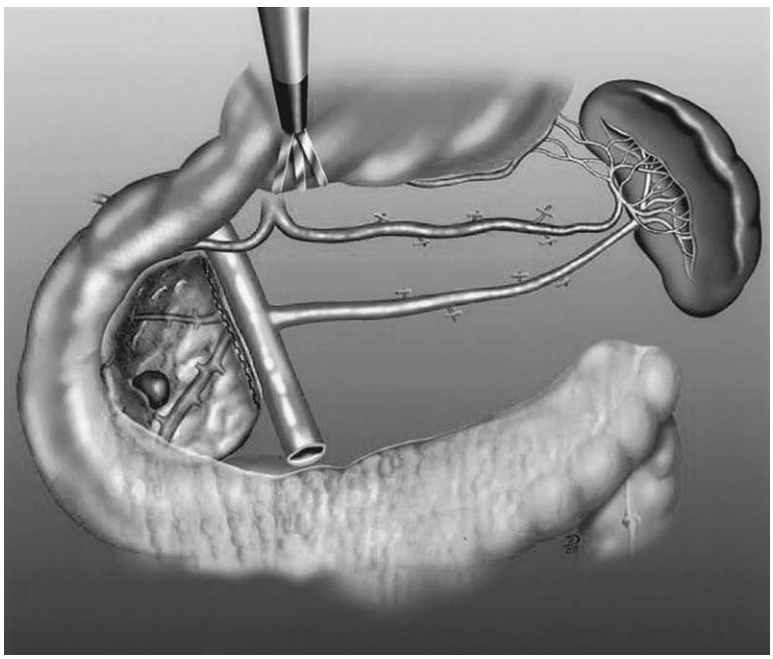

Fig. 8. Spleen-preserving distal pancreatectomy with splenic vessel preservation and insulinoma enucleation from the head of the pancreas.

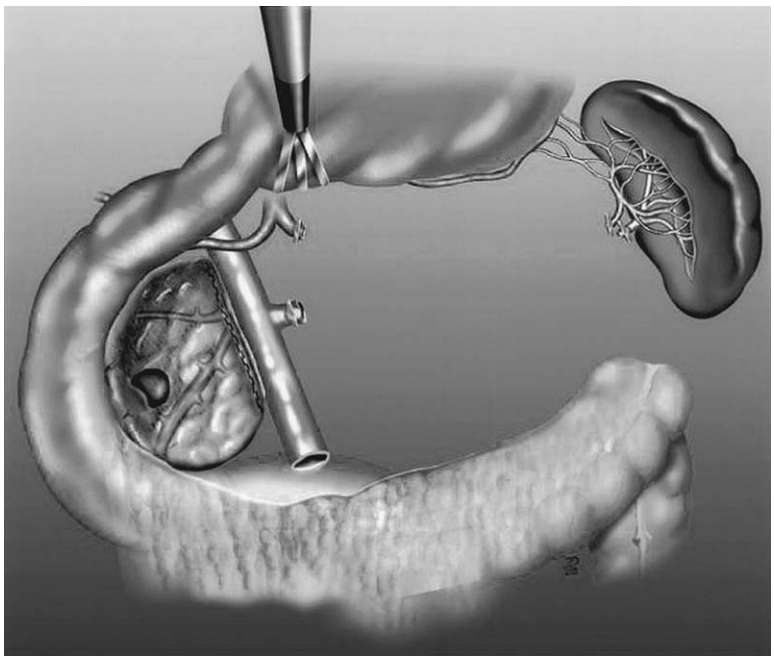

Fig. 9. Spleen-preserving distal pancreatectomy without splenic vessel preservation and insulinoma enucleation from the head of the pancreas.

vein is divided between clips. After pancreatic transection (30 mm endoscopic linear stapler), the splenic artery is divided between clips. The left pancreas is then lifted up and mobilized posteriorly with the splenic artery and vein. The latter are clipped and divided as they emerge from the pancreatic tail to enter the hilum of the spleen. The spleen is kept vascularized solely from the short gastric vessels and the left gastroepiploic vessels (Fig. 9). LapUS is mandatory to rule out a macroscopic tumor in the head of the pancreas. Enucleation, after the principles described above, should be performed for any tumors identified in the pancreatic head.

HAND-ASSISTED LAPAROSCOPIC SURGERY

Hand-assisted laparoscopic surgery (HALS) has been developing over the past 10 years. This technology permits the insertion of the hand of the surgeon or the assistant into the insufflated peritoneal cavity without loss of the positive-pressure pneumoperitoneum. However, HALS does have a number of constraints, one important—there is encroachment of the external workspace, hindering ideal positioning of the instrument ports. In our view, there are no indications for the use of HALS in the treatment of insulinomas by laparoscopic enucleation or resection.

POSTOPERATIVE CARE AND MANAGEMENT OF COMPLICATIONS

Generally, the nasogastric tube is not used, and clear liquids are allowed on postoperative day 1, and the diet is progressively advanced to low-fat soft solids. The major operative complications are pancreatitis, abscess, fistula, and pseudocyst formation. However, pancreatic fistula remains the most common serious complication of tumor resection. The concentration of amylase in the drainage is measured from day 1. The drain is removed on day 5 if there is no indication of pancreatic leak. However, the closed-suction drain should be left in place in case of pancreatic fistula. Patients with low-volume pancreatic fistula (less than 200 ml per day) may be discharged to home with the drain in situ; the drain is removed at 3 weeks. Patients with high-volume pancreatic fistulas may require fasting and parenteral nutrition. Octreotide 200 U subcutaneously 3 times a day may be used to reduce the volume of pancreatic fistula.

Whenever possible, spleen-preserving distal pancreatectomy should be undertaken without sacrifice of the splenic vessels rather than with the Warshaw technique (where the vessels are resected with the specimen and the splenic circulation maintained via the short gastric vessels), because instances of both focal and massive splenic infarction have been reported after the latter technique.[5,19]

CONCLUSION

The published studies on laparoscopic resection of insulinomas indicate that this approach is feasible and safe. Laparoscopic enucleation of the adenoma is sufficient in most instances. However, when the tumor is large and near the tail of the pancreas, it is best to perform laparoscopic distal pancreatectomy with spleen salvage. When the tumor is large and involves the head of the pancreas, a Whipple procedure is safer than laparoscopic enucleation of a large, deep-seated tumor in this region. Conversion to open exploration should be considered for tumors that cannot be identified accurately or for those located close to vascular structures that prevent safe resection. It seems that the incidence of postoperative complications is similar in open surgery and laparoscopic surgery. However, the use of laparoscopic approach minimizes parietal damage, the hospital stay is relatively short, and an early return to previous activities was observed in most patients.[17,18]

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Review Article

Management of Hepatocellular Carcinoma

Janice N. Cormier, M.D., K. Tyson Thomas, M.D., Ravi S. Chari, M.D., C. Wright Pinson, M.D., M.B.A.*

Hepatocellular carcinoma (HCC) is one of the most common tumors globally, with varying prevalence based on endemic risk factors. In high-risk populations, including those with hepatitis B or C or with cirrhosis, serum α-fetoprotein (AFP) and screening ultrasound have improved detection of resectable HCC. Treatment options, including surgical resection, for patients with HCC must be selected based on the number and size of hepatic tumors, underlying hepatic function, patient condition, and available resources. An approach, which has been summarized shows the corresponding treatment choices under given clinical circumstances. For cirrhotic patients with less than three tumor nodules of a size less than 3 cm or a solitary HCC less than 5 cm, liver transplantation offers long-term survival similar to that observed in patients transplanted for nonmalignant disease. Ablative treatment using either chemical or thermal techniques provides locally effective tumor destruction. Transcatheter arterial chemoembolization (TACE) is commonly used for palliation of unresectable tumors as well as an adjunct to surgical resection, treatment of tumors before transplant, and in conjunction with other ablative therapies in a multimodality approach. Regional approaches to chemotherapy have produced more encouraging results than systemic chemotherapy, although both remain ineffective for long-term tumor control. Several newer treatment modalities are under investigation, including gene therapy, tagged antibodies, isolated perfusion, and novel radiotherapy techniques. (J GASTROINTEST SURG 2006;10:761–780)

KEY WORDS: Hepatocellular carcinoma, HCC, liver resection, liver transplantation, chemoembolization, TACE, hepatic artery infusion, cirrhosis, cryosurgery, percutaneous ethanol injection, PEI, radiofrequency ablation, RFA

BACKGROUND

Hepatocellular carcinoma (HCC) represents one of the most common malignancies globally, accounting for nearly one million new cases per year.[1] In Western populations, the incidence of HCC is low but increasing, with 2.4 cases per 100,000 diagnosed annually between 1991 and 1995.[2] This low-incidence rate, compared with China, southeast Asia, and southern Africa, is due to environmental factors related to chronic hepatitis B infection, which is the single most important cause of HCC worldwide. In the west, alcohol and hepatitis C are the major risk factors for HCC, with hepatitis B virus infections playing a secondary role. Untreated HCC has an extremely poor prognosis, with a median survival of 1–8 months[3] and a 5-year survival of around 3%.[4] HCC accounts for a mortality rate of 1.7 per 100,000 persons per year in Western populations.[2] Though considered incurable in the past, management has undergone major changes over the last two decades. Improved outcomes are in part attributable to earlier detection by using screening methods in high-risk populations, advances in imaging, more accurate patient assessment, improved surgical techniques, and innovation of regional therapies.

Treatment of HCC is multidisciplinary. The involvement of hepatologists, oncologists, radiologists,

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as well as surgeons, is necessary to provide the most up-to-date care and to ensure the best outcomes. Many therapies are available in the armamentarium for HCC, but there has been no consensus on standard of care. With the emergence of new technologies, established therapies become more or less used.

PATIENT ASSESSMENT

Screening

Patients with HCC are identified either because they have symptomatic disease prompting further evaluation or because they have known risk factors that have led to screening studies in an effort to detect HCC at an early stage. Screening for de novo disease in "at risk" patients may include measurement of tumor markers, periodic radiographic imaging, or a combination of the two. Alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA-II, also known as des-γ-carboxy prothrombin or DCP) are the two most well-studied serum markers widely used in patient screening. Although the sensitivity and specificity of serum AFP are only 39%–50% and 76%–86%, respectively,[5–7] some studies have documented increased numbers of patients with tumor detected at stages amenable to resection.[8,9] Similarly, the sensitivity of PIVKA-II, a product created by hepatocytes exposed to warfarin-type agents or with nutritional deficiency of vitamin K, has been reported to range from 24%–80%, with specificity of 90%–99% depending upon the detection modality and the cutoff value used for detection.[10,11] The best use of tumor markers may occur when two or more are used in conjunction for screening, as in the case of PIVKA-II and AFP,[11] or the combination of PIVKA-II, AFP, and the hepatoma-specific band of gamma glutamyl transferase[12] where sensitivity reaches 66% and 88%, respectively.

The application of imaging modalities for screening is limited by cost, availability of imaging, and threshold for tumor detection. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography have all been applied to screening, with variable results.[13–16] Ultrasound is more user dependent but less expensive and more widely available than either of the other two modalities. Over the last decade, AFP and routine use of transabdominal ultrasound have become the most used method for early detection of HCC, although the cost-effectiveness of these approaches is debatable.[17] Some investigators have suggested that regular screening improves survival by detecting smaller lesions (less than 2 cm), with a 5-year survival of more than 62% compared with the 30% 5-year survival in patients with larger lesions. In populations at high risk for HCC, it has been shown that 30%–50% of patients can be diagnosed with resectable HCC[18,19]; this represents a doubling over an unscreened population. Others argue the improved outcomes in patients identified with early-stage tumors result only from lead-time bias, and that the real efficacy of screening has yet to be determined.[20]

Treatment Selection

The treatment approach for patients with HCC has evolved into a complex task that incorporates information regarding tumor extent, the severity of underlying hepatic dysfunction (because 80%–90% of patients with HCC have cirrhosis), the general medical condition of the patient, and available resources. Specific tumor considerations include size, number and distribution of nodules, and local anatomic conditions such as vascular and bile duct relationships. If resection is considered, the position of the lesion is important in determining the amount of liver tissue to be sacrificed as well as the volume of remaining functional parenchyma.

To help select patients for appropriate treatments, current diagnostic imaging aids in detection of extensive intrahepatic disease, vascular involvement, underlying cirrhosis, and extrahepatic metastases. High-resolution triple-phase CT, CT angioportography, and MRI with or without MR angiography all provide sensitive and often complimentary data. However, difficulty still exists in recognizing very small (less than 1 cm) tumors that might be amenable to therapy. Extrahepatic disease, including regional periportal lymph nodes as well as distant metastases, must be excluded. Positron emission tomography with 18-fluorodeoxyglucose has been useful in the evaluation and clinical decision-making at our institution, as it allows for identification of extrahepatic disease and effects patient treatment strategy in up to 30% of encounters.[21]

Laparoscopy with intraoperative ultrasound is useful in patients with HCC and uncertain imaging studies. Montorsi et al.[22] used laparoscopy and laparoscopic ultrasound to evaluate 70 patients with radiographic studies suspicious for HCC. Five of the patients (7%) were identified with lesions other than HCC. Previously suspicious tumors were confirmed in 22% of patients.[22] Weitz et al.[23] used laparoscopy in 60 potentially resectable patients with HCC before performing laparotomy for hepatectomy. In their series, 14 were spared laparotomy due to upstaging at the time of laparoscopy. Laparoscopy is also useful in staging patients with advanced cirrhosis who are undergoing transplant evaluation. In one report,[24] 18 patients with

advanced cirrhosis and indeterminate staging based on radiographic studies underwent laparoscopy with intraoperative ultrasonography. Initial staging was changed in 66% of patients. An added benefit was the ability to apply laparoscopic ablative techniques at the time of laparoscopic staging.

An important factor in the evaluation of patients, especially those with cirrhosis, is the determination of hepatic reserve. Traditionally, the Child-Pugh classification has been used to approximate hepatic reserve. In general, Child A patients can be considered for resections of up to 50% of liver parenchyma, whereas Child B patients tolerate resections up to 25%. Other groups have emphasized preoperative serum bilirubin or transaminase levels in cirrhotic patients as indicators of the feasible extent of hepatic resection.[25] Makuuchi and Sano[26] advocate the use of total bilirubin in combination with presence or absence of ascites to identify potential operative candidates with the degree of resection dictated by the indocyanine green retention rate. There are recent reports relating the model of end-stage liver disease score to postoperative liver failure and other complications.

Indocyanine green is one of many compounds investigated for the functional assessment of hepatic reserve.[27–29] As an anionic dye, indocyanine green is cleared rapidly by hepatocytes and excreted in unconjugated bile. The clearance of indocyanine green from the bloodstream predicts the risk of postoperative liver insufficiency. The amount of indocyanine green remaining in the bloodstream of a patient with a normal liver at 15 minutes after its injection should be less than 10%.[30] A value of 15%–20% suggests that a two-segment resection will be tolerated, 21%–30% suggests a single segment or wedge resection will be tolerated, and a value greater than 40% indicates that liver failure will probably occur even with a minimal resection.[31] Opting for a nonanatomic resection in patients with more severe liver dysfunction has the benefit of lower perioperative morbidity and mortality when compared with formal anatomic resections, but likely at the expense of reduced long-term survival.[32]

The galactose elimination capacity described by Redaelli et al.[33] is based on the fact that galactose metabolism occurs via the rate-limiting phosphorylation by galactokinase, an enzyme located only in hepatocytes. A galactose elimination capacity of less than 4 mg/min/kg in patients with HCC predicted postoperative complications with a 100% specificity and 52% sensitivity, as well as overall worse survival. Kokudo and colleagues[34] have used a combination of the Child-Pugh score with another functional assay, the asialoglycoprotein receptor quantity, to evaluate cirrhotic patients. This test is based upon technetium 99m-labeled asialoglycoprotein analog combining with a hepatocyte surface glycoprotein and provides a very sensitive surrogate marker of hepatocyte function.

Staging

Staging for HCC has changed over the last two decades as new prognostic factors have been identified through retrospective studies. Current staging systems fall into two broad categories—clinical and pathological. American Joint Committee on Cancer Tumor-Node-Metastasis (AJCC TNM) pathologic staging is the most widely used system, though it depends upon data derived after resection and is not applicable to patients who undergo treatment other than resection.[35] Because of the difficulty of applying pathology-based systems to patients before treatment, many clinical staging systems have been developed.

The Okuda system, described in 1985, segregates patients by tumor size, presence of ascites, and biochemical studies including albumin and bilirubin levels.[3] An alternative system was devised in 1998 by the Cancer of the Liver Italian Program Investigators, which incorporates Child-Pugh stage, tumor morphology, AFP levels, and presence of portal vein thrombosis. An aggregate score from 0–6 is then calculated.[36] This system has been validated in numerous populations and allows for staging of patients without the need for tissue. The Japan Integrated Staging Score from the Cancer Study Group of Japan is another attempt to refine staging for more accurate estimates of survival.[37] It combines Child-Pugh staging with a modified version of TNM staging to create a score from 0–5. Both of these systems add a component of functional capacity by using easily measured variables from laboratory or imaging studies.

The most widely used staging system for HCC is the AJCC TNM staging system (see Table 1).[38] This system classifies patients based on tumor size, number of tumors, vascular invasion, regional node status, and distant metastases. Although it fits with the tumor/node/metastasis pattern of staging used for many other cancers, the TNM system has been criticized as unnecessarily complex[39] and requires tissue for adequate staging.

The diversity of staging systems is often confusing and complicates the ever-expanding literature on treatments of HCC. In a consensus report of the American Hepato-Pancreato-Biliary Association, Henderson et al.[40] recommended the use of the Cancer of the Liver Italian Program system for clinical staging and the AJCC system when pathological specimens were available. This would ease

Table 1. American Joint Committee on Cancer (AJCC) staging system for hepatocellular carcinoma (HCC)[38]

T:	Primary
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors, none > 5 cm
T3	Multiple tumors > 5 cm or tumor involving major branch or portal or hepatic vein
T4	Tumor with direct invasion of adjacent organs other than gallbladder or with perforation or visceral peritoneum
N:	Regional lymph nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Regional lymph node metastasis
M:	Distant metastasis
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Staging:	
Stage I	T1N0M0
Stage II	T2N0M0
Stage IIIA	T3N0M0
Stage IIIB	T4N0M0
Stage IIIC	Any T, N1M0
Stage IV	Any T, any N, M1

communication and reliable comparisons of patient outcomes in the medical literature.

CURRENT TREATMENT OPTIONS

Surgical Resection

A good treatment option for HCC is R0 surgical resection, especially where screening programs identify a significant number of patients with small, asymptomatic lesions. In Western practices, only 15%–30% of patients with HCC are operative candidates due to advanced or multifocal hepatic disease, extrahepatic metastases, or inadequate functional hepatic reserve.[41,42] Of those explored, only 50%–70% will undergo resection. Technical advances including a broader knowledge of segmental anatomy, vascular occlusion techniques, and intraoperative ultrasound have facilitated tumor resections. Intraoperative ultrasound is now commonly used to define tumor size and relationship to major vascular and biliary structures to achieve an adequate tumor margin. Recently, three-dimensional image analysis techniques have become available that estimate liver volumes, perfusion territory, and detailed intrahepatic anatomy that very closely resembles the actual pathologic findings found intraoperatively This can generate an appropriate tactical approach in cases with difficult anatomy and advanced disease to provide adequate margins of resection, either avoidance of large structures or calculation of the volume affected by the watershed, as well as the expected volume of the liver remnant.

Survival data after resection of HCC vary depending on the selection criteria and patient population studied. The results after resection from several recent studies are shown in Table 2. Grazi et al.[43] reviewed the outcomes of 408 patients with cirrhosis and HCC who underwent resection between 1983 and 1998. Operative mortality rates decreased from 9% to 1% in 157 patients who underwent HCC resection after 1992; they attribute these results to better operative techniques and postoperative care. These results are reinforced by recent studies of hepatic resections, where mortality rates range from 0%–8%.

Despite a decrease in operative mortality over the last two decades, the overall survival after resection of HCC has changed little. The most significant reasons for poor overall survival after resection are tumor recurrence and poor liver function. Many analyses have identified prognostic factors for disease recurrence and survival. Tumor at the resection margin[44]; presence of cirrhosis[45]; vascular invasion[46]; absence of a tumor capsule, preresection serum AFP level greater than 10,000 ng/ml, poor preoperative performance status, and advanced tumor grade[47]; number of nodules, microvascular portal vein thrombosis and preoperative AST greater than twice normal,[48] preoperative transcatheter arterial chemoembolization (TACE)[49]; and large volume intraoperative transfusion[50] have all been identified retrospectively as poor predictors of disease-free survival and patient survival. In patients who do not have any of these negative prognostic indicators (solitary lesions less than 5 cm without vascular invasion and a negative surgical margin of more than 1 cm), the 5-year survival rate after resection has been reported[46,51,52] to be as high as 78%. Adjuvant intra-arterial injection of 131-iodine labeled lipiodol is a positive predictor of outcome as it has been shown in one study of French patients with HCC to significantly decrease tumor recurrence rates after curative hepatic resection in a retrospective case-control study.[53]

As an adjunct to liver resection in patients with evidence of decreased hepatic reserve where tumor is confined to one side of the liver, portal vein embolization (PVE) with a variety of agents has been used to induce hypertrophy in the other lobe.[54] A prospective nonrandomized trial in 55 patients with primary or secondary tumors of the right lobe of the liver compared outcomes in patients who underwent

Table 2. Survival rates after resection of HCC in recent studies Overall survival/disease - free survival when available

Author	Yr	N	Operative mortality (%)	1 yr* (%)	3 yr* (%)	5 yr* (%)	8 yr* (%)	10 yr* (%)
De Carlis et al.[173]	2003	154	5	NR	NR	47/NR	NR	28/NR
Daniele et al.[174]	2003	17	NR	82/NR	63/NR	NR	NR	NR
Ercolani et al.[48]	2003	224	NR	83/70	63/43	43/27	NR	NR
Sim and ooi[175]	2003	81	5	79/59	59/30	NR	NR	NR
Wei et al.[176]	2003	155	8	NR	NR	NR	NR	NR
Kanematsu et al.[177]	2002	303	2	84/75	67/41	51/27	NR	20/11
Regimbeau et al.[178] Limited	2002	34	6	NR	NR	35/26	6/0	NR
Regimbeau et al.[178] Anatomic	2002	30	7	NR	NR	54/45	45/21	NR
Poon et al. [179] (Milan criteria)	2002	135	4	90/74	76/50	70/36	NR	35/22
Grazi et al.[43] Pre–1992	2001	107	9	NR	53/49	32/28	NR	NR
Grazi et al.[43] Post–1992	2001	157	1	NR	72/49	49/28	NR	NR
Zhou et al.[180] < 5 cm	2001	1000	2	91/NR	77/NR	65/NR	NR	46/NR
Zhou et al.[180] > 5 cm	2001	1366	4	76/NR	48/NR	37/NR	NR	29/NR
Hanazaki et al.[49]	2000	386	4	NR	51/37	34/23	NR	11/8
Buell et al.[181]	2000	26	0	75/NR	60/NR	38/NR	NR	NR

*NR = not recorded.

right hepatectomy with or without preoperative PVE.[55] In patients with Child A cirrhosis that underwent resection, PVE-induced hypertrophy of future liver remnant volumes in 86% of patients was associated with a significantly lower incidence of complications and led to decreased length of stay compared with those without PVE.

Despite earlier detection, safer operations, and more aggressive treatment of HCC, disease recurrence is likely. The liver is the most common site of tumor recurrence as a result of either multicentric carcinogenesis or intrahepatic metastases derived from primary HCC. Nearly 10% of patients with recurrent tumor undergo repeat resection. Repeat surgical resection provides good long-term benefits in appropriately selected patients; a poor prognostic indicator for these patients is tumor recurrence within 12 months of the first resection.[52,56]

Transplantation

In the past, liver transplantation was performed for patients with HCC who were not candidates for curative resection due to tumor size and/or inadequate hepatic reserve. This approach resulted in high rates of early tumor recurrence. However, it was recognized in this early transplant experience that subsets of patients with small tumors (often those with incidental tumors) and those with the fibrolamellar variant could potentially benefit from transplantation with success rates similar to those in patients transplanted for nonmalignant disease.

Liver transplantation is the only treatment that ensures complete removal of all hepatic foci of tumor as well as tissue with high oncogenic potential for tumor recurrence. Until 1990, the survival rates for patients undergoing liver transplantation for HCC ranged from 15%–35% at 5 years and were strikingly different from patients transplanted for other reasons.[57–60] Bismuth et al.[60] demonstrated that subpopulations of patients with less than 3 tumor nodules, of a size smaller than 3 cm, and no tumor thrombus in the portal vein derived more benefit from transplantation. The Milan criteria described by Mazzaferro et al.[61] cited 4-year survival rates of 85% and disease-free survival of 92% when transplant criteria consisted of either one tumor less than 5 cm or $\leqslant$3 tumors with none larger than 3 cm.

In addition to tumor size and number, survival outcomes may also be defined by other prognostic factors. Iwatsuki and Starzl[62] found that patients who received orthotopic liver transplant for HCC faired no better than those that received resection unless the HCC patients had concomitant cirrhosis.

In multivariate analyses from a retrospective study of 125 patients with HCC, Philosophe et al.[63] reported that hepatitis B virus (+) status was predictive of recurrent HCC after transplantation. This finding was supported by Hemming et al.,[64] who also demonstrated the prognostic importance of vascular invasion. Molmenti and Klintmalm[65] reported data collected from the International Tumor Registry on 790 patients transplanted for HCC. There was significantly higher survival probability for patients with incidentally discovered tumors, no vascular invasion, negative nodes, tumor size ⩽5 cm, and better histologic grade.

The United Network for Organ Sharing currently follows the Milan criteria and allocates organs based on the model of the end-stage liver disease scoring system,[66] but several groups have described the success of transplantation in patients who are outside these criteria. Marsh and colleagues[67] studied factors predictive of recurrence in 307 patients who underwent liver transplantation for HCC from 1981 to 1997. Their analysis showed that the current TNM classification system neither correlated with tumor-free survival nor showed homogeneity in outcomes of patients within the same pTNM category. Yao et al.[68] advocated expanding transplant criteria to a single tumor less than 6.5 cm or ⩽3 tumors with the largest no greater than 4.5 cm and total tumor diameter of ⩽8 cm, because this group of patients showed 1- and 5-year survival rates of 90% and 72.5%.[69] A summary of survival outcomes after transplantation is provided in Table 3, *A– C* .

To help mitigate the shortage of suitable organs for patients with HCC and to help expand indications, transplantation using split-liver cadaveric or adult living donors is becoming more common. Kaihara and colleagues[70] describe 56 patients with HCC that underwent living related right lobe liver transplantation, with an overall survival of 73% at 1 year and 55% at 3 years. An important finding was 15 of 20 patients outside the Milan criteria were alive and disease free at follow-up.

Improved long-term survival in patients undergoing transplantation is aided by improving immunosuppression.[71] Neoadjuvant or adjuvant chemotherapy protocols have improved survival for some patients[72–74] Carr et al.[72] reported a series of patients with advanced HCC who first underwent at least three cycles of intra-arterial chemotherapy before liver transplantation. At 1 year, the survival rate was 91% in the treated groups compared with 43% in those not receiving chemotherapy. Graziadei et al.[75] routinely treated HCC patients with neoadjuvant TACE while on the waiting list. Their 1- and 5-year survival rates for 41 patients transplanted based on Milan criteria were 98% and 93%, respectively, with tumor recurrence in only one patient (2%). TACE was also used to downstage 15 of 36 patients with advanced stage HCC; 10 of those 15 underwent liver transplantation with subsequent 1- and 4-year survival rates of 82% and 41%, respectively. Roayaie et al.[76] studied the effects of preoperative TACE and adjuvant chemotherapy in 80

Table 3A. Survival rates after liver transplantation for HCC based onstage[58,59]

	1 yr	2 yr	3 yr	5 yr
Overall (n = 105)	66%	49%	39%	36%
State I	75%	75%	75%	75%
State II	80%	70%	60%	60%
State III	60%	40%	40%	40%
State IVA	50%	30%	15%	10%

Table 3B. Survival rates after liver transplantation for HCC based on T classification[39]

Group	N	Median survival (mo)	5-yr survival (%)
T1	44	58	50
T2	178	68	56
T3	201	35	31
T4	108	16	21

Table 3C. Survival rates after liver transplantation for HCC based on current common transplantation criteria

Name	Criteria	N	1 yr (%)	5 yr (%)
Milan[61,†]	Within	35	—	85*
	Outside	13	—	50*
UCSF[69,‡]	Within	60	90	75
	Outside	10	50	—
CLIP[182,§]	0	62	92	67
	1	65	80	17
	2	48	52	0
	3	45	37	0
	4	27	4	0
	5	7	0	0
	6	3	0	0
Okuda[182,‖]	1	132	82	35
	2	111	36	0
	3	14	14	0

*4 year survival rate.
†Milan: single tumor <5 cm or ⩽3 tumor nodules all <3 cm.
‡UCSF: single tumor nodule < 6.5 cm or ⩽3 tumor nodules all < 4.5 cm and total diameter < 8 cm.
§CLIP: points based on aggregate score determined by Child-Pugh class, tumor morphology, AFP level, and macrovasular invasion.
‖Okuda: based on number of following present: tumor size ⩾ 50%, ascites, albumin ⩽ 30 g/L bilirubin ⩾ 3 mg%.

patients with HCC greater than 5 cm diameter. Patients received subselective arterial chemoembolization before transplant, followed by intraoperative doxorubicin and systemic doxorubicin postoperatively. An overall survival rate of 44% at 55 months was observed in the 43 patients that proceeded to transplantation; 40% of the patients undergoing transplantation had no evidence of disease recurrence at last follow-up.

Thermal Ablation

Radiofrequency ablation. Because resection is not possible in the majority of patients with HCC because of poor hepatic reserve or comorbid conditions, other less physiologically demanding therapies have been developed to control hepatic tumors. These ablative therapies can also be used in conjunction with resection for secondary, smaller, distant tumors. Radiofrequency ablation (RFA) involves the delivery of energy created by radiofrequency waves to tumors by means of ultrasound-guided electrodes. This energy induces thermal damage with coagulative necrosis of the tumor. The electrodes are insulated along all but the distal portion of the shaft and can be introduced into the tumor at celiotomy or by image-guided laparoscopic or percutaneous techniques. Preliminary studies with radiofrequency-based ablation indicate that this procedure is safe in patients with compensated cirrhosis and small HCC. A 10-minute application of RF thermoablation has been shown to result in complete necrosis of a 3 cm tumor.[77]

Numerous studies compare outcomes with RFA to other previously established therapies for HCC. In a prospective randomized study of 86 patients with compensated cirrhosis and small HCC, RFA was superior to percutaneous ethanol injection (PEI) in terms of complete tumor necrosis (90% vs. 80%) and number of required treatments (1.2 vs. 4.8 sessions) but caused more complications (10% vs. 0%).[78] Pearson et al.[79] compared RFA to cryoablation in 146 patients, 41 with HCC. They determined that treatment-related complications, including one death, were higher (41% compared with 3%) in the group receiving cryoablation, and a recurrence rate with cryoablation of 22% compared with 3% for RFA. These findings were mirrored by a retrospective review of 64 French patients, 36 of whom were diagnosed with HCC.[80] There was a nonsignificant trend toward higher recurrence rates in patients with HCC treated with cryoablation (38% vs. 17% with RFA).

The utility of RFA becomes limited as tumor size increases. It has traditionally been advocated in treatment of tumors less than 3 cm. However, several studies describe techniques by which this method can be employed in treatment of larger tumors with similar results. Hansler et al.[81] used a saline perfusion device to elicit a complete response in 85% of patients with a mean tumor size of 3.1 cm, including 8 with tumors between 3 and 4.5 cm. Technological advances, including increasing larger arrays are theoretically able to handle increasing larger lesions satisfactorily, but data are sparse. Yamakado et al.[82] used TACE before RFA. The rationale was that elimination of blood flow increased the volume of thermal ablation. They treated 108 tumors in 64 patients within 2 weeks of chemoembolization. Complete necrosis was achieved in all tumors, including 43 greater than 3 cm (3.1–12 cm). No local recurrences were detected in 97 tumors less than 5 cm and only 2 of 11 tumors greater than 5cm. Temporary venous occlusion during RFA was used in 10 consecutive tumors measuring greater than 35 mm or located adjacent to large vessels in patients with either metastases to the liver or HCC.[83] These authors report a larger zone of coagulative necrosis and complete necrosis in 90% of tumors when compared with patients undergoing RFA alone. Yamasaki et al.[84] report a retrospective review of 31 patients with 42 HCC lesions less than 4 cm in greatest dimension. There were no differences in number of treatments, duration of treatments, or needle insertions between the 12 patients treated with balloon occlusion and RFA compared with the 19 patients treated by RFA alone. However, they also reported a larger area of coagulative necrosis (37 mm $\times$ 30 mm) in patients treated with RFA during temporary balloon occlusion. Together, these data suggest that lesions between 3 and 5 cm may be amenable to RFA if lesions are located away from large vessels or temporary blood flow is halted by either TACE or balloon occlusion.

Cryosurgical ablation. Cryosurgical techniques have been used as an adjunct to secure adequate tumor margins or as an alternative to surgical resection in patients with limited hepatic reserve or with multiple, bilobar, or recurrent primary liver tumors. Cryosurgery is based on the principle that rapid freezing and thawing of tissue causes cell death. Under the guidance of intraoperative ultrasound, a probe with recirculating liquid nitrogen is placed in the tumor and two or more freeze/thaw cycles are initiated. The zone of destruction is monitored until the leading edge of the ice ball is 1.0 cm beyond the margin of the tumor. The advantage of cryosurgery is that single or multiple tumors can be treated locally without resection of surrounding liver parenchyma in patients with marginal hepatic reserve. The most serious, though relatively uncommon,

complication of cryotherapy is the development of cryoshock syndrome (1% of patients), characterized by disseminated intravascular coagulation and multiorgan failure. Hemorrhage from cracking of the liver, renal dysfunction, biliary disruption with bile leakage, and acute respiratory distress syndrome are seen occasionally as well.[85]

Table 4 reports the outcomes of cryoablation for HCC in recent major series. Zhou et al.[86] reported 167 patients with HCC treated by cryosurgery, with an overall 5-year survival rate of 32%. Patients with small, solitary tumors had a 48% 5-year survival rate. Wren et al.[87] showed cryosurgery was more beneficial when the aim was curative as opposed to palliative. Clavien et al.[88] performed a prospective study focusing on complications and outcomes in 15 patients treated with TACE before cryosurgery who had cirrhosis and unresectable HCC. Complications occurred in 4 of 15 patients, including one death. However, the 5-year actuarial survival was 79% with only three recurrences after a median follow-up period of 2.5 years. Cryoablation seems to be progressively less favored for ablative treatment due to the need for laparotomy and the comparatively increased incidence of complications.

Chemical Ablative Therapy

Percutaneous interstitial treatments under ultrasound guidance are effective in achieving palliation and tumor reduction. Ethyl alcohol (ethanol), acetic acid, hot saline, and chemotherapeutic agents have been used with differing degrees of success. PEI remains a very popular option and the best studied of the chemical ablative techniques. It causes sclerosis and extensive necrosis of tumor cells and thrombosis of tumor vessels. Advantages of PEI over other forms of ablative therapy include the relative ease in regards to outpatient administration, the inexpensive costs compared with other techniques, the lack of special technological equipment other than CT or ultrasound for guidance, and the large number of tumors that may be treated with minimal morbidity at any given session. Disadvantages of this treatment have included difficulty in monitoring completeness of a treatment session, requirement for multiple sessions, and limitations of treating tumors larger than 3 cm.

Several studies have demonstrated complete coagulative necrosis in up to 75% of lesions treated by PEI, with 68%–80% survival at 3 years after initiation of therapy depending upon the size and number of tumors.[89,90] Table 5 reviews the results of percutaneous ablative techniques cited in the recent literature. In a review of 746 patients with HCC and cirrhosis, PEI treatment was associated with a 3- and 5-year survival rate of 68% and 40%, respectively, when tumor nodules were single and $\leqslant$3 cm. That survival data declined as tumor size or number of nodules increased.[91]

PEI is more successful for small, encapsulated, hypovascular tumors that can trap injected ethanol. In patients with well-compensated cirrhosis, larger tumors (greater than 5 cm) can also be treated with PEI but require larger volumes of ethanol and general anesthesia.[92] Several studies have described techniques whereby PEI can be used in larger tumors with satisfactory results. Tanaka et al.[93] first described a combination of TACE and PEI to treat patients with solitary HCC lesions greater than 3 cm. Together, the complete response rate was 83% compared with 20% with TACE alone. This was followed by a randomized, controlled study by Bartolozzi et al.[94] that confirmed a higher complete response, longer survival, and decreased tumor recurrence in the arm of patients treated with both PEI and TACE. The 5- and 7-year survival rates for these patients has been reported to be 35% and 14%, respectively, with stage of cirrhosis and size of largest lesion identified as independent risk factors for survival.[95]

In a large multicenter study of PEI use in patients with cirrhosis and HCC less than 5 cm, the 5-year

Table 4. Cryosurgery for treatment of HCC in recent series

Study	Yr	N	Child class (n)	Morbidity/ mortality	1 yr survival (%)	3 yr survival (%)	5 yr survival (%)	Other treatments
Adam et al.[80]	2002	18	A 7 B 6 C 3 None 2	NR	66			TACE and/or resection
Clavien et al.[88]	2002	15	A 11 B 4	27/7	93	79	79	TACE
Wren et al.[87]	1997	12	A 7 B 4 C 1	8/0				
Zhou et all.[183]	1988	27	NR	0/0	33	13	4	TACE, HA ligation

TACE = Transcatheter arterial chemoebolization; HA = hepatic artery; NR = not recorded.

Table 5. Use of pecutaneous chemical ablation for treatment of HCC in recent series

Study	Year	N	Child class (n)	M/m	1 yr survival (%)	3 yr survival (%)	5 yr survival (%)	Other treatments
Leugn et al.[99]	2003	51	A 13 B 38	NR	79	14	NR	Use of cis-epi gel for palliation
Gournay et al.[97]	2002	55	A 37 B 8 NC 10	38/2	⩽30 mm: 88/DF: 82 >30 mm: 73/DF: 45	70/DF: 38 34/DF: 5	44/DF: 15 17/DF: 5	Compared PEI to resection
Koda et al.[184]	2001	PEI: 26 TACE/PEI: 26	A 14 B 8 A 19 B 5	0/0 0/8	91 100	66 81	38 40	All patients with 1–3 tumors, <3 cm
Lencioni et al.[185]	1998	86	A 48 B 38	0/0	92	69	47	TACE then PEI for tumors > 3 cm
Tanaka et al.[95]	1998	83	A 48 B/C 35	0/0	100 100	82 48	46 21	TACE followed with PEI
Ohnishi et al.[98]	1998	PEI: 29 PAI: 31	A 21/B 8 A 26/B 5	NR	PEI: 82, DF: 59 PAI: 100, DF: 83	NR	NR	None
Bartolozzi et al.[94]	1995	26	A 14 B 12	0/0	100 DF : 85	72 DF : 52	NR	TACE followed by PEI
Livraghi et al.[91]	1995	462 (ONE TUMOR, <5 CM)	A 293 B 149 C 20	NR	A : 98 B : 93 C : 64	A : 79 B : 63 C : 0	A = 47 B : 29 C : 0	Also compared by stage and tumor number
Horiguchi et al.[186]	1994	10 (<1.5 cm) 6 (1.5–3 cm)	NR	NR	<1.5 cm: 90 1.5–3 cm: 82	NR	NR	Compared PEI to resection or TACE

NR = not recorded; TACE = transcatheter arterial chemoembolization; DF = disease-free survival; M = mortality; m= morbidity; Cis-ept– cisplatin-epinephrine injectable gel; PEI = percutaneous ethanol injection; PAI = percutaneous acetic acid injection.

survival of patients with Child A cirrhosis (n = 293) was 47% compared with 29% for patients with Child B cirrhosis (n = 149) and 0% for patients with Child C cirrhosis (n = 20).[91] Life expectancy of Child A patients with a small tumor treated by PEI appeared to be as good as that of similar patients treated with hepatic resection.[96] In fact, Gournay et al.[97] found that PEI was more effective than resection in patients with HCC and a single nodule less than 3 cm in terms of cost and comfort to the patient, with no difference in survival or disease-free survival. Those differences did not translate to patients with larger tumors. In most patients that failed therapy, a second primary tumor was detected (64%–100%). PEI was associated with low risk of severe complications and mortality (0.1%). Major complications with PEI are unusual, but fever and discomfort are not uncommon. Occasionally, peritoneal hemorrhage or hemobilia, biliary sclerosis, or major liver infarction may occur.

Acetic acid has also been used as an agent in percutaneous therapy for HCC. It offers the advantage of better tissue penetration and possibly higher rates of complete response. In a randomized, controlled trial, Ohnishi et al.[98] compared 31 patients treated with percutaneous acetic acid injection to 29 patients treated with PEI. They found that all original tumors were treated successfully with both agents. However, only 8% of tumors treated with percutaneous acetic acid injection recur compared with 37% with PEI. In addition, the 1- and 2-year survival rates were significantly better with percutaneous acetic acid injection (100% and 92%, respectively, compared with 83% and 63%, respectively).

Yet another option for percutaneous treatment of HCC is injection of active chemotherapeutic agents into the tumor. In the past, this technique had not proven successful due to rapid drug diffusion into surrounding normal parenchyma and the systemic circulation. Recent attempts to minimize this limitation have met with some success. Leung et al.[99] described results in 58 patients treated with a gel-based cisplatin-epinephrine mixture. They found 53% of patients responded with either partial or complete response, but median survival was only 27 months, with 3-year survival rates of 14%.

Chemotherapeutic Approaches

Transcatheter arterial chemoembolization. TACE can be used before resection to improve resectability, before transplantation to maintain curability while awaiting a graft, in conjunction with other methods of ablation, or alone as a palliative measure. TACE provides a means of achieving regionally elevated levels of chemotherapeutic agents in the liver while avoiding concomitant systemic toxicity. Concentrated chemotherapeutic agents, such as doxorubicin, cisplatin, or mitomycin C, can be delivered via angiography. Typically, gelatin foam or other inert substances are used to induce embolization that may be temporary or permanent. This serves to increase local chemotherapeutic dwell time and induce tumor ischemia. In addition, lipiodol, an ethiodized poppy seed oil that selectively remains in tumors for long periods may enhance the antitumor effect.

Chemoembolization can be applied to one major branch of the hepatic artery or selectively to individual hepatic segments. TACE takes advantage of relatively selective tumor arterial vascularization. HCC tumors derive approximately 80%–85% of their blood supply from the hepatic artery; normal hepatic parenchyma has a dual blood supply with 80%–85% supplied by the portal vein and the remainder from the hepatic artery.

Relative contraindications of TACE include thrombosis of the portal vein, renal failure, extrahepatic metastases, or advanced liver dysfunction. Child class A and B patients tolerate the procedure well, but mortality rates as high as 40% have been reported in patients with Child class C cirrhosis treated with TACE.[100] TACE has been shown to be of little use in patients with diffusely infiltrating or multifocal tumors.[101]

A decrease in tumor size has been noted in 16%–61% of patients treated with TACE, though the duration of response is variable.[102] The best outcomes with TACE have been observed in patients with encapsulated tumors, small tumors, solitary lesions, and with repeated treatments. Overall results with TACE in Western and Eastern studies, however, have been difficult to interpret, partly due to patient selection and the intent to treat for cure versus palliation. Median survivals, subgroups, and statistical analysis of the predominant series are presented in Table 6, divided according to type of study design. The outcomes in patients with unresectable HCC from prospective randomized trials are mixed with two studies[103,104] showing no improvement in overall survival and two studies suggesting higher survival rates.[105,106]

There is widespread debate about the applicability and validity of these trials.[107,108] Pelletier et al.[103] reported in 1990 a decreased median survival to 4 months in 21 patients receiving TACE compared with a 6-month median survival in patients receiving supportive care only. This is the only study in the Western literature that reports a decreased survival with TACE for patients with HCC. The Group d'Etude et de Traitement du Carcinome Hepatocellulaire[104] reported in 1995 their results with 50 patients undergoing TACE in 24 institutions. Although no

Table 6. TACE for HCC

Author	Yr	Therapy	N	Median survival (mo)	*P*
Prospective randomized					
Pelletier et al.[103]	1990	Dox + gel	21	4	NS
		Supportive care	21	6	
French Study Group.[104]	1995	Cis + lip + gel	50	19	NS
		Supportive care	46	8	
Pelletier et al.[187]	1998	Cis + lip + gel + tamoxifen	37	13	NS
		Tamoxifen	36	12	
Llovet et al.[105]	2002	Dox + lip + gel	40	29	0.009
		Supportive care	35	18	
Lo et al.[106]	2002	Cis + lip + gel	40	12	0.002
		Supportive care	40	6	
Retrospective, matched historical controls					
Vetter et al.[109]	1991	Dox + lip + gel	30	12	<0.001
		Supportive care	30	3	
Bronowicki et al.[110]	1994	Dox, cis, or epi + lip + gel	127	18	<0.0001
		Supportive care	127	5	
Stefanini et al.[111]	1995	Dox + lip + gel	69	21	<0.001
		Supportive care	64	3	
Retrospective, Non matched controls					
Bronowicki et al.[112]	1996	Dox, cis, or epi + lip + gel	42	36	<0.0001
		Supportive care	33	11	
Stuart et al.[113]	1996	Dox + lip + gel	137	14	<0.01
		Supportive care	81	2	
Marcos-Alvarez et al.[114]	1996	Dox + lip + gel	30	13	<0.05
		Supportive care	22	5	
Ryder et al.[115]	1996	Dox + lip + gel	67	9	N/A
		Non surgical therapy	118	3	
Rose et al.[119]	1999	Dox + lip + gel	35	9	<0.0001
		Supportive care	31	3	

Dox = doxorubicin; Cis = cisplatin; epi = epirubicin; lip = lipiodol; gel = gelatin-foam particles or power; NS = not significant; N/A = not applicable.

statistically significant difference was noted in survival when compared with supportive care only, median survivals were increased from 8 to 19 months, and the estimated relative risk of death was 1.4 in the conservatively managed group compared with the chemoembolization group. Llovet et al.[105] used TACE as palliative treatment in a prospective, randomized controlled trial published in 2002 on 112 patients with intermediate stage HCC not felt to be candidates for other therapies. The patients were allocated between an embolization only group, a chemoembolization group, and a supportive care only group. A significant increase in survival for the chemoembolization group was observed when compared with controls (82% and 63%, 1- and 2-year survival, respectively, compared with 63% and 27%). In a study of 80 Asian patients also published in 2002, Lo et al.[106] found that chemoembolization resulted in a survival advantage compared with untreated controls (57% and 26%, 1- and 3-year actuarial survival rates, respectively, compared with 32% and 3%).

The remainder of the studies listed in Table 6 are retrospective, with either historically matched or nonmatched controls. Of note, all of these studies demonstrate a significant improvement in overall patient survival when compared with patients receiving supportive care only.[109–115] Examination of the median survivals of these studies shows a consistent threefold improvement in survival in those patients undergoing TACE.

Variations of TACE exist, including transcatheter arterial chemotherapy and transcatheter embolization alone. These techniques were used more widely in the past but have given way to TACE, given the findings of recent studies. The most significant study with transcatheter embolization alone was a randomized controlled trial in 80 patients conducted by Bruix et al.[116] They found that transcatheter embolization alone slowed tumor growth but did not impact the survival of patients with advanced stage HCC. Madden et al.[117] studied transcatheter chemotherapy with epidoxorubicin suspended in a lipiodal

suspension in 25 patients with advanced unresectable HCC. There was no significant difference between the treated and control groups (median survival of 48 days vs. 51 days, respectively) in terms of survival, but treated patients spent more time in the hospital and received no symptomatic improvement compared with controls.

TACE is typically well tolerated with most patients requiring only an overnight observation. Lopez et al.[118] reported an experience with TACE in unresectable hepatic malignancies and found only transient adverse side effects associated with the postembolization syndrome. Similar results were seen in the series of Rose et al.[119]; overall, we find TACE to be a safe procedure in properly selected patients. Complications of the procedure reported in one series from 1992 include cholecystitis (10%), vasculitis (14%), hepatic decompensation with ascites (14%), jaundice (12%), and renal insufficiency (13%).[100]

Investigations are underway to determine the impact of TACE in the preoperative management of patients undergoing liver resection or transplantation. In a recent report,[120] downstaging or total tumor necrosis was induced by TACE in 62% of patients and was associated with an improved disease-free survival both after liver resection and transplantation. Patients initially excluded from transplantation because of tumor size who respond favorably to TACE have been shown to have a disease-free survival after transplantation that is similar to patients with smaller tumors.

Hepatic arterial infusion chemotherapy (HAI). Given the dual blood supply of the liver, regional chemotherapy has been considered an attractive treatment option because of decreased systemic effects of chemotherapeutic agents. In fact, regional approaches to chemotherapy have produced more encouraging results than systemic chemotherapy for HCC, although these results are still far from optimistic. Several agents including doxorubicin, cisplatin, mitomycin C, floxuridine and α-interferon have produced objective responses of 30%–50% in patients with HCC.[121–125] These responses appear to be threefold greater than in patients receiving systemic therapy, and there are reports of a few month survival advantage. However, patients treated with HAI are selected for their ability to tolerate an operation and tend to have a better overall performance status than the average patient with unresectable HCC.

HAI therapy has been used to downstage unresectable tumors so that patients may undergo surgical resection. Meric et al.[126] performed a retrospective analysis on their patients initially treated with HAI. Twenty-five patients with HCC were included; four of these patients (16%) were able to undergo further treatment consisting of either surgical resection or RFA. None of these four patients showed any evidence of disease recurrence after a mean follow-up of 16 months. Clavien et al.[127] examined the effect of preoperative HAI therapy in 28 patients with unresectable liver tumors, including five patients with HCC. After a mean follow-up of 33 months, four of five patients with HCC had been downstaged to the point that resection was possible. Curative resection was achieved in three patients, and the 3-year actuarial survival was 60%, with the other two patients alive for more than 2 years after resection. Despite these findings, other treatment modalities such as TACE seem like a more pragmatic approach for downstaging.

HAI is well tolerated without the usual systemic toxicities of chemotherapy, but it is associated with an increased risk of regional toxicities such as biliary sclerosis, chemical hepatitis, and acalculous chemical cholecystitis, necessitating weekly biochemical observation. Additional complications associated with hepatic artery infusion include arterial injury, gastric or duodenal malperfusion, infection, and thrombosis of the infusion catheter or hepatic artery.

Systemic chemotherapy. Systemic chemotherapy has been widely used to treat inoperable HCC, but response rates are low (near 20%). The possible explanations include tumor heterogeneity or overexpression of a multidrug resistance gene. Of all the neoplastic agents, doxorubicin is thought to have the most potent activity. However, in the only randomized controlled trial, doxorubicin not only failed to prolong survival but also caused fatal complications due to cardiotoxicity.[128] Numerous other agents including etoposide, cisplatin, eniluracil, 5-fluorouracil, gemcitabine, and epirubicin, have been unsuccessful in producing response rates greater than 30%.[129–132] Current combination regimens based on doxorubicin or 5-fluorouracil demonstrated response rates of 20%–30%.

No single agent or combination of agents given systemically leads reproducibly to greater than 20%–25% response rates. A meta-analysis of randomized and nonrandomized controlled trials[133] showed no survival benefit to adjuvant chemotherapy after resection. Because there has been no demonstrable beneficial effect of systemic chemotherapy on survival rates, the risks of chemotherapy must be balanced against the potential gains.

Other Approaches

Hormonal and immunotherapy. The possible sex hormone dependence of HCC and the presence of tumor hormone receptors have suggested a potential for hormonal manipulation of tumor growth,

particularly by using antiestrogens. Although some of the early smaller trials suggested a survival benefit for the use of tamoxifen, several larger trials have subsequently determined that treatment with tamoxifen does not improve survival compared with placebo.[134,135] Several antiandrogens,[136] including cyproterone acetate[137] and ketoconazole,[138] have also been ineffective.

Systemic interferon therapy has a response rate of only 7%–10%.[139–141] Combinations of systemic chemotherapy[142] or intrahepatic arterial chemotherapy[143] combined with interferon had only marginal effects in patients with locally advanced disease. However, a decrease in recurrence of HCC after ablation by other methods may be possible with the use of interferon[144,145] or with polyprenoic acid.[146] Interferon therapy was shown to increase survival in a group of patients with hepatitis C virus (HCV)-induced HCC after surgical resection.[147] Additionally, eradication of HCV-RNA by use of interferon therapy may decrease the recurrence rates of HCC after curative treatment when compared with contemporaneously matched controls with continued HCV viremia.[148] Interferon therapy used in combination with granulocyte macrophage-colony stimulating factor has shown some ability to prolong survival in a select subset of patients deemed unresectable but positive for the human leukocyte antigen-DR cell marker.[149]

Newer approaches have included the use of somatostatin, a hormone with antimitotic activity. In a study of 58 patients with advanced HCC,[150] subcutaneous octreotide was shown to significantly reduce AFP and possibly increase median survival time (13 months vs. 4 months) as compared with patients receiving placebo. Several studies assessed the role of interleukin-2 (IL-2) and other cytokines as part of various chemotherapeutic regimens; all showed low response rates.[151–153] Palmieri et al.[154] recently showed that ultralow dose IL-2 was associated with a complete response in 2 of 18 patients for 35 and 46 months, and was associated with a mean overall survival of 25 months. Further studies to compare this effect in a controlled, randomized setting are needed.

Radiotherapy. The conventional method of palliative external radiotherapy for pain reduction is not effective in HCC. Proton irradiation provides good effects but is expensive and available in few medical centers. With this method, a large amount of radiation is focused on the tumor, minimizing the exposure of the surrounding liver. An analysis of 83 patients treated with proton radiotherapy showed that 19% had a complete response, 50% a partial response, and 31% no appreciable benefit. The quality of life was unaffected in most patients, and only three patients developed liver failure.[155]

Since reporting the application of conformational three-dimensional radiotherapy in pilot studies of unresectable HCC, Cheng et al.[156] have continued to modify the delivery mechanisms of radiotherapy to prevent or reduce the associated radiation-induced organ damage prone to occur with local high-dose radiation.[157] Although this technique is not widely used, further work in this field may lead to more widespread availability of radiotherapy for unresectable tumors and add at least one more option for control of locally advanced disease.

The advent of selective intra-arterial radiation therapy offers an alternative delivery of radiation that may prove useful. ^{90}Yttrium microspheres are glass-based microspheres with a mean diameter of 25 μm with a variety of dose activity from 81 mCi to 540 mCi delivered transarterially via the hepatic artery. In an excellent review of this technique, Salem et al.[158] report median survival of 23 months for 54 patients with Okuda stage I disease and 11 months for patients with Okuda stage II disease. In an earlier report by Dancey et al.,[159] 22 patients with unresectable HCC were treated with an average of 104 Gy. They report an overall 20% response rate, with a median survival of 54 weeks in nine patients with Okuda stage 1 and 11 patients with Okuda stage 2 disease.

Multimodality Approach

The vast majority of patients with HCC will not be candidates for liver resection or transplantation. The above-mentioned treatment modalities may provide temporary local control of tumors, but recurrence is common due to the high oncogenic potential of the cirrhotic liver. Though an initial treatment may prove successful, physicians must remain vigilant for disease recurrence and open to implementation of other treatment modalities as clinical circumstances change. Takano et al.[160] described this approach in the treatment of 600 patients with HCC from a single Japanese institution. Although 54% of patients were treated with initial hepatic resection, recurrence was observed in 49% of those patients, and additional treatments included reresection, TACE, PEI, and regional chemotherapy. As discussed previously, patients may be candidates for therapy such as TACE or RFA before transplantation as a means of local control while awaiting organ availability. Reresection of recurrent lesions is applicable in some patients with suitable anatomy and clinical performance, but ablation techniques are more commonly applied as the liver disease progresses.

Table 7. Treatment options for HCC

Operative risk	Liver function	Tumor extent				Applicable treatment options
		Mets	Numbers	Volume	Size	
Good	Normal function	0	Limited (≤4)	≤3/4		Resection up to trisectionectomy
Good	Child A or MELD ≤9	0	Limited	≤½		Resection up to lobectomy
Good	Child B or MELD 10–11	0	Limited	<¼		Resection up to segmentectomy
Good	Normal, Child A or B	0	Limited		<3 cm	Resection, RFA, PEI, or cryosurgery
Good	Normal, Child A or B	0	Limited		<4 cm	Resection, PEI, or cryosurgery
Good	Normal, Child A or B	0	Limited		<6 cm	Resection or cryosurgery
Good	Child A or B	0	Multiple	Extensive		Chemoembolization and/or PEI
Fair, poor	Child B or C or MELD >11	0	1 3		≤5 cm or ≤3 cm	Transplantation
Good	Child A or B	+	Any	Any	Any	Systemic chemotherapy or clinical trial
Poor	Child C	+	Any	Any	Any	Supportive care

Patient performance, liver function as assessed by Child class or MELD, and extent of tumor (shown in the first 3 columns) together influence the choice of treatment (shown in the last column). MELD = model of end-stage liver disease.

ON THE HORIZON

Gene Therapy

Advances in genetic engineering promise opportunities for novel treatments of HCC. Several strategies have been proposed including transfection of tumor cells with gene-encoded viruses or synthetic vectors. These could potentially facilitate cell suicide, enhance expression of tumor specific antigens, augment cytokine-mediated immunity, alter oncogene and tumor-suppressor activity, or enhance responsiveness to chemotherapeutic agents.[161] One such attempt at treating HCC by using gene therapy focused on the delivery of the suicide gene herpes simplex virus thymidine kinase via an HIV vector.[162] Others have focused on the induction of apoptosis using adenoviral vectors to transduct the TRAIL (tumor necrosis factor related apoptosis-inducing ligand) gene[163] to avoid the risk of hepatitis associated with soluble TRAIL.[164] Tumor necrosis in addition to active secretion of cytotoxic agents by transfected tumor cells has been reported by Tran et al.[165] in trials using plasmid encoded metalloproteinase inhibitors. Results from these studies are encouraging, but highlight the difficulty in translating this research to common practice given the variable uptake in tumor cells, potential for damage to surrounding normal hepatocytes, and application to a diversity of patients potentially with biologically different tumors. Numerous problems must be resolved before the successful clinical application of gene therapy for HCC. Key developments will include more efficient gene delivery systems with better tumor specificity and prolonged transgene expression.

Tagged Antibodies

Intrahepatic arterial infusion of ^{131}I-labeled anti-HCC monoclonal antibody (Hepama-1 mAb) has been studied as a method of cytoreduction for the treatment of unresectable HCC. In a comparison of 32 patients receiving infusion of monoclonal antibody (Hepama-1 mAb) via the hepatic artery and 33 patients treated with only intrahepatic-arterial chemotherapy, the post-treatment resection rate was 53% compared with 9%, with an overall 5-year survival rate that was significantly higher in the antibody-treated group (28% vs. 9%).[166]

Isolated Perfusion

Although systemic drug exposure is limited after HAI, hepatobiliary toxicity has prevented dose escalation. To circumvent this problem, several groups have developed techniques, both operative and percutaneous, for isolating the venous outflow of the liver to allow delivery of increased dosages of drugs while reducing systemic exposure.[167,168] Ku and colleagues[169] have developed a single catheter technique for percutaneous isolated liver chemoperfusion. A quadruple lumen-balloon catheter is used to isolate and capture total hepatic venous outflow and direct filtered blood to the right atrium to administer high-dose regional therapy. Using an intra-arterial infusion of high-dose doxorubicin in single or multiple treatments, a significant response rate of 63% was observed in 28 patients with advanced HCC. These authors recently reported their

experience with a phase II study of patients with advanced HCC by using reductive resection of tumor and locally positive nodes followed by isolated hepatic perfusion with doxorubicin. Of 25 patients enrolled in the prospective study, 22 were able to undergo hepatic perfusion, with 86% achieving some objective tumor response for an overall actuarial survival rate of 42% at 5 years.[170]

Immunotherapy

Use of the body's natural defense mechanisms for tumor destruction theoretically offers a safe, effective mechanism to induce tumor necrosis or maintain disease stability. Some researchers are attempting this feat with the use of autologous cells to battle HCC. Cytotoxic T-lymphocytes are efficient destroyers of other cell types when triggered by antigen stimulating cells. Ladhams et al.[171] are utilizing dendritic cells derived from patient sera and pulsing these cells with tumor markers derived from their own HCC tumors. They describe two patients with unresectable, untreatable disease managed in such a way; one died 3 months into treatment, whereas the other was alive over 3 years after therapy.

Conclusions

Treatment options for patients with HCC must be selected on the basis of number and size of hepatic tumors, underlying hepatic function, patient condition, and available resources. One approach is summarized in Table 7, showing the corresponding choice of treatment under given clinical circumstances. Regardless of the specific therapy, patients with well-preserved hepatic function and a single, small incidental tumor identified during screening programs have better outcomes than patients with advanced liver disease and/or large tumors. As a result of efforts in early detection, resection, transplantation, and cytoreduction with sequential resection or ablation, some patients with HCC are living longer. However, recurrence and metastasis together with decreased underlying liver function remain the major obstacles to prolonged survival.

Currently, there is no standard therapy for advanced hepatocellular carcinoma. Many options exist and a response rate has been reported with interstitial therapies such as TACE, HAI chemotherapy, and PEI. The choice of individual treatment options is largely dependent upon patient factors, facility resources, and physician experience.

Future management of HCC will, in part, rely on preventative strategies, including immunization to hepatitis B in at-risk patients as well as efforts to decrease cirrhosis of any origin. Vaccination of high-risk populations has been shown to result in a decline in the incidence of hepatitis B- related liver cancer.[172] In addition, we must continue to elucidate the genetic events leading to hepatocarcinogenesis in an effort to ultimately interrupt the cascade of events leading to hepatocellular carcinoma.

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Pneumatosis Intestinalis and Gas in the Portal Venous System

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KEY WORDS: Pneumatosis intestinalis, portal vein air, intestinal necrosis

CASE REPORT

A 65-year-old male patient with history of hepatitis C cirrhosis was admitted to the intensive care unit for treatment of *Staphylococcus aureus* pneumonia. On hospital day 5, the patient was noted to have a distended rigid abdomen. He became hemodynamically unstable, requiring the administration of large amounts of intravenous fluid to maintain his blood pressure. The patient's white blood cell count increased from a baseline of 12,000 cells/μL to 31,000 cells/μL. His serum lactate increased from 2.0 to 5.9 mmol/L. A computed tomography (CT) scan of the abdomen revealed extensive pneumatosis intestinalis (PI) (Fig. 1) and a large amount of air in the hepatic portal venous system (Fig. 2). Emergent exploratory laparotomy revealed massive necrosis of the small bowel, from the ligament of Treitz to the terminal ileum. In view of the fatal nature of the injury, no resection was performed. The patient was placed on comfort care and died 36 hours postoperatively.

DISCUSSION

Portal venous gas (PVG) in adult patients is a rare finding. Although it is sometimes benign, as has been reported after simple medical procedures such as colonoscopy or barium enema,[1] PVG usually carries an

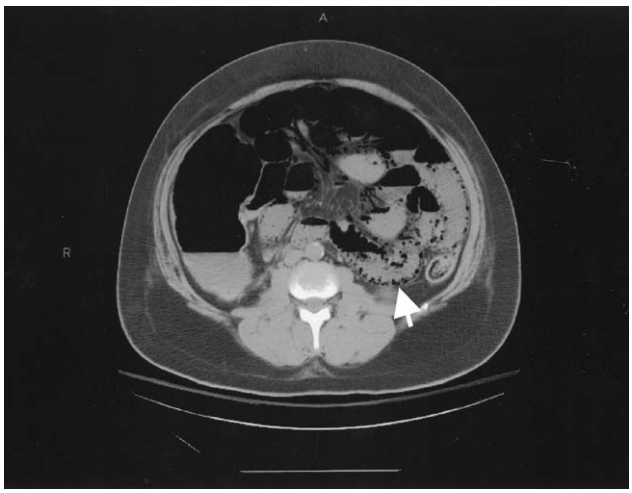

Fig. 1. Computed tomography scan demonstrating extensive pneumatosis intestinalis (*arrow*).

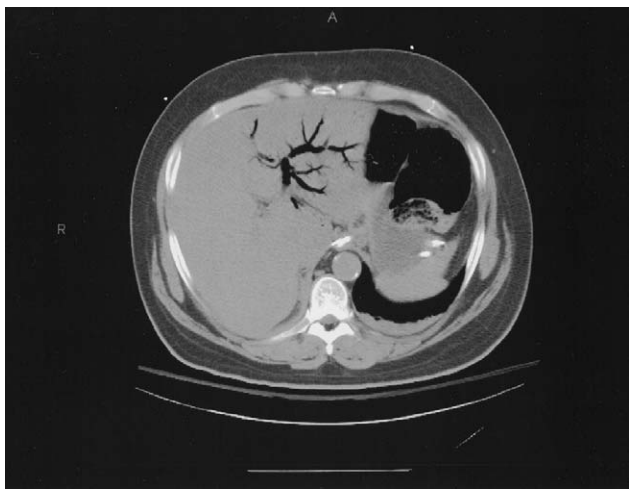

Fig. 2. Computed tomography scan demonstrating a large amount of gas in the hepatic portal venous system.

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unfavorable prognosis. The underlying etiology for PVG is most frequently intestinal ischemia, but other causes such as ulcerative colitis, Crohn's disease, and intra-abdominal abscess have been identified.[2] Regardless of the underlying etiology, the finding of PVG is associated with about 40% mortality due mainly to coexisting disease. PI is the radiologic finding of gas within the wall of the intestine. The significance of PI is largely dependent on the underlying pathologic process. Causes of PI can be traumatic (e.g., blunt trauma), mechanical (e.g., endoscopy), infectious (e.g., *Clostridium difficile*), or drug induced (e.g., cytotoxic chemotherapeutic agents). The combination of PI and portal venous gas is indicative of full-thickness bowel necrosis in about 80% of patients.[3] The CT scan of the patient in this case showed an unusually large amount of portal venous air. The etiology of bowel necrosis is usually multifactorial and can be attributed to severe peripheral vascular disease, the characteristic low-flow state that occurs in critically ill patients or with mesenteric venous thrombosis. The exact etiology in this patient was not determined, because the family refused to give consent for a postmortem examination. We believe that the most likely etiology was a low-flow state.

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Persistent Portal Venous Gas

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This case report describes a patient diagnosed with ongoing portal venous gas, initiated by a rather common *Campylobacter* enterocolitis and maintained by septic thrombophlebitis and possibly by chronic cholecystitis. Cholecystectomy attenuated the patient's septic condition. The etiology of portal venous gas determines both the patient's prognosis and the choice for either conservative or surgical treatment. This report describes persistence of portal venous gas for a long period and a possible role for chronic cholecystitis as a cause. (J GASTROINTEST SURG 2006;10:783–785)

KEY WORDS: Portal venous gas, *Campylobacter jejuni*, sepsis, cholecystectomy

CASE REPORT

A 52-year-old man was admitted to a peripheral hospital with diarrhea, spiking fever up to 40°C, and hypotension, 1 week after eating a chicken sandwich. His wife had the same complaints, although they were less severe. His medical history included hypertension, hypercholesterolemia, and a perianal abscess. Physical examination of the abdomen was unremarkable. Blood tests showed severe leukocytosis (47.8×10^9/L) and thrombopenia (38×10^9/L).

Despite antibiotic treatment the patient remained in a septic state, and developed renal failure with serum creatinine levels up to 415 μmol/L. Computed tomography (CT) 3 days after admission showed the presence of gas in the superior mesenteric vein, in the portal vein, and throughout its intrahepatic branches. Blood cultures drawn on admission grew *Staphylococcus aureus*, *Streptococcus bovis II*, and *Escherichia coli*. *Campylobacter jejuni* was cultured from his feces. Follow-up CT, taken 10 days later because of persistent fever, still showed gas in the portal vein as well as partial portal vein thrombosis, while no intra-abdominal fluid collections were seen. The diagnosis of septic thrombophlebitis was made.

Because of persistent septic episodes under appropriate antibiotic treatment, the patient was referred to our hospital 4 weeks after his first admission. A CT scan on arrival showed an increase in both portal/intrahepatic and superior mesenteric gas (Fig. 1) but no evidence of abdominal infection, bowel ischemia, or an intestinal-portal fistula. To rule out an ongoing intra-abdominal sepsis, an exploratory laparotomy was performed 6 days later. During this procedure, an infiltrated gallbladder region was seen and cholecystectomy was performed, while no further abnormalities of the abdomen were observed. Histologic examination of the gallbladder showed signs of chronic ulcerative cholecystitis and a single subserosal venule with recanalized thrombosis. Retrospective analysis of the earlier CT scans did not reveal any signs of cholecystitis.

After cholecystectomy and under continuous antibiotic treatment, the fever diminished and laboratory values normalized within the next week. Control CT scan showed a decrease of portal gas but an almost complete portal vein thrombosis. The patient recovered uneventfully and was discharged with oral anticoagulant treatment and continuous intravenous antibiotics (cefuroxim 3000 mg/24 hours) for 3 months. Follow-up ultrasound showed recanalization of the portal vein. A colonoscopy was normal.

DISCUSSION

Hepatic portal venous gas (HPVG) is a rare finding that was first described by Wolf and Evans in 1955.[1]

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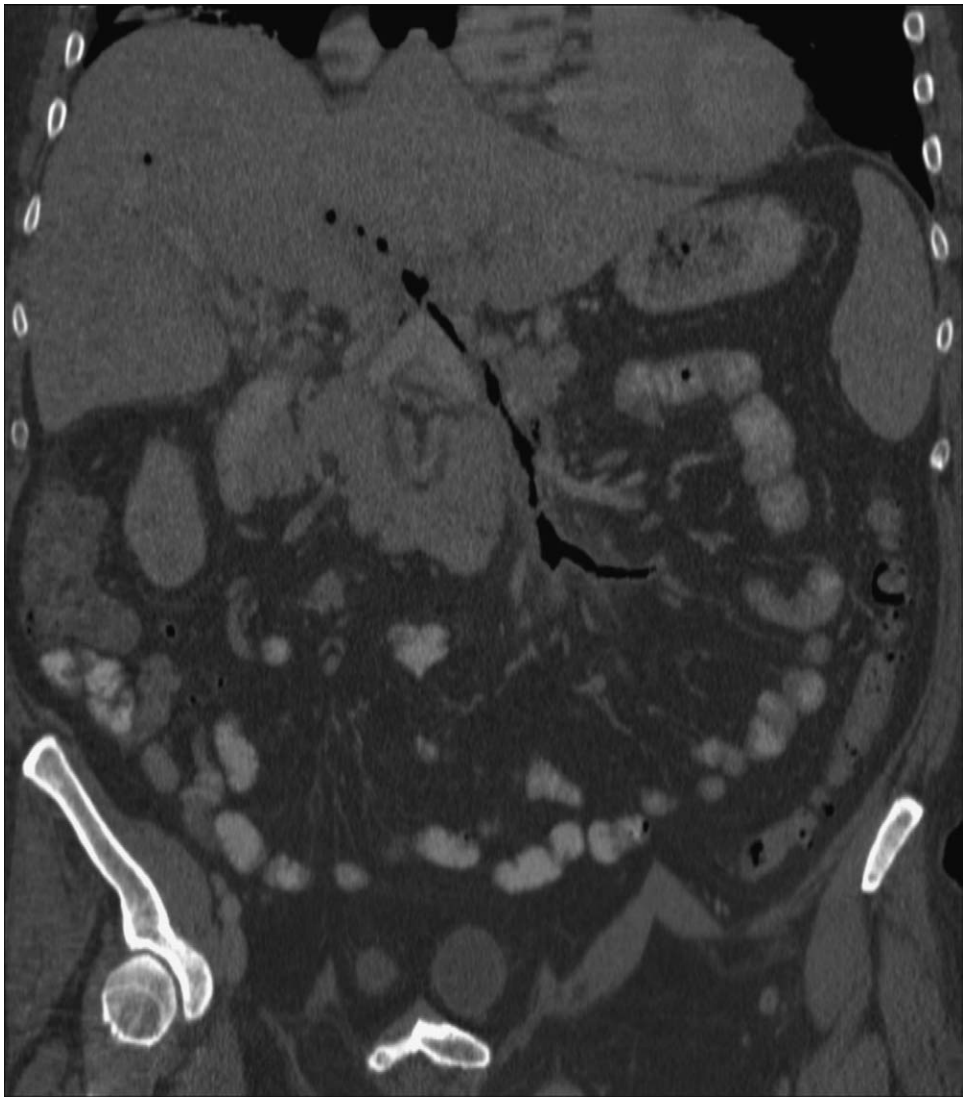

Fig. 1. Multiplanar reconstruction of abdominal computed tomography scan, showing intrahepatic, portal venous, and superior mesenteric venous gas in a 52-year-old patient with ongoing sepsis.

It most frequently originates from bowel ischemia (43%), digestive tract dilatation, or intraperitoneal abscesses.[2] Also, inflammatory bowel disease, fistulas, gastric ulcers, intraperitoneal infections or tumors, and iatrogenic causes have been described. In infants, it is associated with necrotizing enterocolitis. In association with bowel ischemia, mortality of patients in whom HPVG is found is 75%, but overall mortality is 39%.[2]

In the literature, several propositions have been made on how to deal with this finding. Some authors have suggested to use the radiologic presence of pneumatosis intestinalis as an indication for surgical intervention.[3] Others propose the use of a flow chart for the management of HPVG patients.[4] In such a chart, clinical and radiologic suspicion of bowel ischemia is the most important distinguishing factor between conservative treatment and immediate surgery. If the patient's condition does not improve under conservative treatment, surgical intervention can still be mandatory in a later stage. We followed this strategy.

This case report describes a period of at least 6 weeks in which our patient retained portal and superior mesenteric venous gas. To our knowledge, persistence of portal venous gas for such a long period has not been described before. We hypothesize retrospectively that *Campylobacter* enterocolitis initiated our patient's condition, which was maintained by portal thrombophlebitis. The chronic cholecystitis,

which most likely was secondary to the portal thrombophlebitis, might have been maintaining the fever since our patient's condition improved after cholecystectomy. A relationship between HPVG, portal vein thrombosis, and acute cholecystitis has been described before,[5,6] but until now no relation with chronic cholecystitis has been reported.

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