Review Article

Management of Rectal Cancer

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In the year 2003, an estimated 42,000 new cases of rectal cancer are predicted to occur in the United States alone.[1] Despite this alarming statistic, the age-adjusted cancer death rates from cancer of the colorectum have steadily declined over the past two decades. The reason for this improvement is a direct consequence of colorectal cancer screening, diagnostic tests, surgical technique, chemoradiation, and medical support. At the beginning of the twentieth century, therapy for rectal cancer involved perineal excision or fecal diversion to palliate symptoms of bleeding or obstruction. Miles recognized that effective treatment of rectal cancer required removal not only of the primary tumor but also of lymphatic routes of spread, and in 1908 he revolutionized the treatment of rectal cancer by introducing abdominoperineal resection (APR). Subsequently, lesser operations that spare the anal sphincter have been reintroduced with acceptable results in selected patients. In addition, more extensive operations that remove involved neighboring structures along with locally advanced tumors may now be done with a reasonable chance of long-term survival and good quality of life in some patients. During the past decade, chemotherapy and radiation have been shown to be of benefit in both adjuvant and neoadjuvant settings. In this article, an overview of current management practices for rectal cancer, with an emphasis on surgical options, is presented.

DIAGNOSIS

History and Physical Examination

Questions are asked pertaining to family history of colorectal cancer, bleeding, change in bowel habits, and weight loss. Masses are sought on abdominal and digital rectal examination. If the tumor is within the reach of the examining finger, its size, the presence of ulceration, and fixation to neighboring structures are noted. The entire large bowel is evaluated by colonoscopy or flexible sigmoidoscopy/double-contrast barium enema to exclude synchronous lesions. Tissue is sent for pathologic examination. In emergency situations such as complete colonic obstruction and/or colonic perforation, extensive diagnostic testing may delay needed surgery. In these instances the diagnosis of colorectal cancer may be made at operation. CT scans are used to identify the relationship of the primary tumor to neighboring structures and to search for metastases. For low rectal cancers, transrectal ultrasound imaging (TRUS) is done to determine depth of tumor invasion and lymphatic involvement.[2,3] Patients with tumors that show bowel wall penetration or lymph node positivity may be considered for preoperative chemoradiation therapy. Anal sphincter function is assessed by questions pertaining to fecal incontinence, physical examination and, if necessary, anal manometric evaluation.[4] Appropriate stoma sites are marked if an ostomy is a possibility.[5] The importance of colorectal cancer screening in the absence of symptoms is emphasized. Adults at average risk should begin colorectal screening at age 50 by means of (1) annual fecal occult blood test, (2) flexible sigmoidoscopy every 5 years, (3) annual fecal occult blood test plus flexible sigmoidoscopy every 5 years, (4) double-contrast barium enema every 5 years, or (5) colonoscopy every 10 years.[6]

SURGERY FOR RECTAL CANCER

The primary aim of surgery for rectal cancer is the removal of the tumor-bearing segment and all metastases. Complications from surgery should be

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minimal, and the functional result should be satisfactory. Operations may be done with ether curative or palliative intent (Table 1).

When the carcinoma together with regional lymph nodes is removed en bloc, with no known tumor remaining either locally or at distant sites, the resection is considered curative. When the tumor is resected but there is carcinoma remaining locally or at a distance, the resection is deemed palliative. A palliative operation such as laparotomy with biopsy or with fecal diversion alone is one in which the primary cancer is not removed. Local excision involves removal of the carcinoma without regional lymphadenectomy.[7] Inadequate resection will result in local cancer recurrence, a devastating complication that may produce pelvic and sciatic nerve root pain, ureteric/intestinal/lymphovascular obstruction, bleeding, foul necrotic discharge, fecal incontinence, and ultimately death. In addition to survival prospects, functional results must be taken into account. Although anastomosis of the proximal colon to the distal rectal stump is almost always preferable to colostomy, the overall result will be considered poor if the patient experiences severe incontinence after surgery because of anal sphincter dysfunction or because the reservoir function of the rectum has been lost.

Therapy is chosen that will optimize the chance for cure, minimize the possibility of local recurrence, and provide the best possible functional result. Although several pathologic factors associated with local recurrence have been identified (Table 2), these are defined after surgery. The choice of operation depends on things that can be measured with reasonable accuracy before surgery; these include tumor location, degree of local penetration for low lesions, the presence or absence of large metastases, the presence of obstruction, and anal sphincter function.

Table 1. Operations for rectal cancer

Potentially curative
Abdominoperineal resection
Anterior resection with sphincter preservation
Local procedures
Transanal excision
? Contact radiotherapy
Proctectomy with en bloc excision of involved neighboring structures
Palliative
Diversion ± resection
Cryotherapy
Fulguration

Table 2. Factors associated with increased risk of local recurrence

Measurable preoperatively
Distal location
Invasion through the bowel wall/fixation to neighboring structures
Lymph node positivity
Determined intraoperatively
Perforation iatrogenic
Determined postoperatively
Advanced stage
Poor differentiation
Positive distal margin of resection
Positive radial margin of resection
Perforation
Perineural invasion
Venous invasion

References 74, 75, 76, 77, 78, 79, 80.

OPERATIONS

Abdominoperineal Resection

Abdominoperineal resection, as described by Miles, is the standard to which other procedures are compared with regard to the cancer-specific end points of survival and local recurrence[8] (Fig. 1). The operation accounts for the possibility of lymphatic spread in all directions: upward accompanying the superior rectal vessels, lateral along the middle rectal vessels, and downward toward the inguinal nodes. It achieves the greatest possible distal margin of resection by removing the anus in continuity with the rectum. For rectal tumors the direction of lymphatic spread nearly always follows the inferior mesenteric artery to the aorta. Therefore inferior mesenteric artery ligation near or at its origin at the aorta and inferior mesenteric vein ligation near the lower border of the pancreas are done to maximize lymphatic clearance. The bowel is divided at the junction between the sigmoid and descending colon. The rectum is mobilized with its mesorectum. The fascia of Denonvillier is taken with the specimen for low anterior tumors. The entire sphincter mechanism is removed with a cuff of levator ani muscle, ischiorectal fat, and perianal skin. Rectal mobilization poses special technical problems because the rectum is encased within the narrow confines of the pelvis. Injury may occur to neighboring structures including the ureter, urethra, prostate, vagina, and presacral veins. Sexual dysfunction may occur because of injury to the urogenital nerves, prostate, and vagina. Men may experience impotence or retrograde ejaculation if the nervi erigentes are disrupted. The posterior wall of the vagina is removed in continuity with the tumor

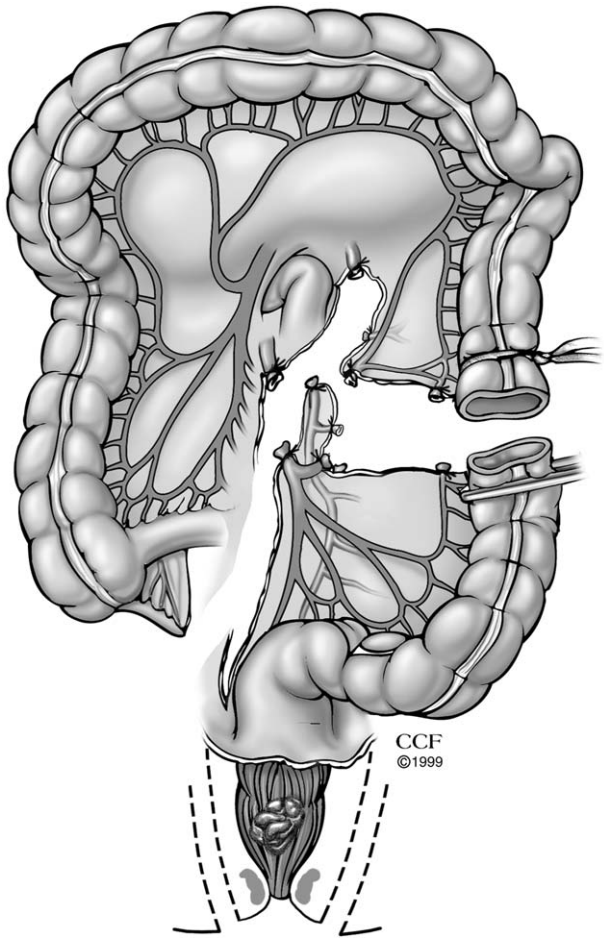

Fig. 1. Abdominoperineal resection for carcinoma of the rectum. High ligations of the inferior mesenteric artery and vein are done. The sigmoid colon, rectum, and anal sphincter are removed.

if there is invasion of that structure. In the male, invasion of the base of the bladder or prostate may require pelvic exenteration for cure. Fixation of cancer to the sacrum requires en bloc distal sacrectomy for curative resection.

Less Radical Operations

The natural desire of patients to preserve the normal route of defecation, to avoid a colostomy, and to avoid radical surgery has driven efforts to find operations of lesser magnitude than APR that will not compromise the chance for cure. Such operations are justified when the perceived risk of inadequate resection and consequent local recurrence is low.

Anterior Resection

Rectal mobilization is identical to that done for APR. However, distal to the tumor, the rectum is transected and an anastomosis is created between the descending colon and the distal rectal cuff or anus, or the distal rectum is closed as a low rectal stump (Fig. 2). This operation is permissible for two reasons: (1) lymphatic drainage is upward and (2) distal intramural spread is uncommon. The incidence and significance of distal intramural tumor spread has been examined since the 1940s. In 1943, Dukes[9] examined 1500 specimens of rectal cancer removed by APR and found distal spread in only 6.5. More recently, in 1981, Pollett and Nicholls[10] studied 334 patients who had undergone radical restorative operations for single rectal adenocarcinoma with respect to the length of rectum below the tumor and survival. They found that crude 5-year survival and cancer-specific death rates were similar whether the distal rectal length was 2 cm or less, 2 to 5 cm, or greater than 5 cm, suggesting that a margin of less than 2 cm

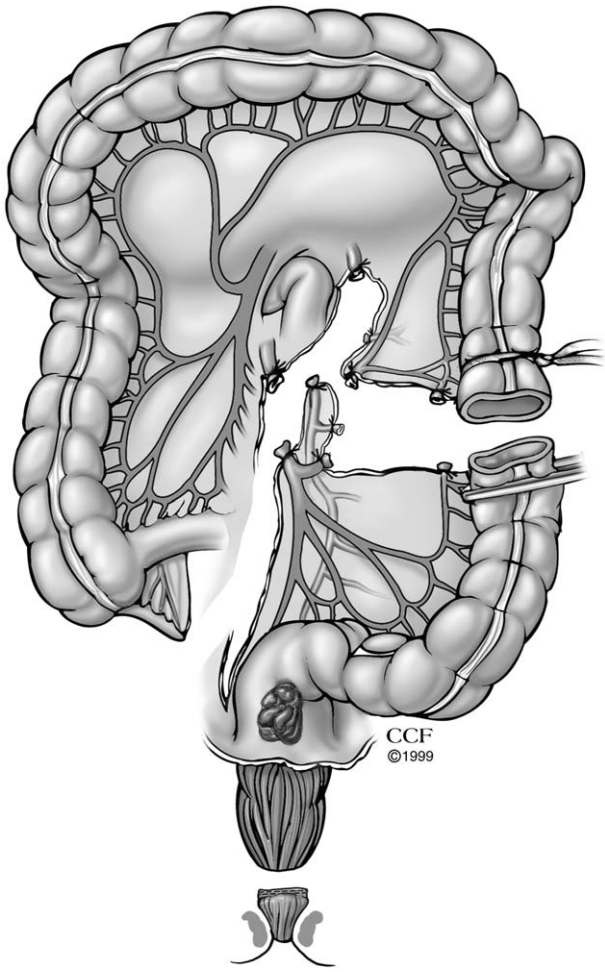

Fig. 2. Anterior resection for carcinoma of the rectum. The sigmoid colon and rectum with their lymphovascular bed are resected with at least a 2.5 cm margin of rectum distal to the tumor.

below a rectal carcinoma does not adversely affect survival or local recurrence. In 1983, Williams et al.[11] examined 50 consecutive specimens obtained from APR specimens for rectal carcinoma 5 to 10 cm from the anal verge for distal spread. No distal spread was seen in 76%; 14% had distal spread for ⩽1 cm and only 10% had spread ⩾1 cm. Each of the patients with ⩾1 cm of distal spread had a poorly differentiated Dukes' C carcinoma, and each was dying of distant metastases within 3 years of operation. These investigators also studied the results of anterior resection for carcinoma of the rectum a minimum of 5 years after operation to find out if patients with a wide distal margin (>5 cm) fared better than patients with a small margin (<5 cm). The outcome was as good in patients with the small distal margin as in those with the wide distal clearance. In 1995, Shirouzo et al.[12] examined 610 consecutive specimens of resected rectal carcinomas. Distal spread for stage I, II, III, and IV disease was 0%, 1.2%, 9.7%, and 38.8%, respectively. Most patients with distal spread had a lower survival rate and died of distant metastases rather than local recurrence, even after curative surgery.

These studies show that a distal resection margin placed at 1 cm distance from the lower edge of the tumor is tumor free in most patients. If the distal spread is greater than 1 cm, a longer resection does not necessarily improve the prognosis. At the present time, a distal margin of resection of 2.5 cm is considered adequate distal clearance for anterior resection with no compromise of survival or local clearance compared to APR. This means that most tumors 6 cm or more from the anal verge or 2 to 3 cm from the anorectal junction are suitable for restorative resection.[13,14] There is increasing evidence that surgical technique and surgeon experience affect outcome.[15]

Technical Considerations

Mesorectal Excision. In 1982, Heald et al.[16] described five cases where minute foci of adenocarcinoma were demonstrated in the mesorectum several centimeters distal to the apparent lower edge of a rectal cancer. They recommended that all cancers of the mid and low rectum be excised with the entire mesorectum and its investing fascia intact, a technique that has become known as total mesorectal excision (TME) (Fig. 3).

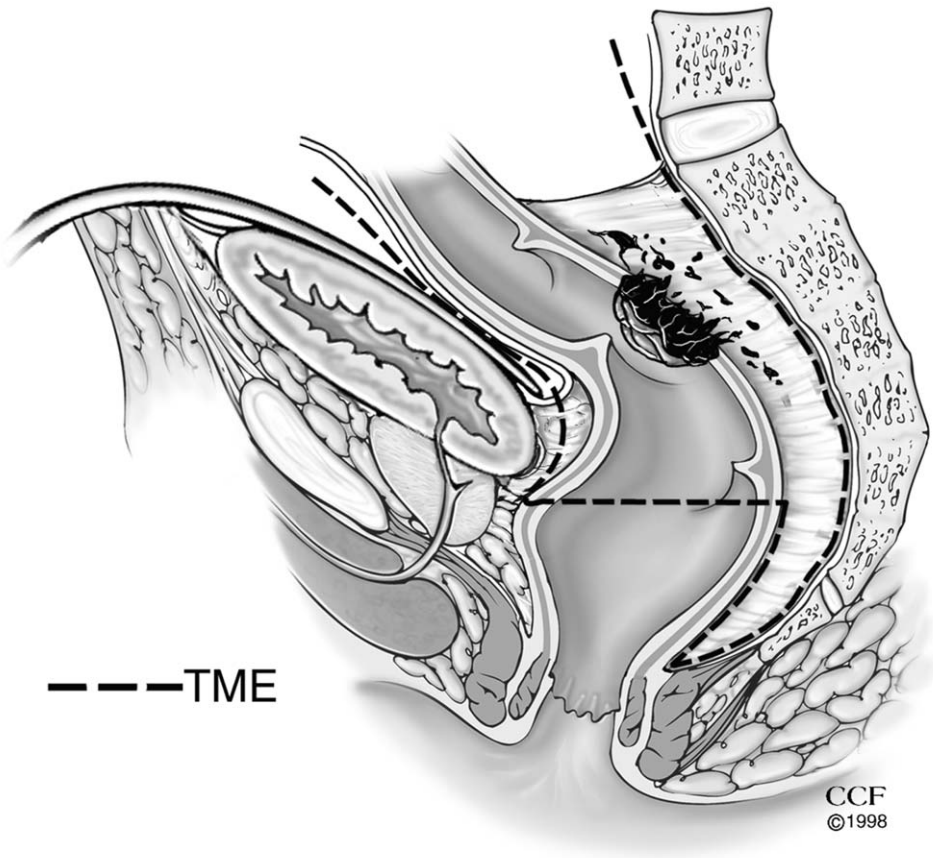

Fig. 3. Total mesorectal excision (*TME*). The entire rectal mesentery is removed with the operative specimen.

With the use of TME, local recurrence rates as low as 3.5% have been reported.[17] Therefore a strong argument can be made for adopting TME as the standard operation for mid and low rectal cancers.[18] For low rectal cancers, the problem of inadequate mesorectal excision is apt to occur deep in the pelvis when the distal rectum is cleared of pararectal tissue before division. For tumors of the upper rectum, TME is not required. A 5 cm distal margin with tumor-specific mesorectal excision results in a low rate of local recurrence and good 5-year survival.[19]

Abdominopelvic Lymph Node Dissection

Metastases occur in nodes on the lateral pelvic side wall associated with the iliac and obturator vessels. Whether extended abdominopelvic lymph node dissection confers any survival advantage was examined as early as 1960 by Deddish,[20] who described abdominopelvic dissection of lymph nodes performed in conjuction with either Miles' resection or anterior resection of the distal sigmoid and upper rectum. This procedure involved excision of lymph node–bearing tissues from the para-aortic and vena caval regions between the ureters from the duodenum down to the levator ani muscles, including the presacral, common, external and internal iliac, and obturator spaces. In a nonrandomized study, Hojo et al.[21] compared the results of conventional lymphadenectomy with those of wide pelvic lymphadenectomy. Stage for stage the cumulative 5-year survival was better among those patients who had undergone internal iliac node dissection. However, blood loss, operative time, and complications including urine voiding failure and sexual dysfunction were more pronounced in the group who underwent extended resection. Moreira et al.[22] compared 95 patients who underwent rectal resection with lateral lymph node dissection with 83 who underwent rectal resection without lateral lymph node dissection. Only 10 of the patients (11%) had lateral lymph node involvement. Local recurrence and overall 5-year survival rates were 7% and 76%, respectively, in patients undergoing extended lymphadenectomy and 16% and 72%, respectively, in those who had resection alone. Despite the tendency toward decreased local recurrence and improved survival seen in these studies, there are no randomized trials to prove or disprove the effectiveness of abdominopelvic lymph node dissection. Therefore the technique has not gained wide acceptance.

Reconstruction After Low Anterior Resection

The arterial supply to the descending colon comes from the superior mesenteric artery via the marginal artery. Ligation of the inferior mesenteric vein at the lower border of the pancreas provides adequate length for the descending colon to reach as low as the anus. Methods of reconstruction after proctectomy include anastomosis of the descending colon to the distal rectum or anus using either a straight tube of colon or a colonic reservoir (Fig. 4). Anastomosis may be done immediately or after a delay following coloanal pull-through.[23a,b] A temporary loop ileostomy generally is created when low anastomoses are used because the septic sequelae of anastomotic disruption, a relatively common complication of low colorectal anastomosis, can be life-threatening. The construction of low colorectal anastomosis has been greatly facilitated by the introduction of circular stapling devices.[24] Ultralow anastomoses are created by removal of the mucosa of the anal canal above the dentate line and suture of the colon to the anal canal.[25] Methods that employ a reservoir (colonic J-pouch/coloplasty) have been developed to overcome the 6 to 12 months needed to lessen the symptoms of frequency and urge incontinence seen after low colorectal anastomosis or straight anastomoses.[26–28] Although coloanal reconstruction may be technically feasible, it is not always the best choice. For example, a patient with disseminated disease may not live long enough to benefit from a coloanal anastomosis because of the time needed to achieve temporary ileostomy closure and the additional time needed for pouch accommodation. Predictably, a patient with a weak anal sphincter will have a poor functional result. Anorectal injury due to surgical manipulation of the anal sphincter or pelvic irradiation to the pelvic colon and anal sphincter also can cause defecation problems including incontinence and urgency.[29] Under these circumstances, resection with colostomy and low Hartmann's pouch may be the best option[30,31] (Fig. 5).

Local Therapy for Low Rectal Cancer

The optimal goal of local therapy is to cure the patient while preserving the rectum. It is attractive because it offers the opportunity to avoid major surgery. Local treatment is justified by studies that identified a subset of cancers that have a low incidence of lymphatic involvement. In 1966, Morson and Busey[32,33] examined 2084 operative specimens and found that for well-differentiated and fairly well-differentiated tumors, the chance of lymphatic metastases is low until penetration of the rectal wall has occurred. Local therapy is only appropriate for selected patients. Because of the inaccuracy of preoperative staging, most low rectal cancers still are best treated by anterior resection with complete removal of the rectum and mesorectum. Candidates for local therapy include patients who cannot withstand major curative surgery

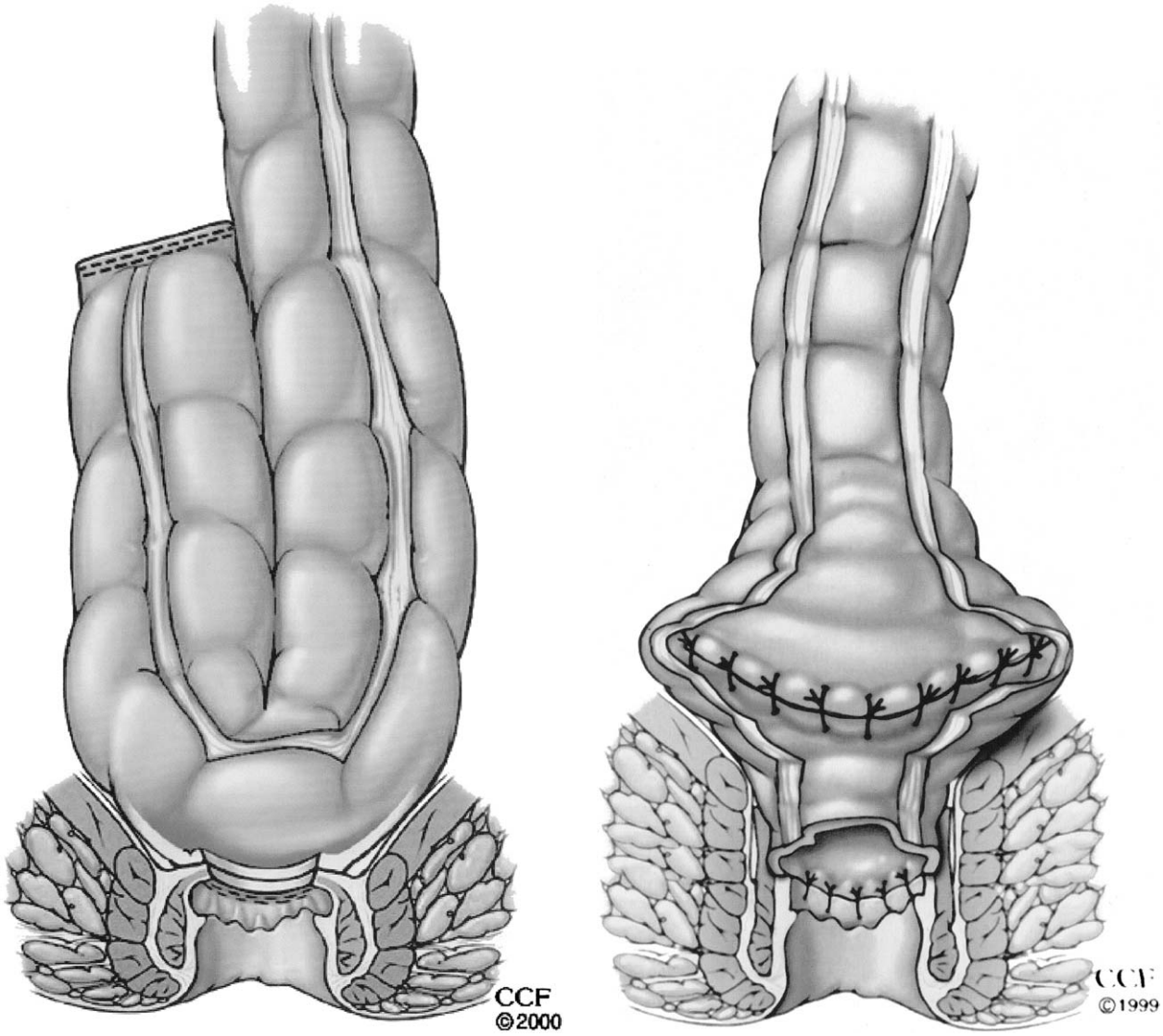

Fig. 4. Coloplasty. **Left**, Colonic J-pouch. A pouch, 5 cm in length, serves as a reservoir that improves postoperative function. **Right**, A longitudinal colostomy is made in between the taenia that is closed transversely creating a reservoir.

and those who refuse it. Techniques include local excision,[34] transanal endoscopic microsurgery,[35] electrocoagulation,[36] and contact radiotherapy.[37] Selection criteria for local therapy in the treatment of rectal cancer are presented in Table 3. From a practical standpoint, tumors suitable for local excision must be accessible, small, and perceived to be confined to the rectal wall. Patients under consideration for local therapy undergo TRUS staging. TRUS accurately predicts the depth of tumor invasion in 75% of cases and mesorectal lymph node involvement with 83% accuracy[38] (Fig. 6). Local excision of properly selected rectal cancers can provide long-term survival. Close follow-up after local excision is needed so that radical salvage surgery can be considered if recurrence is detected.[39,40] Transanal endoscopic microsurgery has increased the scope of local excision to those higher in the rectum.[41,42]

ADJUVANT THERAPY

In 1990, the National Institutes of Health Consensus Conference made recommendations for adjuvant therapy[43] for patients with colon and rectal cancer; these are presented in Table 4.[44]

The recommendations for rectal cancer are based primarily on the findings of large randomized trials

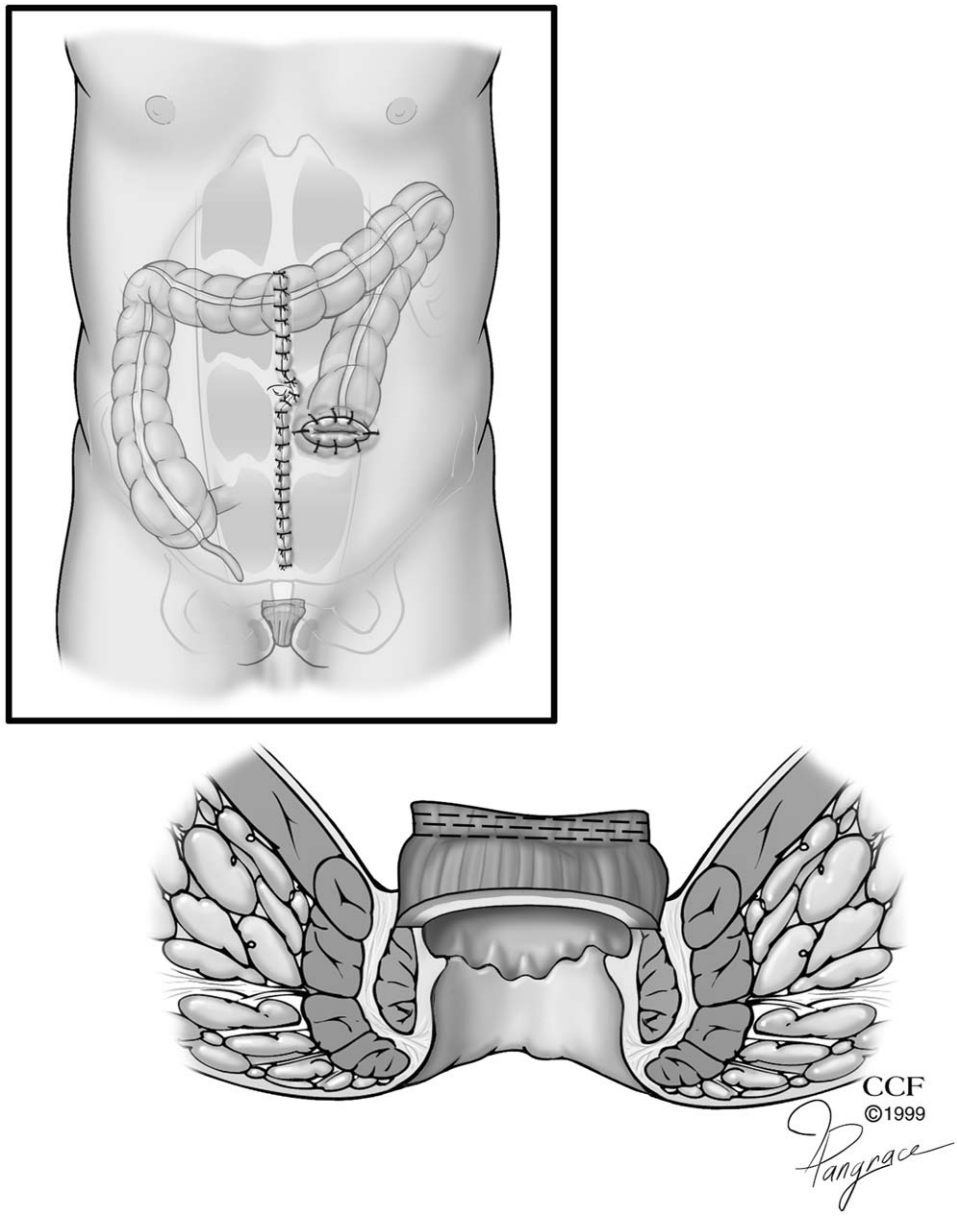

Fig. 5. Extended Hartmann's operation for carcinoma of the rectum.

conducted by the Gastrointestinal Tumor Study Group (GITSG)[45] and the North Central Cancer Treatment Group (NCCTG).[46] These studies showed that a combination of postoperative radiation therapy and chemotherapy significantly decreases the pelvic recurrence rate and increases the overall survival rate compared with surgery alone in patients with stage II and III rectal cancer. This approach has become the standard of care for patients with cancer penetration through the rectal wall and/or positive lymph nodes (pT3N0–2 tumors) who are at greatest risk for local pelvic recurrence or distant metastases. Advocates of a purely surgical solution to low rectal carcinoma maintain that local recurrence is due to inadequate surgery, and radiation therapy should not be used to make up for defective surgical technique.[47] For example, Enker et al.[48] studied 246 consecutive patients with Dukes' B (T3N0M0) and Dukes' C (TanyN1–2M0) primary rectal carcinomas who underwent surgery according to the principle of TME. The Kaplan-Meier 5-year survival rates for Dukes' B and C lesions were 86.7% and 64.0%, respectively. The pelvic recurrence rate for Dukes' B and C rectal carcinomas (T3N0M0 and TanyN1–2M0) was 7.3% (18/246). Adjuvant radiation was of no statistical benefit in preventing local recurrences. The authors recommend that the current role of combined-modality adjuvant therapy should be reconsidered in patients

Table 3. Selection criteria for local therapy in treatment of rectal cancer

Tumor characteristics favoring local treatment
Mobile
<3 cm in diameter
Exophytic rather than ulcerated
Well to moderate differentiation (no colloid or "signet ring" cells, vascular or lymphatic invasion)
Confined to bowel wall (by endoluminal ultrasound)
Palpable or judged to be below the peritoneal reflection
Patient characteristics favoring local treatment
Unfit for major surgical procedure
Unwilling to undergo major surgical procedure
Extensive distant metastases

Table 4. National Institutes of Health Consensus Conference recommendations for adjuvant therapy for rectal cancer

No adjuvant therapy is recommended for stage I patients
Patients with stage II/III rectal cancer are at high risk for recurrence and warrant adjuvant therapy

who have undergone resection in accordance with TME. In addition, McFarlane et al.[49] compared 135 consecutive operations for Dukes' B2 and Dukes' C cancer, both anterior resection and APR performed by TME for tumors less than 12 cm from the anal verge. Results of TME alone were found to be substantially superior to the best reported (NCCTG) from conventional surgery plus radiation therapy or chemotherapy: 5% local recurrence at 5 years compared with 25% and 13.5%, respectively; and 22% overall recurrence compared with 62.7% and 41.5%, respectively. More recently Nissan et al.[50] found that in patients who have cancer of the lower one third of the rectum, sharp pelvic dissection can result in a low rate of local recurrence even without radiation therapy. Nevertheless, evidence from randomized studies shows that adjuvant therapy improves the results at both the best and worst centers.[51] Adjuvant therapy has been examined both preoperatively and postoperatively with radiotherapy and/or chemotherapy. Randomized studies have shown that preoperative irradiation improves local control of rectal cancer.[52] In addition, improved survival with preoperative radiation therapy has been found in two studies.[53,54] A study comparing preoperative and postoperative irradiation in adenocarcinoma of the rectum concluded that preoperative short-term, high-dose radiotherapy decreases the local recurrence rate relative to postoperative radiotherapy.[55] In a meta-analysis of 18 trials involving 4000 patients, preoperative x-ray therapy significantly reduced local recurrence by 50%.[56] Studies to confirm the value of preoperative vs. postoperative chemoradiation, as well as studies to indicate a need for radiation therapy after total mesorectal excision, have not yet been done.

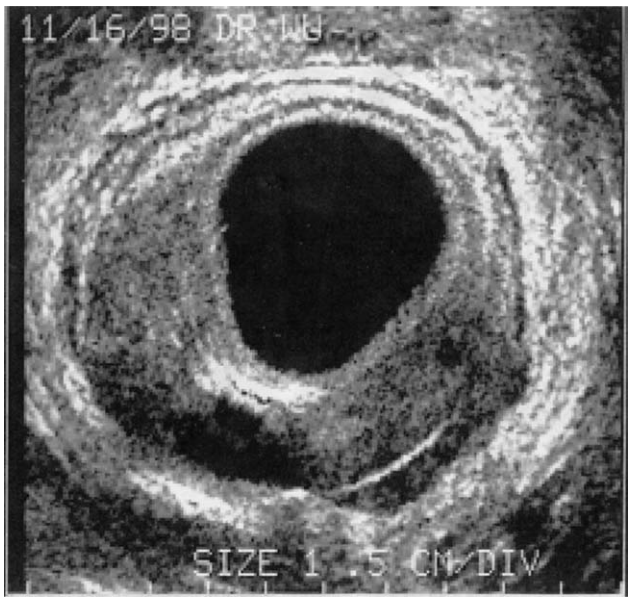

Fig. 6. Transrectal ultrasound image of a low rectal cancer showing invasion through the submucosa. The outer border of the tumor is scalloped consistent with invasion through the muscularis propria. The ultrasonic stage is uT3N0.

Whether preoperative or postoperative radiation therapy is better is controversial. Morbidity is higher with postoperative radiation because of damage to the colon, anal sphincter, and small bowel; however, the exact stage of the tumor is known. When radiation therapy is given preoperatively, the precise stage is not known; however, the anatomy is undisturbed by surgery and injury to normal intestine is less. Radiotherapy given before operation can render operable a locally extensive tumor offering a good chance for local control.

LOCALLY ADVANCED ADENOCARCINOMA OF THE RECTUM

Five percent of patients with rectal cancer have locally advanced (T4) tumors with direct invasion into other organs, such as the vagina, uterus, bladder, prostate, or sacrum. It is important to recognize contiguous involvement by other structures because exenteration or partial sacral resection may be required for surgical cure. With en bloc resection, 5-year survival rates of 50% may be possible.[57] Shirouzou et al.[58]

reported 26 patients who underwent total pelvic exenteration for locally advanced colorectal cancer. Total pelvic exenteration is warranted for patients with stage II locally advanced colorectal carcinoma. The major morbidity of wide excisional procedures in these cases must be balanced against the possibility of long-term cure.

FOLLOW-UP OF COLORECTAL CANCER

Follow-up after surgery for colorectal carcinoma is individualized, taking into consideration the risk of recurrent disease and metachronous cancer as well as the age and general health of the patient. Most recurrences after operations for cure of colorectal carcinoma occur within 2 years. Common sites of recurrence are the liver, lungs, primary tumor bed, peritoneum, and lymph nodes. Galandiuk et al.[59] studied 818 patients who had undergone curative resection for Dukes' B2 or C2 carcinoma of the rectum and examined patterns of recurrence. The median time to recurrence was 16.7 months (range 1 to 7.5 years). Local/regional recurrence was more common for rectal cancer (52 vs. 42%). The most common sites of recurrence were hepatic (33%), pulmonary (22%), local or regional (21%), intra-abdominal (18%), retroperitoneal (10%), and peripheral lymph nodes (4%). Chung et al.[60] found that the groups at highest risk for local failure were those with extension of tumor through the bowel wall. The absolute 5-year survival rate for those with tumor through the wall vs. within the wall was 40% and 79%, respectively[61,62]; 80% to 90% of local recurrences occur within 2 years.[63] In general, patients are seen for follow-up every 3 to 6 months for 2 years, then every 6 months for 2 years, and then yearly. Specific inquiries are made concerning weight loss, change in bowel habits, bleeding, or pain. The abdomen is examined for tenderness, masses, or lymphadenopathy. The perineum is examined if APR was done. A digital rectal examination and flexible sigmoidoscopy are done in patients who have undergone restorative surgery for rectal cancer. Colonoscopy is performed at 1 year and repeated at 3- to 5-year intervals thereafter if no abnormalities are found. Determination of carcinoembryonic antigen levels is controversial but is usually done. For a single elevation greater than 10 ng/dl or two persistent elevations, further studies, such as colonoscopy and chest, abdominal, and pelvic CT, are performed to look for recurrent disease. MRI, radioimmunoscintigraphy, and positron emission tomography can be considered if results of other tests are negative.[64,65]

MANAGEMENT OF RECURRENT COLORECTAL CANCER

Patients in whom recurrent tumors are found may be considered for surgery, chemotherapy, or radiation for cure or palliation. Patients with isolated local recurrences may be eligible for surgical resection. Major resective surgery is not offered if the disease is so widespread that there is no chance for cure. Resection of recurrent colorectal cancer may result in improved survival in selected cases.[66,67] Intraoperative irradiation is being used at some institutions for the treatment of locally advanced and locally recurrent rectal cancer.[68]

RECTAL CANCER AND LAPAROSCOPY

Laparoscopic colectomy for colorectal cancer is controversial because of uncertainty as to the effect of laparoscopic resection on long-term survival. Benefits of laparoscopic surgery include shorter hospitalization and earlier return of pulmonary and gastrointestinal function.[69] Early reports show no apparent short-term oncologic disadvantages.[70–73] Prospective randomized trials currently are underway to determine the ultimate role of laparoscopic resection in the treatment of colorectal cancer.

SUMMARY

The management of rectal cancer is multidisciplinary, involving surgeons working with medical and radiation oncologists. Surgical options include radical resection with or without restoration of bowel continuity and a variety of local procedures. Adjuvant therapy may decrease the incidence of local recurrence in some cases. Laparoscopic resection has introduced a new approach to major resection that can be done following oncologic principles with encouraging early results with regard to survival. The choice of operation depends on the experience of the surgeon and on the individual characteristics and preferences of the patient.

REFERENCES

1. Jemal A, Murray T, Samuels A, et al. Cancer Statistics, 2003. CA Cancer J Clin 2003;53:5–26.
2. Orrom WJ, Wong WD, Rothenberger DA, et al. Endorectal ultrasound in the preoperative staging of rectal tumors: A learning experience. Dis Colon Rectum 1990;33:654–659.
3. Beynon J, Mortensen NJ, Foy DMA, et al. Preoperative assessment of mesorectal lymph node involvement in rectal cancer. Br J Surg 1989;76:276–279.
4. Timmcke AE. Methodology and applications of water perfusion anal manometry. In Smith LE. Practical Guide to

Anorectal Testing, 2nd ed. New York: Igaku-Shoin, 1995, pp 27–50.
5. Oakley JR, Fazio VW. Ileostomy. In Fielding LP, Goldberg SM, eds. Rob and Smiths Operative Surgery. Surgery of the Colon, Rectum and Anus, 5th ed. Oxford: Butterworth-Heineman, 1993, pp 243–269.
6. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2003. CA Cancer J Clin 2003;53:27–43.
7. Davis NC, Newland RC. Terminology and classification of colorectal adenocarcinoma: The Australian clinico-pathological staging system. Aust N Z J Surg 1983;53:211–221.
8. Miles WE. A method of performing abdomino-perineal excision for carcinoma of the rectum and the terminal portion of the pelvic colon. Lancet 1908;2:1812–1813.
9. Dukes CE. The surgical pathology of rectal cancer. Proc R Soc Med Lond 1943;37:131–144.
10. Pollett WJ, Nicholls RJ. Does the extent of distal clearance affect survival after radial anterior resection for carcinoma of the rectum. Gut 1981;22:872.
11. Willliams NS, Dixon MF, Johnston D. Reappraisal of the 5 centimetre rule of distal excision for carcinoma of the rectum: A study of distal intramural spread and patient's survival. Br J Surg 1983;70:150–154.
12. Shirouzu K, Isomoto H, Kakegawa T. Distal spread of rectal cancer and optimal distal margin of resection for spincter-preserving surgery. Cancer 1995;76:388–392.
13. Nicholls RJ, Hall C. Treatment of non-disseminated cancer of the lower rectum. Br J Surg 1996;83:15–18.
14. Lavery IC, Lopez-Kostner F, Fazio VW, et al. Chances of cure are not compromised with sphincter-saving procedures for cancer of the lower third of the rectum. Surgery 1997; 122:779–785.
15. Porter GA, Soskolne CL, Yakimets WW, Newman SC. Surgeon-related factors and outcome in rectal cancer. Ann Surg 1998;227:157–167.
16. Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? Br J Surg 1982;69:613–616.
17. McAnena OJ, Heald RJ, Lockhart-Mummery HE. Operative and functional results of total mesorectal excision with ultralow anterior resection in the management of carcinoma of the lower one-third of the rectum. Surg Gynecol Obstet 1990;170:517–521.
18. Beart RW. Mesorectal excision for rectal carcinoma: The new standard? Adv Surg 1999;32:193–203.
19. Zaheer S, Pemberton JH, Farouk R, et al. Surgical treatment of adenocarcinoma of the rectum. Ann Surg 1998;227:800–811.
20. Deddish MR. Surgical procedures for carcinoma of the lower portion of the left colon and rectum, with five-year end results following abdominopelvic dissection of lymph nodes. Am J Surg 1960;99:188–191.
21. Hojo K, Sawada T, Moriya Y. Analysis of survival, voiding and sexual function after wide ileopelvic lymphadenectomy in patients with carcinoma of the rectum, compared with conventional lymphadenectomy. Dis Colon Rectum 1989; 32:128–133.
22. Moreira LF, Hizuta A, Iwagaki H, Tanaka N, Orita K. Lateral lymph node dissection for rectal carcinoma below the peritoneal reflection. Br J Surg 1994;81:293–296.
23a. Turnbull RB Jr, Cuthbertson A. Abdominorectal pull-through resection for cancer and for Hirschprung's disease. Clev Clin Quart 1961;28:109–115.
23b. Cutait DE, Figlioni FG. A new method of colorectal anastomosis in abdominoperineal resection. Dis Colon Rectum 1961;4:335–342.
24. Knight CD, Griffen FD. An improved technique for low anterior resection of the rectum using the EEA stapler. Surgery 1980;88:710–714.
25. Parks AG, Percy JP. Resection and sutured colo-anal anastomosis for rectal carcinoma. Br J Surg 1982;69:301–304.
26. Lazorthes F, Fages P, Chiotasso P, Lemozy J, Bloom E. Resection of the rectum with construction of a colonic reservoir and colo-anal anastomosis for carcinoma of the rectum. Br J Surg 1986;73:136–138.
27. Parc R, Tiret E, Frileux P, Moszkowski E, Loygue J. Resection and colo-anal anastomosis with colonic reservoir for rectal carcinoma. Br J Surg 1986;73:139–141.
28. Fazio VV, Mantyh CR, Hull TR. Colonic "coloplasty": Novel technique to enhance low colorectal or coloanal anastomosis. Dis Colon Rectum 2000;43:1448–1450.
29. Dahlberg M, Glimelius B, Graf Wilhelm, Påhlman L. Preoperative irradiation affects functional results after surgery for rectal cancer. Dis Colon Rectum 1998;41:543–551.
30. ReMine SG, Dozois RR. Hartmann's procedure: Its use with complicated carcinomas of sigmoid colon and rectum. Arch Surg 1981;116:630–633.
31. Doci R, Audisio RA, Bozzetti F, Gennari L. Actual role of Hartmann's resection in elective surgical treatment for carcinoma of rectum and sigmoid colon. Surg Gynecol Obstet 1986;163:49–53.
32. Morson BC. Factors influencing the prognosis of early cancer of the rectum. Proc R Soc Med 1966;59:607–608.
33. Morson BC, Bussey HJR, Samoorian S. Policy of local excision for early rectal cancer. Gut 1977;18:1045–1050.
34. Nivatvongs S, Wolff BG. Technique of per anal excision for carcinoma of the low rectum. World J Surg 1992;16:447–450.
35. Buess G, Mentges B, Manncke K, et al. Technique and results of transanal endoscopic microsurgery in early rectal cancer. Am J Surg 1992;163:63–70.
36. Eisenstat TE, Oliver GC. Electrocoagulation for adenocarcinoma of the low rectum. World J Surg 1992;16:458–462.
37. Papillon J, Berard PH. Endocavitary irradiation in the conservative treatment of adenocarcinoma of the low rectum. World J Surg 1992;16:451–457.
38. Beynon J, Mortensen NJMcC, Foy DMA, et al. Preoperative assessment of mesorectal lymph node involvement in rectal cancer. Br J Surg 1989;76:276–279.
39. Chakravarti A, Compton CC, Shellito PC, et al. Long-term follow-up of patients with rectal cancer managed by local excision with and without adjuvant irradiation. Ann Surg 1999;230:49–54.
40. Bleday R, Breen E, Jessup JM, et al. Prospective evaluation of local excision for small rectal cancers. Dis Colon Rectum 2001;40:388–392.
41. Buess G, Kipfmuller K, Heald R, et al. Tansanale endoskopische Mikrochurugie beim Rektum carcinom. Chirurg 1989;60:901–904.
42. Winde G, Nottberg H, Keller R, Schmid KW, Bünte H. Surgical cure for early rectal carcinomas (T1): Transanal endoscopic microsurgery vs. anterior resection. Dis Colon Rectum 1996;39:969–976.
43. Kemeny N, Saltz L, Cohen A. Adjuvant therapy of colorectal cancer. Surg Oncol Clin North Am 1997;6:699–722.
44. NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990;264:1444–1450.
45. Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med 1985;312:1465–1472.
46. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709–715.

47. McArdle CS, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival BMJ 1991;302:1501–1505.
48. Enker WE, Thaler HT, Cranor ML Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. J Am Coll Surg 1995;181:335–346.
49. MacFarlane JK, Ryall RDH, Heald RJ. Mesorectal excision for rectal cancer. Lancet 1993;341:457–460.
50. Nissan A, Guillem JG, Paty PB, et al. Abdominoperineal resection for rectal cancer at a specialty clinic. Dis Colon Rectum 2001;44:27–36.
51. Holm T, Johansson H, Cedermark B, et al. Influence of hospital and surgeon related factors on outcome after treament of rectal cancer with or without preoperative radiotherapy. Br J Surg 1997;84:657–663.
52. Wheeler JMD, Warren BF, Jones AC, Mortensen NJ. Preoperative radiotherapy for rectal cancer: Implications for surgeons, pathologists and radiologists. Br J Surg 1999;86: 1108–1120.
53. Marsh PJ, James RD, Schofield PF. Adjuvant preoperative radiotherapy for locally advanced rectal carcinoma: Results of a prospective, randomized trial. Dis Colon Rectum 1994; 37:1205–1214.
54. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997;336:980–987.
55. Frykholm GJ, Glimelius B, Påhlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: Final treatment results of a randomized trial and an evaluation of late secondary effects. Dis Colon Rectum 1993;36:564–572.
56. NHS Executive. Improving Outcomes in Colorectal Cancer: The Reseach Evidence. Wetherby: Department of Health UK, 1998.
57. Divine RM, Dozois RR. Surgical management of locally advanced adenocarcinoma of the rectum. World J Surg 1992;16:486–489.
58. Shirouzu K, Isomoto H, Kakegawa T. Total pelvic exenteration for locally advanced colorectal carcinoma. Br J Surg 1996;83:32–35.
59. Galandiuk S, Wieand HS, Moertel CG, et al. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. Surg Gynecol Obstet 1992;174:27–32.
60. Chung CK, Stryker JA, Demuth WE Jr. Patterns of failure following surgery alone for colorectal cancer J Surg Oncol 1983;22:65–70.
61. Rich T, Gunderson II, Lew R, et al. Patterns of recurrence of rectal cancer after potentially curative surgery. Cancer 1983;52:1317–1329.
62. Phillips RKS, Hittinger R, Blesovsky I, et al. Local recurrence following "curative" surgery for large bowel cancer: I. The overall picture. Br J Surg 1984;71:12–16.
63. Goligher JC, Dukes CE, Bussey HJR. Local recurrence after sphincter-saving excisions for carcinoma of the rectum and rectosigmoid. Br J Surg 1951;39:199–211.
64. Wolff BG, Bolton J, Baum R. Radioimmunoscintigraphy of recurrent, metastatic, or occult colorectal cancer with technetium Tc 99m 88BV59H21-2V67-66 (HumaSPECT-Tc), a totally human monoclonal antibody: Patient management benefit from a phase III multicenter study. Dis Colon Rectum 1998;41:953–962.
65. Flanagan FL, Dehdashti F, Ogunbiyi OA, et al. Utility of FDG-PET for investigating unexplained plasma CEA elevation in patients with colorectal cancer. Ann Surg 1998; 227:319–323.
66. Hida J, Yasutomi M, Shindoh K, et al. Second-look operation for recurrent colorectal cancer based on carcinoembryonic antigen and imaging techniques. Dis Colon Rectum 1996; 39:74–79.
67. Wanebo HJ, Antoniuk P, Koness RJ, et al. Pelvic resection of recurrent rectal cancer: Technical considerations and outcomes. Dis Colon Rectum 1999;42:1438–1448.
68. Gunderson LL, Nelson H, Martenson JA, et al. Intraoperative electron and external beam irradiation with or without 5-fluorouracil and maximum surgical resection for previously unirradiated, locally recurrent colorectal cancer. Dis Colon Rectum 1996;39:1379–1395.
69. Milsom JW, Böhm B, Hammerhofer KA, et al. A prospective, randomized trial comparing laparoscopic versus conventional techniques in colorectal cancer surgery: A preliminary report. J Am Coll Surg 1998;187:46–57.
70. Fleshman JW, Nelson H, Peters WR, et al. Early results of laparoscopic surgery for colorectal cancer: Retrospective analysis of 372 patients treated by Clinical Outcomes of Surgical Therapy (COST) Study Group. Dis Colon Rectum 1996;39:S53–S58.
71. Köcklering F, Reymond MA, Schneider C, et al. The Laparoscopic Colorectal Surgery Study Group. Prospective multicenter study of the quality of oncologic resections in patients undergoing laparoscopic colorectal surgery for cancer. Dis Colon Rectum 1998;41:963–970.
72. Franklin ME, Rosenthal D, Abrego-Medina D, et al. Prospective comparison of open vs. laparocopic colon surgery for carcinoma: Five year results. Dis Colon Rectum 1996;39: S35–S46.
73. Hong D, Tabet J, Anvari M. Laparoscopic vs. open resection for colorectal adenocarcinoma. Dis Colon Rectum 2001;44: 10–19.
74. Rich T, Gunderson LL, Lew R, et al. Patterns of recurrence of rectal cancer after potentially curative surgery. Cancer 1983;52:1317–1329.
75. Phillips RKS, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following "curative" surgery for large bowel cancer: I. The overall picture. Br J Surg 1984;71:12–16.
76. Phillips RKS, Hittinger R, Bleseovsky L, Fry JS, Fielding LP. Local recurrence following "curative" surgery for large bowel cancer: II. The rectum and rectosigmoid. Br J Surg 1984; 71:17–20.
77. Porter GA, O'Keeke GE, Yakimets WW. Inadvertent perforation of the rectum during abdominoperineal resection. Am J Surg 1996;172:324–327.
78. Pilipshen SJ, Heilweil M, Quan SHQ, Sternberg SS, Enker WE. Patterns of pelvic recurrence following definitive resections of rectal cancer. Cancer 1984;53:1354–1362.
79. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopatholocal study of lateral tumour spread and surgical excision. Lancet 1986;2:996–999.
80. Horn A, Dahl O, Morild I. Venous and neural invasion as predictors of recurrence in rectal cancer. Dis Colon Rectum 1991;34:798–804.

Clinical Risk Score Correlates With Yield of PET Scan in Patients With Colorectal Hepatic Metastases

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Although positron emission tomography (PET) detects occult metastatic disease in approximately 20% of patients with isolated hepatic colorectal metastases, it is associated with false negative results in up to 16%. We hypothesized that patients with a poorer prognosis (as defined by clinical risk score [CRS]) would have a higher yield from PET. All patients with colorectal liver metastases who were imaged by means of PET between 1998 and 2002 were identified from a prospective PET database. All patients were assigned a CRS, with one point added for each of five preoperative factors (disease-free interval <1 year, tumor size >5 cm, tumor number >1, carcinoembryonic antigen >200, and node-positive primary lesion). A total of 85 PET scans were reviewed. In half the patients (53%), PET provided no additional information over conventional imaging. Occult extrahepatic disease was detected or questionable findings seen on conventional imaging were confirmed in 20% of PET scans, whereas PET readings were inaccurate in 27%. PET findings were correlated with CRS in a subset of 63 patients presenting with a first occurrence of hepatic colorectal metastases. Among patients with a CRS of 0, no patient had extrahepatic disease detected by PET and 57% had false positive readings, whereas among patients with a CRS of 1 or more, 14% were found to have additional disease that was detected only by PET, and there were no false positive readings ($P < 0.001$, Fisher's exact test). Patients with isolated hepatic colorectal metastases and a CRS of 0 should undergo conventional imaging alone prior to surgical exploration. (J GASTROINTEST SURG 2004;8:150–158)

KEY WORDS: Colorectal hepatic metastases, PET scan

Colorectal hepatic metastases are potentially curable with complete surgical resection. Although most patients have a recurrence, a 5-year survival rate of up to 40% is possible.[1,2] Unfortunately, many patients have a recurrence, even in the early postoperative period, as a result of occult metastatic disease that is present at the time of resection. In an attempt to improve the selection of patients for hepatic resection, positron emission tomography (PET) has been evaluated to assess for extrahepatic disease in those patients presenting for hepatic resection. Overall, various series evaluating the use of PET in patients with presumed isolated hepatic metastases have shown that approximately 20% of patients have occult extrahepatic disease.[3,4] In addition, a recent meta-analysis evaluating patients with recurrent colorectal cancer demonstrated a change in management in 29% of patients because of findings on PET scans.[5] Although these results seem promising, the majority of patients undergoing PET do not benefit from this procedure and may in fact be mismanaged as a result of false negative or false positive findings, which occur in up to 16% of patients.[4] Despite this, the near-routine use of PET in patients with hepatic colorectal metastases has become commonplace in many institutions.

To assess the risk of recurrence after hepatic resection for colorectal metastases, a clinical risk score has

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been developed that predicts prognosis.[1] The clinical risk score (CRS) is comprised of the following five factors, all of which can be determined preoperatively: (1) node-positive primary lesion; (2) disease-free interval from resection of the primary tumor to time of metastasis of less than 12 months; (3) number of hepatic tumors greater than 1; (4) largest hepatic tumor greater than 5 cm; and (5) preoperative carcinoembryonic antigen level greater than 200. Each criterion is assigned one point and the sum represents the CRS. The strength of the CRS is that it is predictive not only of survival[1] but also of resectability.[6] The clinical significance of these findings is that a higher CRS correlates with a greater likelihood of occult metastatic disease found either at the time of surgery or manifesting as recurrent disease after resection. Because of this, we hypothesized that the CRS may also be predictive of the yield of the PET scan. If this correlation exists, the CRS may be helpful in determining which patients should undergo PET prior to surgical intervention.

METHODS

Patient Population

Patients with presumed isolated hepatic colorectal metastases undergoing preoperative evaluation were identified from a prospective PET database. PET scans were obtained between November 1998 and April 2002. Hospital records were reviewed to determine patient demographics, imaging findings, operative and perioperative data, and outcome. All patients were assigned a CRS by adding one point for each of the following five factors: (1) node-positive primary lesion; (2) disease-free interval from resection of the primary tumor to the time of metastasis of less than 12 months; (3) number of hepatic tumors greater than 1; (4) largest hepatic tumor greater than 5 cm; and (5) preoperative carcinoembryonic antigen level greater than 200.

Preoperative Evaluation

Findings from conventional cross-sectional imaging studies (CT and MRI) and PET scans were recorded from radiologic reports, and the results of these tests were compared. The results of these imaging tests were correlated intraoperative ultrasound (IOUS) findings and operative results. IOUS has been used for all patients undergoing hepatic resection at our institution since 1992 and is performed jointly by the operating surgeon and a dedicated radiologist.

PET Technique

Patients were evaluated at the University of Wisconsin Hospital with the use of a GE Advance PET scanner (Milwaukee, WI). All patients were fasted for 4 hours before the examination. Imaging was initiated 45 to 60 minutes after intravenous administration of ^{18}F-fluorodeoxyglucose, using a dose of 0.14 mCi/kg, with a minimum dose of 10 mCi. Images were obtained from the orbital-meatal line to midthigh. Acquisition parameters included 6 minutes per bed position for the emission study and 2 minutes per bed position for the transmission images. Reconstruction of images included nonattenuation-corrected images and attenuation-corrected images. The PET scans were read by one of three radiologists specializing in nuclear medicine. The CT scan reports and/or images and clinic notes were available to the radiologist reading the PET scan.

Definitions

PET findings were categorized as follows: (1) PET results corresponded with conventional imaging; (2) PET detected additional disease not seen on conventional cross-sectional imaging; (3) PET confirmed findings on cross-sectional images that were unable to be definitively read as benign or malignant; (4) false negative findings on PET scan; and (5) false positive findings on PET scan. False positive and false negative PET findings were confirmed by pathologic examination, operative findings including IOUS images, or progression of disease on follow-up imaging.

Statistical Analysis

The efficacy of PET was analyzed using the five-category system outlined above. The hypothesis of independence was tested using Fisher's exact test. Survival was analyzed by log-rank analysis. Computations were performed using SAS software (6.12 for Windows, SAS Institute, Cary, NC). Differences were considered significant at $P < 0.05$.

RESULTS

Patient Population

A total of 85 PET scans were obtained from 73 patients with hepatic colorectal metastases. Ten patients were evaluated on two separate occasions, and one patient was evaluated three times. The median age was 60 years (range 39 to 83 years). There were 19 women and 54 men. The median follow-up for surviving patients was 18.6 months.

The majority of the PET scans (78 of 85; 92%) were obtained from patients undergoing evaluation for potential hepatic resection. Seven scans were obtained from patients who were being assessed for placement of an hepatic artery infusion pump because

of unresectable hepatic metastases. Two of these patients had recurrent hepatic metastases after prior resection, and five patients were being evaluated for a first occurrence of hepatic metastases. PET scans were obtained to evaluate for recurrent hepatic colorectal metastases after liver resection in 17 patients.

Clinical Data

At the time of presentation of the primary colorectal tumor, 55 patients had colon cancer, 28 had rectal cancer, and three had multiple tumors. At the time of diagnosis of the primary tumor, the American Joint Committee on Cancer stages were as follows: I, 4%; II, 15%; III, 26%; IV, 49%, and unknown, 6%.

Chemotherapy records were reviewed to assess the interval between the discontinuation of chemotherapy and the date that the PET scan was obtained. At the time the PET scans were obtained, 16% of patients (14 of 85) had received chemotherapy within 1 month, whereas 11% (9 of 85) had chemotherapy within 1 to 3 months of PET.

Imaging Studies

Preoperative imaging before PET included abdominal/pelvic contrast-enhanced CT scan (84 of 85; 98%), chest CT scan (32 of 85; 38%), and liver MRI (11 of 85; 13%). Some of these scans were performed at the referring institution. All patients had a preoperative x-ray examination of the chest. IOUS was performed in all patients undergoing hepatic resection.

Overall PET Results

The overall findings from the 85 PET scans evaluated are presented in Table 1. The sensitivity and specificity of PET were 75% and 50%, respectively, compared to conventional imaging, which included any of the prior imaging findings (CT, ultrasonography, or MRI). The positive and negative predictive values for PET were 94% and 83%, respectively.

Table 1. Overall PET scan results in patients with metastatic colorectal hepatic metastases

PET findings	n	%
Confirmed cross-sectional imaging	45	53
Detected additional disease not seen on conventional imaging	10	12
Confirmed questionable findings on CT scan	7	8
False positive	4	5
False negative	19	22
TOTAL	85	100

The overall benefit of PET in these patients, including both detection of additional disease not seen on conventional imaging and confirmation of questionable findings on CT scans, was 20%. Disease that was not visualized by conventional imaging was detected on PET scans in 10 patients. This included eight patients with extrahepatic disease and two patients with liver lesions that were not seen on CT scans. In the seven PET scans that confirmed questionable findings on cross-sectional imaging, four patients had PET scans consistent with benign disease and three patients had PET scans consistent with malignant disease. Therefore additional metastatic disease that was either not seen on conventional images or was difficult to definitively differentiate between benign and malignant etiologies was detected in a total of 13 patients. This included four patients with retroperitoneal lymphadenopathy, four patients with liver lesions, two patients with lung metastases, one patient with bone metastases, one patient with carcinomatosis, and one patient with carcinomatosis and bone metastases. These findings were confirmed by biopsy in five patients, by progression of disease in four patients, and by IOUS imaging in one patient who subsequently underwent liver ablation. In three patients, the findings of extrahepatic disease were not verified by pathologic examination or progression, but the patients died of progression of the recurrent disease seen on the initial CT scan at 4, 4, and 13 months, respectively, after the PET was performed.

Although 20% of PET scans were beneficial to patient management, 27% of the scans were potentially detrimental because of false positive or false negative readings. False positive findings were seen in the liver alone (n = 3) and in the liver and pelvis (n = 1). All four patients underwent exploratory laparotomy; in two patients no abnormality was found on IOUS imaging of the liver, whereas in two patients wedge biopsies of hypoechoic lesions showed benign pathology. The false positive pelvic lesion was due to a pelvic abscess. No recurrent cancer was found in this patient on follow-up colonoscopy 14 months after the PET. All three patients with false positive lesions in the liver alone were followed with CT scans, and none had progression in the liver or at other sites at a median follow-up of 18.5 months.

The site of disease in patients with false negative PET scans is shown in Table 2. The average size of false negative PET readings was 1.5 cm (range 0.5 to 4 cm). All patients with lung metastases had lesions that were seen on CT scans of the chest, but these lesions were negative on PET. In four patients with peritoneal metastases and one patient with lymphadenopathy, the disease was discovered intraoperatively.

Table 2. False negative PET scans in 19 patients including means of detection at time PET was obtained

Site of disease	n	Detection of disease at time of PET		Confirmation of false negative PET		
		Conventional imaging	Intraoperative finding	Pathology	IOUS	Progression of disease
Liver	8	3	5	2	3	3
Lung	5	5		2		4
Peritoneal disease	4	4		3		1
Portal/celiac lymphadenopathy	2	1	1	1		1

IOUS = intraoperative ultrasound.
Methods used to confirm false negative findings are as noted. IOUS, performed jointly by the surgeon and a dedicated body-imaging radiologist, was used for evaluating lesions that were subsequently ablated intraoperatively.

One patient with lymphadenopathy had enlarged porta hepatis nodes seen on CT scans, which were negative on PET. Among the eight patients with liver metastases, three were visualized by conventional imaging, whereas five were seen by IOUS imaging. In the 19 patients with false negative PET readings, lesions were confirmed by biopsy (n = 8), by IOUS (n = 4, which demonstrated classic findings for colorectal metastases in patients undergoing ablation), and by progression of disease on serial CT scans (n = 8).

The yield of the PET scans was analyzed according to the interval from the last chemotherapy to the date of the PET (<3 months vs. ⩾3 months). There was no correlation between a short (<3 months) interval between chemotherapy and the yield of the PET scan. There was no difference in the false negative rate in patients who had recently received chemotherapy. Among patients who had not received recent chemotherapy, 21% had false negative readings, whereas in patients who had received recent chemotherapy, the false negative reading was 24% ($P = 0.5$; Fisher's exact test).

Correlation of PET Results With Clinical Risk Scores

A total of 63 patients presented with a first occurrence of hepatic colorectal metastases. The median CRS was 2. The distribution of clinical risk scores is displayed in Table 3. Because the CRS correlates with resectability and prognosis in patients with resectable hepatic metastases, but has not been evaluated in patients with unresectable disease or recurrence of liver metastases after resection, we chose to evaluate the correlation between CRS and PET findings in this subset of patients.

Overall results of PET in these 63 patients are presented in Table 4. There was a significant association between the CRS and the yield on the PET scan, such that among patients with a CRS of 0, none had extrahepatic disease detected by PET and four (57%) of seven patients had false positive readings, whereas among patients with a CRS of ⩾1, 8 (14%) of 56 were found to have extrahepatic disease detected only by PET, and there were no false positive readings ($P < 0.001$, Fisher's exact test).

Surgical Findings and Procedures

From December 1998 to April 2002, a total of 98 patients underwent exploratory operations for potential resection of colorectal hepatic metastases at the University of Wisconsin Hospital. Fifty-two of these patients (53%) underwent preoperative PET at a median interval of 25 days before surgery and are included in this report. Of these 52 patients, 75% (39 of 52) had liver metastases that were amenable to either surgical resection or complete tumor ablation. Ten percent (5 of 52) did not have metastatic liver lesions (4 false positive PET scans and one false positive CT scan), but one underwent colon resection and in one case, a rectal abscess was drained. Therefore

Table 3. Distribution of clinical risk scores in 63 patients presenting with a first occurrence of potentially resectable hepatic metastases

CRS	n	%
0	7	11
1	15	24
2	16	25
3	19	30
4	6	10
5	0	0
TOTAL	63	100

CRS = clinical risk score.

Table 4. Correlation between PET findings and clinical risk scores

PET findings	CRS 0		CS ⩾1	
	n	%	n	%
Confirmed cross-sectional imaging	2	29	29	52
Detected additional disease not seen on conventional imaging	0		8	14
Confirmed questionable findings on CT scan	1	14	4	7
False positive	4	57	0	
False negative	0		15	27
TOTAL	7	100	56	100

CRS = clinical risk score.

8 (15%) of 52 patients who underwent exploratory operations were found to have unresectable disease; half of these patients underwent placement of a hepatic artery infusion pump. Surgical procedures in patients with metastases included liver resection (with or without cryoablation) in 35 patients and cryoablation alone in four patients. Two patients underwent wedge resection for PET-positive lesions that were benign.

Survival and Recurrence

Among the 39 patients undergoing curative resection or ablation for a first occurrence of hepatic colorectal metastases, the 2-year survival was 75% (median survival not reached). The median recurrence-free survival was 24.6 months, whereas the 1-year recurrence-free survival was 62%. A total of 11 patients (28%) had a recurrence within the first year, and four had a recurrence within the first 6 months after surgery. Sites of disease in the 15 patients with known recurrences included the liver (n = 7), liver and other sites (n = 4, including one patient each with peritoneal metastases, bone metastases, intra-abdominal lymphadenopathy, and intrathoracic adenopathy), lung (n = 3), and lung and local recurrence in the pelvis (n = 1). All patients with early recurrences in the first 6 months had a recurrence in the liver.

DISCUSSION

Conventional radiologic imaging by means of abdominal and pelvic CT scanning is the most widely utilized imaging test to evaluate liver anatomy and assess for the presence of extrahepatic disease in patients with hepatic colorectal metastases who are undergoing preoperative evaluation. Unfortunately, even in patients with resectable disease, the recurrence rate is high.[1,3] Clearly this is because of undetected occult carcinoma that is present at the time of liver resection, either within the liver or in extrahepatic sites, which was not detected on conventional imaging. Because PET can detect hypermetabolic lesions in any location, the usefulness of PET in detecting extrahepatic disease in patients undergoing preoperative evaluation for colorectal hepatic metastases has been evaluated.[3–5,7] Because detection of occult metastatic disease preoperatively can spare patients unnecessary surgery, the level of enthusiasm has been high for evaluating PET scans in these patients.

Part of the difficulty in evaluating the yield of PET scans in these studies is that the technology of CT scanning has evolved markedly in recent years. With the introduction of multidetector helical CT within the past 5 years, the ability to achieve thin-section contrast-enhanced images of the abdomen and chest has been radically altered, thereby allowing a technique of truly dynamic contrast-enhanced CT and CT angiography. The resultant high-quality images have allowed improved detection of both liver and extrahepatic disease in these patients, thus potentially decreasing the likelihood that PET will improve on the results of conventional imaging studies. Therefore evaluating the technique used in comparison CT scans is important when analyzing the results of PET studies. Because of this, results from prospective studies, such as those from Ruers et al.,[7] are preferred because all patients had the same preoperative imaging evaluation.

Although the present study was retrospective and imaging studies were obtained from different institutions using a variety of equipment and techniques, these patients represent a typical university referral practice in which many patients present with CT scans of sufficient quality that there is no indication to repeat them. Although this is a potential weakness of our study, it is also representative of common clinical practice and thus may better reflect the actual yield of PET scans in tertiary referral centers.

The overall results of recent series evaluating PET in patients with resectable colorectal liver metastases are presented in Table 5. Only larger series that have been published since 1999 are included. As seen in Table 5, our series had a higher rate of false negative readings and a lower rate of detection of disease not seen on conventional imaging compared to other series, whereas the false positive rate of 5% falls within the range reported by others. One strength of the present study is its size compared to other series. In addition, all patients with false negative or false positive PET scans had confirmation of these findings by means of biopsy, IOUS, or serial CT scans.

Table 5. Summary of recent PET series evaluating patients with colorectal hepatic metastases

Reference	n	Follow-up (mo)	Dates of study	Detection of additional disease not seen on conventional imaging	False positive	False negative
Desai et al.[8] (2003)	42	17.4 (mean)	11/98–8/99	14 (33%)	2 (5%)	6 (14%)
Ruers et al.[7] (2002)	51	Not given	11/98–9/99	8 (16%)	1 (2%)	2 (4%)
Strasberg et al.[4] (2001)	43	24 mo (median)	4/95–2/99	10 (25%)	0	7 (16%)
Topal et al.[15] (2001)	91	23 mo (mean)	7/90–12/98	10 (11%)	6 (6.6%)	7 (7.7%)
Fong et al.[3] (1999)	40	7 mo (median)	6/96–6/98	9 (23%)	2 (5%)	4 (10%)
Present series	85	17.7 mo (median)	11/98–4/02	10 (12%)	4 (5%)	19 (22%)
TOTAL	352			61 (17%)	15 (4%)	45 (13%)

Clearly, the means by which PET findings are verified is important in evaluating false positive and negative readings. It is particularly important to define the follow-up period for patients with false positive findings in order to determine their true incidence. The actual incidence of false positive readings is significant because patients with positive PET scans may not be offered the option of definitive surgery and thus may miss an opportunity for curative resection. Unfortunately, several previous series did not define the means by which PET-positive lesions were proved to be carcinoma[4,7,8] or the length of follow-up.[3,7,9,10]

One possible explanation for the high rate of false negative readings in our study is the inclusion of patients with unresectable liver metastases who were undergoing evaluation for hepatic arterial chemotherapy. Alternatively, because these patients have a high risk of occult extrahepatic disease, PET may result in greater detection of extrahepatic disease. Because extrahepatic disease is a contraindication to hepatic artery infusional chemotherapy, PET may spare patients an unnecessary laparotomy and thus we included these patients in this study. Only seven patients were included who had unresectable disease on conventional imaging, and were being evaluated for hepatic artery pump placement. Among these patients the PET scan added no information over conventional imaging in five of them and demonstrated false negative findings in two. Clearly these few patients did not unnecessarily weight the study toward a greater number of false negative readings and did not improve the yield of PET scans by finding additional disease that was not seen on conventional imaging. Although the number of patients was small, there was no correlation with the yield of PET scans in patients with unresectable disease compared to those with resectable disease ($P = 0.6$, chi square analysis).

One prior study in which PET results are questionable because of a low rate of resectability is that of Desai et al.[8] This study reported that 33% of patients had additional disease detected on PET scans that was not visualized by conventional imaging. This is the highest rate of any contemporary study. One possible explanation is that this may be due to inadequate conventional imaging. One additional problem in interpreting the results of this study is that the number of patients with colorectal hepatic metastases who underwent operative exploration was only 7 (28%) of 25, and only two (29%) of seven were resectable at the time of surgery. This is clearly not in keeping with our own findings and those of other recent series in which the resectability rate was as high as 80%.[11] Thus this may be a reflection of nihilism regarding the possibility of curative resection in these patients. Because of this, it is difficult to generalize these results to other studies with more widely accepted resectability rates.

In evaluating false negative findings on PET scans, one concern is that the true incidence of false negative readings may be underestimated. This is because patients who present with early recurrences after resection, clearly the result of missed disease on PET scans, are not categorized as false negative. In the study by Fong et al.,[3] at a short median follow-up of 7 months, 40% of patients had a recurrence after liver resection, whereas other series have reported recurrences as early as 3 months after resection.[4] In the present series, 4 (10%) of 39 resected patients had a recurrence less than 6 months after surgical resection. Clearly these early recurrences represent disease that was present at the time of resection but was not detected on PET. Unfortunately, recurrence is often not analyzed as a factor in evaluating results of PET.[7–10] It is clear that PET fails to detect clinically relevant extrahepatic disease that is not reported as a true false negative. Although a fraction of these findings are likely due to disease that is below the level of detection by PET, at least some of these early recurrences are due to true false negative findings on PET. Thus the rate of false negative findings is likely higher than reported.

The varying results among studies evaluating PET results suggest that institutional differences exist in the methods used to obtain and interpret PET scans.

This demonstrates the reason why single-institution studies are important in evaluating new technology. More important, this emphasizes the fact that surgeons should use the imaging evaluation that is most accurate at their institutions.

Part of the difficulty in interpreting PET scans is the near-complete absence of anatomic landmarks, which clearly limits the radiologist's ability to accurately localize glucose-avid lesions. One way to overcome this problem and decrease inaccurate readings on PET scans is through the use of combined PET-CT technology. The technology of PET-CT includes images that are acquired at the same time; the resultant images are then coregistered and analyzed together as fused images.[12,13] Recent PET-CT models include both a multidetector helical CT scanner and a clinical PET scanner, both of which include hardware-fused images. Results of series that used this technology in patients with lung or head and neck tumors have shown a reduction in both false negative and false positive readings.[12,13] This is likely due to the increased ability to assign physiologic or malignant character to hypermetabolic lesions when the precise anatomic site is identified. Therefore this recent technology may serve as one means of improving the ability of PET scans to accurately localize and characterize metabolic lesions, thus improving overall accuracy.

The CRS is a valuable tool for evaluating patients with hepatic colorectal metastases, primarily because all of the factors that determine the CRS are known preoperatively. Because all patients with hepatic colorectal metastases are by definition stage IV, the CRS offers a more refined way to assess prognosis. Because the CRS has been shown to correlate with the presence of occult extrahepatic disease, either at the time of surgery[6] or manifesting as recurrence,[1] we hypothesized that the CRS should also correlate with the yield of the PET scan, and thus may help improve patient selection for those undergoing PET.

Because the CRS has not been correlated with outcome in patients presenting with recurrent colorectal metastases[14] or with unresectable disease, we analyzed only those patients presenting with a first occurrence of hepatic colorectal metastases. The yield of PET scans in patients with a CRS of 0 was significantly different from the yield in patients with a CRS of 1 or greater. Among patients with a CRS of 0, none had additional disease detected on PET that was not seen on conventional imaging, and four patients had false positive findings. The fact that PET did not detect additional metastatic disease in any patient with a CRS of 0 is expected, because patients with a low CRS have minimal risk of occult metastatic disease. Because of this we recommend conventional imaging only in patients with a CRS of 0. Although these findings need to be verified in larger series, the implication is that the use of the CRS to improve patient selection for preoperative PET may improve the overall yield.

An interesting phenomenon was the large number of false positive findings in the CRS 0 group, particularly when no patient with a CRS of 1 or greater had false positive readings. There was a highly significant difference in the rate of false positive findings between these two groups ($P < 0.0001$, chi-square analysis), but the reason for this difference is unclear. Because the correlation of CRS with PET findings has not been evaluated in other series, it is impossible to know how our results compare with those from other institutions. There is no obvious reason why patients with a low CRS would have an increased risk of false positive lesions in the liver. However, the finding of a high false positive rate in the group with a CRS of 0 may be less important than the fact that there were no findings of additional disease detected on PET in these patients. Because of this we believe that patients with a CRS of 0 should not undergo PET, both because PET adds no useful data and because it may yield false positive readings that may result in unnecessary laparotomy. Larger studies evaluating the correlation of the CRS with PET findings may further distinguish which patients with a CRS of 1 or higher should be evaluated by means of PET.

CONCLUSION

Although PET holds promise for detection of occult extrahepatic disease in patients with colorectal hepatic metastases, false positive and false negative results affect its overall utility. Patients at low risk of metastatic disease (CRS = 0) should not undergo PET before surgical exploration because these patients have a low rate of detection of extrahepatic disease and a high rate of false positive findings. Larger prospective studies evaluating both the yield of PET and its cost-effectiveness are essential before we can routinely recommend its use in all patients with isolated hepatic colorectal metastases.

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REFERENCES

1. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. Ann Surg 1999;230:309–318.
2. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system

to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer 1996;77:1254–1262.
3. Fong Y, Saldinger PF, Akhurst T, Macapinlac H, Yeung H, Finn RD, Cohen A, Kemeny N, Blumgart LH, Larson SM. Utility of 18F-FDG positron emission tomography scanning on selection of patients for resection of hepatic colorectal metastases. Am J Surg 1999;178:282–287.
4. Strasberg SM, Dehdashti F, Siegel BA, Drebin JA, Linehan D. Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma: A prospective database study. Ann Surg 2001;233:293–299.
5. Huebner RH, Park KC, Shepherd JE, Schwimmer J, Czernin J, Phelps ME, Gambhir SS. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. J Nucl Med 2000;41:1177–1189.
6. Jarnagin WR, Conlon K, Bodniewicz J, Dougherty E, DeMatteo RP, Blumgart LH, Fong Y. A clinical scoring system predicts the yield of diagnostic laparoscopy in patients with potentially resectable hepatic colorectal metastases. Cancer 2001;91:1121–1128.
7. Ruers TJ, Langenhoff BS, Neeleman N, Jager GJ, Strijk S, Wobbes T, Corstens FH, Oyen WJ. Value of positron emission tomography with [F-18]fluorodeoxyglucose in patients with colorectal liver metastases: A prospective study. J Clin Oncol 2002;20:388–395.
8. Desai DC, Zervos EE, Arnold MW, Burak WE Jr, Mantil J, Martin EW Jr. Positron emission tomography affects surgical management in recurrent colorectal cancer patients. Ann Surg Oncol 2003;10:59–64.
9. Boykin KN, Zibari GB, Lilien DL, McMillan RW, Aultman DF, McDonald JC. The use of FDG-positron emission tomography for the evaluation of colorectal metastases of the liver. Am Surg 1999;65:1183–1185.
10. Lai DT, Fulham M, Stephen MS, Chu KM, Solomon M, Thompson JF, Sheldon DM, Storey DW. The role of whole-body positron emission tomography with [18F]fluorodeoxyglucose in identifying operable colorectal cancer metastases to the liver. Arch Surg 1996;131:703–707.
11. Jarnagin WR, Fong Y, Ky A, Schwartz LH, Paty PB, Cohen AM, Blumgart LH. Liver resection for metastatic colorectal cancer: Assessing the risk of occult irresectable disease. J Am Coll Surg 1999;188:33–42.
12. Hany TF, Steinert HC, Goerres GW, Buck A, Von Schulthess GK. PET diagnostic accuracy: Improvement with in-line PET-CT system: Initial results. Radiology 2002;225:575–581.
13. D'Amico TA, Wong TZ, Harpole DH, Brown SD, Coleman RE. Impact of computed tomography-positron emission tomography fusion in staging patients with thoracic malignancies. Ann Thorac Surg 2002;74:160–163.
14. Petrowsky H, Gonen M, Jarnagin W, Lorenz M, DeMatteo R, Heinrich S, Encke A, Blumgart L, Fong Y. Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: A bi-institutional analysis. Ann Surg 2002;235:863–871.
15. Topal B, Flamen P, Aerts R, D'Hoore A, Filez L, Van Cutsem E, Mortelmans L, Penninckx F. Clinical value of whole-body emission tomography in potentially curable colorectal liver metastases. Eur J Surg Oncol 2001;27:175–179.

Discussion

Dr. J. Fischer (Boston, MA): There is really a rather stark contrast between a CRS score of 0 and a CRS score of 1, and perhaps it was almost predictable, but why do you think it is that way actually? One conclusion you can draw is do not bother with a CRS score of 0. Is that what you are saying?

Dr. C. Schüssler-Fiorenza: Patients with a CRS of 0 are less likely to have extrahepatic disease or occult metastatic disease present at the time of laparotomy. Thus one would expect a decreased utility of PET in this group, and that is exactly what we found in this study.

The reverse question is why wasn't there a higher yield of PET in patients with a high CRS, where you would expect more extrahepatic disease. This may be related to the relatively small size of our study. Clearly, evaluating the yield of PET according to the CRS should be replicated in a larger series of patients to see if these correlations continue. That is what clinically makes sense to me.

Dr. Fischer: On the contrary, if this were replicated in a larger series, what you would say is if the CRS is 0—don't get a PET and don't spend the money, which might be very useful.

Dr. Schüssler-Fiorenza: That is correct.

Dr. J. Eagon (St. Louis, MO): What percentage of the patients had received chemotherapy before undergoing PET, and did that affect the false negative or false positive readings?

Dr. Schüssler-Fiorenza: Of the 85 patients, 14 of them had received chemotherapy within 1 month; an additional nine had undergone chemotherapy within 3 months. When we evaluated this, we were not able to demonstrate any statistical significance in the yield of PET according to whether the patient had recently received chemotherapy. Again, the number of patients receiving chemotherapy may not have been sufficient to show statistical significance.

Dr. C. Schmidt (Indianapolis, IN): I am intrigued by the false negative rate, which seems high. There are some recent studies that are prospective in nature looking at PET scans. Dr. Yuman Fong has written on this subject.

I am curious as to what technology was used? The technology is changing very rapidly, and older PET

scans used a SPECT-type technology, whereas newer CT-PET scans have resolution in the 1 cm or even sub-1 cm range; I wonder if you could comment on the potential effect of that on your false negative rate?

Dr. Schüssler-Fiorenza: We used a GE Advance PET scanner. I cannot comment on whether all patients received one of the newer techniques or not, especially since our accrual began in 1998. It is true that our rate of false negative readings was somewhat higher than in other studies; this may either reflect the PET scanner used or it may illustrate the fact that PET scanning is a user-dependent technology.

One of the newer developments that we are interested in evaluating is the PET-CT scan, which we think may help improve accuracy in staging patients with metastatic colorectal cancer by providing greatly improved anatomic correlation, compared to current PET scans. As this technology becomes more developed, we will need to evaluate how this can help us to better select patients who are candidates for surgical resection of colorectal liver metastases.

Extensive Preoperative Testing Is Not Necessary in Morbidly Obese Patients Undergoing Gastric Bypass

Archana Ramaswamy, M.D., Rodrigo Gonzalez, M.D., C. Daniel Smith, M.D.

Morbidly obese patients are considered at high risk for perioperative complications and often undergo extensive testing for preoperative clearance. We analyzed prospectively collected data from 193 patients undergoing weight loss surgery between November 2000 and November 2002. Preoperative chest x-ray examination, pulmonary function tests, noninvasive cardiac testing, and blood work were performed routinely. Preoperative testing identified abnormalities on eight chest x-ray films (4%) and 29 electrocardiograms (15%), none of which required preoperative intervention. Spirometry was abnormal in 41 patients (21%); logistic regression identified preexisting asthma as predictive of obstructive physiology (odds ratio [OR] 3.3; 95% confidence interval [CI] 1.2 to 8.9), and body mass index as predictive of restrictive physiology (OR 1.1; 95% CI 1.01 to 1.2). Arterial blood gases identified only one case of severe hypoxemia requiring intervention. Mild hypoxemia was associated with increasing age (OR 14.5; 95% CI 1.8 to 114). Echocardiography demonstrated four abnormalities (2%); previous history of cardiac disease was the only risk factor (OR 14.5; 95% CI 1.8 to 114). Complete blood count did not identify 84% and 50% of the patients with iron (n = 31) and vitamin B_{12} (n = 12) deficiencies, respectively. Age, body mass index, and history of asthma were associated with abnormal pulmonary function tests and previous cardiac disease with abnormal cardiac testing. These tests are not mandatory as a routine preoperative evaluation and can be used selectively on the basis of medical history. (J GASTROINTEST SURG 2004;8:159–165)

KEY WORDS: Morbid obesity, gastric bypass, preoperative care

The prevalence of obesity in the United States has been steadily increasing; it is currently estimated that more than 60% of the population is overweight and more than 30% is obese.[1] The number of surgical weight loss procedures performed has mirrored the increasing prevalence of obesity, and it is estimated that 100,000 procedures will be performed in 2003.[2] Obesity is a risk factor for the development of several chronic disease states including diabetes,[3–6] heart disease,[3,7,8] hypertension,[3,5,9] sleep apnea,[10–12] and other respiratory problems.[11,12] Although the mechanisms that lead to the development of these medical morbidities have not been completely clarified, they may be due in part to changes in cytokines, hormones, and elevated cardiorespiratory demands. Morbidly obese patients are often feared to be high-risk patients, even when medical comorbidity is not clearly apparent. The necessary extent of preoperative testing has not been defined.

MATERIAL AND METHODS

Analysis was performed on data that had been prospectively collected from patients being evaluated for weight loss surgery between November 2000 and November 2002. During this time, all patients underwent routine comprehensive preoperative evaluation. Blood work included a comprehensive metabolic profile, complete blood count, coagulation studies, thyroid function tests, and anemia studies. Chest x-ray abnormalities were identified from radiology reports. Noninvasive cardiac testing included an electrocardiogram (ECG) and stress echocardiogram.

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An abnormal ECG was defined as bundle branch block, nonsinus rhythm, ST-segment abnormality, T-wave abnormality, or left ventricular hypertrophy. Dobutamine stress echocardiography (DSE) abnormalities were defined as evidence of valvular dysfunction or wall motion abnormalities at maximum heart rate. Few patients underwent exercise stress testing (n = 4) or nuclear myocardial scintigraphy (n = 7) (when DSE was unsuccessful). Cardiac catheterization was performed as indicated on the basis of noninvasive cardiac test abnormalities. Pulmonary function test abnormalities were divided into restrictive and obstructive physiology, or combined defects. Arterial blood gas values were used to identify individuals with hypoxemia, significant hypercapnia (pCO_2 >47), or significant acid-base imbalance.

Statistical analysis was performed using multivariate logistic regression to identify predictors of abnormal test results.

RESULTS

A total of 193 patients were included in the analysis. Baseline characteristics are presented in Table 1. Mean age was 42 years (± 10 years), and 170 patients (88%) were female. Mean body mass index (BMI) was 50 kg/m^2 (± 8 kg/m^2). At least one medical comorbidity was present in 139 patients (72%). Of the 28 patients with preexisting pulmonary disease (excluding obstructive sleep apnea), the majority (86%) reported a history of asthma.

Blood Work

Complete blood count identified 11 cases of mild anemia; five were associated with iron deficiency and one with vitamin B_{12} deficiency. Conversely, iron studies identified deficiencies in 31 patients (16%), but only five (16%) had an associated abnormal complete blood count demonstrating anemia. Virtually all of the patients with iron deficiency were women (97%). Vitamin B_{12} deficiency was noted in 12 patients (6%), all women, with only one having anemia identified on complete blood count. All patients with deficiencies were treated preoperatively. Coagulation studies identified an elevated international normalized ratio in only one patient who was being treated with warfarin.

Few anomalies were identified on comprehensive metabolic profile; three patients had mild hypokalemia, two had moderately high liver enzyme levels (steatosis on liver biopsy), and one had mildly elevated creatinine (known mild renal failure). Hypoalbuminemia was noted in 25%, although it was severe (<3.0 mg/dl) in only one patient who was given protein supplements preoperatively. Thyroid function tests were abnormal with high thyroid-stimulating hormone levels in six individuals (3%); four of them had known hypothyroidism and two had normal values on repeat testing.

Table 1. Study population characteristics

Patient characteristics	
Age (mean ± SD)	42 yr (±10)
Sex	
Male	23 (12%)
Female	170 (88%)
Weight (mean ± SD)	303 pounds (±52)
BMI (mean ± SD)	50 kg/m^2 (±8)
Current smoker	41 (21%)
Medical comorbidities	
Hypertension	103 (53%)
Diabetes mellitus	53 (27%)
Dyslipidemia	26 (13%)
Heart disease	13 (7%)
Obstructive sleep apnea	60 (31%)
Other pulmonary disease	28 (15%)

Pulmonary Tests

Chest x-ray examination identified eight minor abnormalities, including mild cardiomegaly in three, granuloma three, and a small unchanged lesion in two. None of these findings elicited any further workup preoperatively.

Results of pulmonary function tests were abnormal in 41 patients (21%). Obstructive physiology was identified in 22 (54%); the majority were classified as mild airflow obstruction (n = 20), with one each being classified as moderate and severe airflow obstruction. These patients were treated with bronchodilators as indicated by the bronchodilator response on measured flow rates. Logistic regression identified preexisting asthma as the only predictor of obstructive physiology with an odds ratio (OR) of 3.3 (95% confidence interval [CI] of 1.2 to 8.9). Restrictive physiology was identified in 17 patients (41%), all with mild restrictive impairment. Univariate logistic regression identified age, sex, BMI, and obstructive sleep apnea as predictors of restrictive physiology. However, multivariate logistic regression, when adjusted for the preceding covariates, identified only BMI as a statistically significant predictor (OR 1.1; 95% CI 1.01 to 1.2). This can be interpreted as a 10-point increase in BMI (e.g., 45 to 55) being associated with a 2.1-fold increase in the risk of restrictive lung disease as identified on pulmonary function testing. Two patients had combined obstructive and restrictive physiology.

Arterial blood gas measurements identified hypoxemia in 36 patients (17%), of which only one patient was identified as having severe hypoxemia. This patient was a 61-year-old woman with a BMI of 60 who was then given preoperative home oxygen therapy. Univariate logistic regression identified age and sex as predictors of hypoxemia. Multivariate logistic regression, when adjusted for BMI, sex, obstructive sleep apnea, and previous history of pulmonary disease, still yielded significant parameter estimates for age (OR 1.05; 95% CI 1.01 to 1.09). Severe abnormalities in both pulmonary function tests and/or arterial blood gases prompted planned postoperative admission to the intensive care unit for observation.

Noninvasive Cardiac Testing

Abnormal ECGs were identified in 29 patients (15%). All anomalies were minor and did not prompt any further intervention. DSE, or other stress tests in a few patients, identified four patients with abnormalities. All of them subsequently underwent cardiology assessment. Two of the patients had a history of cardiac disease and one had a history of stroke. These three patients had low ejection fractions on DSE and were cleared for surgery. One patient, without any history of cardiac or vascular abnormalities, had DSE evidence of inducible ischemia. She then underwent cardiac catheterization, the results of which were normal, and was subsequently also cleared for surgery. Logistic regression identified a history of heart disease as the only risk factor for an abnormal DSE (OR 14.5; 95% CI 1.8 to 114). Among patients with a history of heart disease, two (15%) had an abnormal DSE. If the algorithm proposed by the American College of Cardiology/American Heart Association[12] is applied to this study population, 94% of the patients would not have undergone DSE prior to surgery. Among the 12 patients who would have needed DSE, three (25%) had abnormal findings. The only patient who had evidence of inducible ischemia, and would not have required DSE according to the algorithm, was the same patient who then underwent cardiac catheterization with normal results.

DISCUSSION

Studies looking at the relationship between obesity and perioperative complications in patients undergoing laparoscopic surgery have reported no increase in risk.[13–18] These studies have reported on small samples and do not describe what preoperative tests, if any, were performed. Surgeons are increasingly performing more elective procedures on obese patients, but frequently only after extensive preoperative evaluation. Extensive testing of all patients was once routine. This practice has been questioned over the past 20 years, and guidelines have been proposed based on the available evidence that is of benefit for the patient.

Routine preoperative chest x-ray examinations have a low yield in patients who are healthy, female, 60 years of age or less, and free of respiratory disease.[19] The frequency with which routine preoperative chest x-ray films are influencing management has been reported to be as low as 0.1 % according to a meta-analysis.[20] As a result of these findings, some recommend preoperative chest x-ray examinations only for patients over 50 years of age, with preexisting cardiac or pulmonary disease, or on the basis of physical findings.[21] We noted abnormalities in 4%, with none requiring any further investigation.

A preoperative ECG is recommended for men over 40 years of age, women over 50, or individuals with cardiac risk factors.[21,22] Because morbid obesity is a risk factor for heart disease, it is reasonable that all of these patients undergo routine preoperative ECG. None of the abnormal ECGs in our study population (15%) elicited any further investigations. This is somewhat misleading because by the time the ECG was reviewed results from DSE were also usually available, and thus obviated any further decision-making based on abnormal ECGs.

The relationship between obesity and heart disease is likely via various pathways. Obesity-related hypertension, diabetes mellitus, and dyslipidemia are all risk factors for coronary artery disease. In addition, obesity is an independent risk factor for coronary artery disease. Obesity has also been associated with an increased risk of heart failure.[8] This may develop as a complication of hypertension and diabetes mellitus either directly or via their causation of coronary artery disease and myocardial infarction. In addition, heart failure may also be the end result of obstructive sleep apnea leading to pulmonary hypertension and right ventricular failure.

DSE has been beneficial in patients with vascular disease as a noninvasive cardiac test, because these individuals are often unable to attain their maximum heart rate during exercise stress testing because of claudication. Similarly, obese patients also are often limited in their ability to exercise, and DSE is the most cost-effective stress test in this situation. DSE has a high negative predictive value but low positive predictive value for the outcome of postoperative cardiac complications in patients undergoing major noncardiac vascular procedures.[23,24] Because the postoperative incidence of cardiac events is lower in patients undergoing bariatric surgery, when compared to vascular surgery, we can surmise that the positive

predictive value of DSE in this population will be even lower. In a non–cardiac surgery population, even when American College of Cardiology/American Heart Association guidelines are followed for selecting patients to undergo DSE, only 4 of 85 demonstrated evidence of inducible ischemia, and only in one of those patients was the preoperative coronary angiogram abnormal, necessitating preoperative revascularization.[25] Given the low positive predictive value and specificity of DSE, a number of patients with false positive test results will then undergo invasive testing, with the concomitant risks.

Physiologic changes in lung function in obesity are attributed to decreases in lung compliance from the weight of the abdomen and chest wall, as well as increased airway resistance, possibly from small airway narrowing.[26] Abnormalities noted on spirometry can vary from an isolated decrease in expiratory reserve volume to decreases in total lung capacity, forced expiratory volume in 1 second (FEV_1), maximum voluntary ventilation, and functional residual capacity.[12] Both obesity and obstructive sleep apnea are risk factors for the development of postoperative pulmonary complications.[27] An association between preoperative spirometry and postoperative complications has not been demonstrated in patients undergoing abdominal surgery[27] or in morbidly obese patients undergoing gastric bypass.[28] Analysis of arterial blood gases often reveals an increased alveolar-arterial oxygen gradient, hypoxemia, or hypercarbia in obese individuals. Preoperative pulmonary risk assessment is not improved by routinely analyzing arterial blood gases.[27] Our analysis showed an association between a history of asthma and obstructive physiology, between BMI and restrictive physiology, and between age and hypoxemia. All of these relationships seem logical. Although spirometry and arterial blood gases incur little risk to the patient, patient discomfort and cost (~$750 at our institution) need to be considered because no moderate or severe abnormalities were noted in patients without a history of pulmonary disease, or at the upper spectrum of BMI and age.

Routine preoperative blood work consisting of electrolyte, renal function, complete blood count, and coagulation studies has been repeatedly shown to have a low incidence of abnormal results (0.3% to 6.5%, pooled results from various studies) with an even lower proportion of these results leading to an alteration in patient management (0% to 2.6%).[21] Our rate of detected abnormalities falls within the above-mentioned range, although it does seem reasonable to continue to routinely gather information on electrolyte levels, renal function, and complete blood counts because many of our patients are taking diuretics or other medications, and the operative procedure can infrequently be associated with significant postoperative bleeding. Coagulation studies, however, are likely not indicated unless a history of bleeding tendencies is elicited from the patient.

Vitamin B_{12} or iron deficiency was noted in 22% of our study population. After gastric bypass, deficiencies of iron (33% to 49%) and vitamin B_{12} (37% to 70%) are relatively common.[29–31] It therefore seems prudent to detect any deficiencies preoperatively and institute supplementation before proceeding with a procedure that is likely to worsen this.

The association between obesity and hypothyroidism has been demonstrated,[32] as has the benefit of small doses of thyroid hormone supplementation on dyslipidemia in obesity.[33] Given that L-thyroxin is the fifth most commonly prescribed medication in the United States,[34] it can be appreciated that screening for hypothyroidism and subclinical hypothyroidism is widespread among primary care providers. This can be proposed as an explanation for the low yield in thyroid function test abnormalities identified in patients arriving for preoperative screening.

Preoperative screening tests may have such a low rate of identifying latent medical problems because most of these obese patients have had significant medical supervision prior to surgical referral. After a report demonstrating low rates of physician reporting and intervention in obesity,[35] the importance of screening and identifying comorbid conditions in obese patients has been emphasized in the primary care setting.[36–43] Patients are mainly referred to us by primary care physicians, although some are referred by medical specialists. The extensiveness of prescreening in our patient population is unknown. However, because all of these patients have undergone physician-supervised diets before being referred for surgery, it can be assumed that basic blood tests, including electrolytes, renal function, complete blood count, and thyroid function tests, have probably been previously performed. Other screening tests were probably uncommonly performed. The only exception to this may be pulmonary function tests because 31% of patients referred had already been diagnosed with sleep apnea based on sleep studies.

When deciding which investigations should be performed routinely, we need to consider the cost-effectiveness and the possible benefit for the patient. In particular, tests should not be done if they are not going to alter management, or if they are associated with a low positive predictive value, which can lead to further tests, some of which may be invasive and associated with risks. Blood tests are relatively inexpensive; however, there are always 5% of individuals who will fall at the extremes of the bell curve and outside predetermined "normal values." When numerous low-yield

tests are performed, the risk of obtaining a false positive result is compounded, again leading to further unnecessary testing.

In summary, we found that abnormal cardiac test results were associated with a history of cardiac disease; abnormal pulmonary function was associated with BMI and asthma history for spirometry and age for arterial blood gases. Iron and B_{12} deficiency were not reliably predicted from routine complete blood count determinations of anemia. Thyroid function tests, coagulation studies, and chest x-ray examinations have a low yield, with no change in management based on abnormal test results. We propose that routine preoperative investigations in obese patients should include complete blood count, electrolytes, ECG, and anemia studies. Further investigations, including coagulation studies, chest x-ray examination, cardiac stress tests, and pulmonary function tests, should be selectively performed on the basis of patient history of bleeding tendencies, cardiopulmonary disease, or evidence-based pathways already in place in institutions guiding the ordering of preoperative tests.

REFERENCES

1. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US Adults, 1999-2000. JAMA 2002;288:1723–1727.
2. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Working Group on Bariatric Surgery, Executive Summary, May 2002.
3. Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, Rimm E, Colditz GA. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med 2001;161:1581–1586.
4. Colditz GA, Willett WC, Rotnisky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995;122:481–486.
5. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olsen JE, Hong C-P, Sellers T, Lazovich D, Prineas RJ. Associations of general and abdominal obesity with multiple health outcomes in older women: The Iowa Women's Health Study. Arch Intern Med 2000;160:2117–2128.
6. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961–969.
7. Harris TB, Ballard-Barbasch R, Madans J, Makuc DM, Feldman JJ. Overweight, weight loss, and risk of coronary heart disease in older women: NHANES I Epidemiologic Follow-up Study. Am J Epidemiol 1993;137:1318–1327.
8. Kenchaiah S, Evans JC, Levy D, Wilson PWF, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. N Engl J Med 2002;347:305–313.
9. Field AE, Byers T, Hunter DJ, Laird NM, Manson JE, Williamson DF, Willett WC, Colditz GA. Weight cycling, weight gain, and risk of hypertension in women. Am J Epidemiol 1999;150:573–579.
10. Kyzer S, Charuzi I. Obstructive sleep apnea in the obese. World J Surg 1998;22:222–226.
11. O'Brien PE, Dixon JB. The extent of the problem of obesity. Am J Surg 2002;184:4S–8S.
12. Koenig S. Pulmonary complications of obesity. Am J Med Sci 2001;321:249–279.
13. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froelich JB, Gusberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL Jr. ACC/AHA Guideline update for perioperative cardiovascular evaluation for noncardiac surgery: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Non Cardiac Surgery). J Am Coll Cardiol 2002;39:542–553.
14. Bai SW, Lim JH, Kim JY, Chung KA, Kim SK, Park KH. Relationship between obesity and the risk of gynecologic laparoscopy in Korean women. J Am Assoc Gynecol Laparosc 2002;9:165–169.
15. Holub Z, Jabor A, Kliment L, Fischlova D, Wagnerova M. Laparoscopic hysterectomy in obese women: A clinical prospective study. Eur J Obstet Gynecol Reprod Biol 2001;98:77–82.
16. Kuo PC, Plotkin JS, Stevens S, Cribbs A, Johnson LB. Outcomes of laparoscopic donor nephrectomy in obese patients. Transplantation 2000;69:180–182.
17. Tuech J-J, Regenet N, Hennekinne S, Pessaux P, Bergamaschi R, Arnaud J-P. Laparoscopic colectomy for sigmoid diverticulitis in obese and non-obese patients. Surg Endosc 2001;15:1427–1430.
18. Birgisson G, Park AE, Mastrangelo MJ, Witzke DB, Chu UB. Obesity and laparoscopic repair of ventral hernias. Surg Endosc 2001;15:1419–1422.
19. Silvestri L, Maffessanti M, Gregori D, Berlot G, Gullo A. Usefulness of routine preoperative chest radiography for anaesthetic management: A prospective multicentre pilot study. Eur J Anaesthesiol 1999;16:749–760.
20. Archer C, Levy AR, McGregor M. Value of routine preoperative chest x-rays: A meta-analysis. Can J Anaesth 1993;40:1022–1027.
21. Smetana GW, Macpherson DS. The case against routine preoperative laboratory testing. Med Clin North Am 2003;87:7–40.
22. Marcello PW, Roberts PL. Cost effectiveness in surgery. "Routine" preoperative studies. Which studies in which patients? Surg Clin North Am 1996;76:11–23.
23. Poldermans D, Fioretti PM, Forster T, Thomson IR, Boersma E, El-Said EM, du Bois NAJJ, Roelandt JRTC, van Urk H. Dobutamine stress echocardiography for the assessment of preoperative cardiac risk in patients undergoing major vascular surgery. Circulation 1993;87:1506–1512.
24. Eichelberger JP, Schwarz KQ, Black ER, Green RM, Ouriel K. Predictive value of dobutamine echocardiography just before noncardiac vascular surgery. Am J Cardiol 1993;72:602–607.
25. Morgan PB, Panomitros GE, Nelson A, Smith DF, Solanki DR, Zornow MH. Low utility of dobutamine stress echocardiograms in the preoperative evaluation of patients scheduled for noncardiac surgery. Anesth Analg 2002;95:512–516.
26. Unterborn J. Pulmonary function testing in obesity, pregnancy, and extremes of body habitus. Clin Chest Med 2001;22:759–767.
27. Arozullah AM, Conde MV, Lawrence VA. Preoperative evaluation for postoperative pulmonary complications. Med Clin North Am 2003;87:153–173.
28. Crapo RO, Kelly TM, Elliott CG, Jones SB. Spirometry as a preoperative screening test in morbidly obese patients. Surgery 1986;99:763–767.
29. Amaral JF, Thompson WR, Caldwell MD, Martin HF, Randall HT. Prospective hematologic evaluation of gastric exclusion for morbid obesity. Ann Surg 1985;201:186–193.

30. Brolin RE, Gorman RC, Milgrim LM, Kenler HA. Multivitamin prophylaxis in prevention of post-gastric bypass vitamin and mineral deficiencies. Int J Obes 1991;15:661–668.
31. Brolin RE, Gorman JH, Gorman RC, Petschenik AJ, Bradley LJ, Kenler HA, Cody RP. Are vitamin B_{12} and folate deficiency clinically important after Roux-en-Y gastric bypass? J GASTROINTEST SURG 1998;2:436–442.
32. Rimm AA, Werner LH, Van Yserloo B, Bernstein RA. Relationship of obesity and thyroid disease in 73,532 weight-conscious women. Public Health Rep 1975;90:44–51.
33. Krotkiewski M, Holm G, Shono N. Small doses of triiodothyronine can change some risk factors associated with abdominal obesity. Int J Obes 1997;21:922–929.
34. Krotkiewski M. Thyroid hormones in the pathogenesis and treatment of obesity. Eur J Pharmacol 2002;440:85–98.
35. Stafford RS, Farhat JH, Misra B, Schoenfeld DA. National patterns of physician activities related to obesity management. Arch Fam Med 2000;9:631–638.
36. Kushner RF, Weinsier RL. Evaluation of the obese patient. Practical considerations. Med Clin North Am 2000;84:387–399.
37. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Arch Intern Med 1998;158:1855–1867.
38. National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity, and health risk. Arch Intern Med 2000;160:898–904.
39. Bray GA. Health hazards of obesity. Endocrinol Metab Clin North Am 1996;25:907–919.
40. Kyzer S, Charuzi I. Obstructive sleep apnea in the obese. World J Surg 1998;22:222–226.
41. Eckel RH. Obesity and Heart Disease. A statement for healthcare professionals from the nutrition committee, American Heart Association. Circulation 1997;96:3248–3250.
42. Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, Rimm E, Colditz GA. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med 2001;161:1581–1586.
43. Colditz GA, Willett WC, Rotnisky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995;122:481–486.

Invited Discussion—Expert Commentator

Dr. Bruce D. Shirmer (Charlottesville, VA): This abstract describes the data from preoperative testing of 193 patients undergoing gastric bypass for severe obesity. The authors routinely performed not only the usual blood work but also pulmonary function tests, arterial blood gas tests, chest x-ray examinations, and non-invasive cardiac tests as part of the preoperative evaluation. They have demonstrated that a history of asthma and a history of cardiac disease should be the indications for performing routine preoperative pulmonary and cardiac function tests, respectively, and that these tests have a low yield with regard to finding pathology in otherwise asymptomatic patients. Their finding that thyroid testing is of low yield has been experienced by all of us doing this work, but I personally would not recommend abandoning that preoperative screening, especially in view of the medicolegal implications of not addressing the issue preoperatively. The same is probably true for serum cortisol levels, which we still obtain routinely preoperatively, and I have not had a positive one yet in more than probably 1500 screened patients.

With this study the authors have supplied further important data that justify making the preoperative assessment of patients undergoing gastric bypass the same as that for any preoperative patient—that is, the clinical picture should dictate the tests ordered. The finding of unsuspected anemias is important and has been our experience as well. However, in view of the fact that most of the patients are women in their reproductive years makes iron deficiency a given in a certain percentage of the population. Because gastric bypass is known to potentially cause deficiencies in iron and B_{12} absorption, it is appropriate to establish a preoperative baseline level of these parameters, and preoperatively treat deficiencies.

The authors have not addressed other areas where preoperative testing may also be clinically indicated, if not routine. We screen all of our patients for gallstones with preoperative ultrasonography, and we base our postoperative therapeutic strategies for potential gallstone formation on this information. We also perform routine preoperative endoscopy in patients with symptoms of GERD who are taking nonsteroidal anti-inflammatory drugs, or have a history of ulcer disease or gastritis or upper gastrointestinal bleeding. There are increasing data to suggest that we should test more for sleep apnea in this patient population. It is also unclear what role preoperative testing plays with regard to bone density or osteoporosis, given the concern for potential calcium malabsorption and osteoporosis after gastric bypass, the true incidence of which is still unknown. Results of such preoperative tests should also be scrutinized in future studies just as the Emory group has done for cardiac and pulmonary function testing.

Discussion

Dr. B. Bass (Baltimore, MD): Let me just do a quick survey here. Who routinely performs dobutamine stress tests in their patients?

Dr. Bass: Not too many, I see. Are you suggesting that we should do anemia studies?

Dr. A. Ramaswamy: I do believe that anemia studies are indicated. They are inexpensive. We are identifying about 30% of patients who have deficiencies, and we are performing a malabsorptive operative procedure, which we know can be associated with B_{12} and iron deficiencies postoperatively. Identifying these deficiencies and supplementing them preoperatively is reasonable.

Dr. Bass: What is your B_{12} regimen?

Dr. Ramaswamy: Most patients are given monthly subcutaneous injections, with a minority taking intranasal supplementation.

Dr. M. Murr (Tampa, FL): The most common undiagnosed entity in bariatric patients is obstructive sleep apnea. I found that 40% of all who come through the office for bariatric surgery have moderate-to-severe sleep apnea, and I wonder if you have instituted a policy of performing sleep studies? You alluded to blood gases and pulmonary function tests, but you did not mention anything about sleep studies.

Dr. Ramaswamy: We have not been doing sleep studies routinely in these patients. Approximately 30% of our patients have been diagnosed with sleep apnea based on screening by a primary care physician prior to consultation with us. Undiagnosed patients are sent for sleep studies based only on symptoms.

Dr. Murr: Can I follow on Dr. Bass' question regarding the dobutamine stress test? I may have missed it, but you indicated that you perform this test on everyone who comes in. What were the interventions that you did based on abnormal results of these studies?

Dr. Ramaswamy: One patient had evidence of inducible ischemia. This patient, who had no cardiac risk factors except for obesity, then underwent cardiac catheterization, the results of which were normal. There were three other patients who had abnormalities. They all had a history of either cardiac disease or stroke, and based on the cardiology consultation, no further interventions were done. They were medically optimized and brought to surgery.

Dr. S. Bowers (San Antonio, TX): I think that the denominator in your study is a little bit biased by selection in that all of your patients actually met the criteria and went on to have surgery. I wonder if you could tell us how many patients had to have their surgery cancelled because of cardiac morbidity, severe sleep apnea, or uncontrolled pulmonary disease?

Dr. Ramaswamy: Our study group included all patients undergoing evaluation for weight loss surgery, not just those who proceeded with surgery. Actually, not all of these patients had gone on to surgery at the time of analysis. Some patients were still going through the process of being evaluated. We were looking at how many tests were abnormal and what intervention then proceeded from there. So I do not actually know how many went on to surgery except for those specific patients. I mentioned who had abnormal dobutamine stress echocardiograms or pulmonary function tests, where the individuals were medically optimized prior to surgery.

Dr. M. Patti (San Francisco, CA): I enjoyed your presentation and I agree with most of what you say, but following up on the question that was asked before, what are your exclusion criteria? When do you tell a patient, I'm sorry, you have reached a point where we cannot operate? And specifically in patients who have sleep apnea and require a sleep apnea machine, do you assess preoperatively pulmonary artery pressures, and if you do, what is considered a pulmonary artery pressure where the anesthesiologist will not put those patients to sleep? When you assess pulmonary function tests, what FEV1 do you consider a cutoff?

Dr. Ramaswamy: We have not had any specific FEV1 as a cutoff. Severe abnormalities in pulmonary function have mostly prompted planned perioperative admission to the intensive care unit. All patients with diagnosed obstructive sleep apnea bring in their nasal CPAP machines, and continue with this treatment in the immediate postoperative period.

We are not routinely assessing preoperative pulmonary artery pressures in patients who are being treated for sleep apnea. Need for invasive monitoring is left up to the anesthesiologist, but we have not had any anesthesiologists decide not to proceed with the operation.

In terms of who we are refusing right now, we have instituted our policy based on some of our previous work, which suggested that patients with a BMI over 55 were at risk for increased perioperative complications. These patients are streamlined to medical weight loss until the desired BMI is reached, following which they are offered surgery. This cutoff was instituted recently, so there were individuals with a BMI above 55 who were included in this study population.

Kupffer Cell–Derived Fas Ligand Plays a Role in Liver Injury and Hepatocyte Death

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Liver injury is an important prognostic indicator during acute pancreatitis. The aim of this study was to determine the role of Fas ligand (FasL) in hepatocyte injury. Liver parenchymal enzymes were measured in cocultures of hepatocytes and Kupffer cells treated with elastase. FasL and FasL mRNA were measured in elastase-treated Kupffer cells. Hepatocytes were treated with FasL and their viability was assessed by monotetrazolium (MTT), apoptosis by flow cytometry, as well as caspase-3 and p38–mitogen-activated protein kinase (MAPK) by immunoblotting. Elastase increased aspartate aminotransferase and lactate dehydrogenase in cocultures of hepatocyte and Kupffer cells ($P < 0.040$). Elastase increased FasL production from Kupffer cells ($P = 0.02$) and upregulated FasL mRNA (FasL/beta-2 microglobulin (BMG): 0.23 ± 0.03 vs. 0.11 ± 0.003; $P = 0.04$). FasL increased alanine aminotransferase and lactate dehydrogenase ($P < 0.03$) and reduced hepatocyte viability by 45% ($P = 0.01$). FasL increased the number of dually labeled cells with AnnexinV/7AAD ($P = 0.03$) while upregulating cleavage of caspase-3 and the phosphorylation of p38-MAPK. FasL antibody attenuated the FasL-related increase in dually labeled cells ($P = 0.02$), the cleavage of caspase-3, and phosphorylation of p38-MAPK. Pancreatic elastase upregulates FasL within Kupffer cells. FasL induces hepatocyte injury and death and upregulates p38-MAPK and caspase-3 within hepatocytes. The ability to manipulate interactions between Kupffer cells and hepatocytes may have important therapeutic implications. (J GASTROINTEST SURG 2004;8:166–174)

KEY WORDS: Pancreatitis, Kupffer cells, Fas ligand, liver injury, hepatocyte apoptosis

Liver injury is a manifestation of the systemic inflammatory response during acute pancreatitis and is an important clinical prognostic indicator in that setting. The morbidity and mortality associated with severe acute pancreatitis is largely attributable to an exacerbation of the systemic inflammatory response and the subsequent distant organ dysfunction.[1]

We have demonstrated that pancreatic elastase plays a major role in extrapancreatic, organ-specific cytokine production suggesting that it may be the link between localized inflammation of the pancreas and the systemic manifestations of pancreatitis along with distant organ injury.[2–4] In addition, work from our laboratory has demonstrated that pancreatitis-associated liver injury is mediated by tumor necrosis factor (TNF) that is produced within tissue resident macrophages.[2,3] In that regard, the liver is a unique organ because Kupffer cells are the largest population of fixed tissue macrophages, which have been shown to have a distinct role in sepsis and hemorrhage.[5,6] However, the severe degree of liver parenchymal injury could not be solely attributed to TNF-mediated apoptosis or cell death. Therefore we explored whether other macrophage-derived cytokines play a role in pancreatitis-associated liver injury.

Fas is a cell surface protein belonging to the TNF receptor family, whereas Fas ligand (FasL) is a

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member of the TNF family. FasL is mainly produced by activated lymphocytes such as T cells and natural killer (NK) cells; it works as an effector of these cytotoxic cells to remove cells infected by virus or cancer cells. Although Fas-induced apoptosis is reported to promote parenchymal cell damage in liver disease, acute renal failure, glomerular injury, and thyroiditis, there is paucity of information regarding FasL expression in Kupffer cells during acute pancreatitis.[7] Furthermore, the effects of FasL on hepatocytes during acute pancreatitis have not been characterized. The current study was undertaken to determine the role of FasL in hepatocyte injury in an established in vitro model.

METHODS

Animals were cared for in accordance with the guidelines from the Department of Laboratory Animal Medicine at the University of South Florida, a facility accredited by the American Association for Accreditation of Laboratory Animal Care.

Hepatocyte Tissue Cultures

Hepatocytes were isolated from male Sprague-Dawley rats (300 to 350 g) by digestion with collagenase as described previously.[8,9] Livers were perfused in situ through the portal vein until cleared of blood with 10 mmol/L HEPES-buffered saline solution (0.15 mol/L NaCl, 0.42 g/L KCl, 0.99 g/L glucose, 2.1g/L NaCO3, and 0.19 g/L EDTA) and then perfused for 4 to 7 minutes with modified HEPES-buffered saline (no EDTA, 3.5 mmol/L $CaCl_2$, 1% bovine serum albumin (BSA), and 0.025% collagenase). The liver parenchyma was then dispersed manually, filtered through a 200 μm then through a 70 μm pore mesh (CellMicroSieve; BioDesign Inc. of New York, Carmel, NY) and centrifuged twice for 3 minutes at 50 *g* to remove nonparenchymal cells. Hepatocytes were plated at a density of approximately 1.0×10^6 in 12-well primary tissue culture plates (Becton Dickinson Labware, Franklin Lakes, NJ) with Dulbecco's modified eagle medium (DMEM; Atlanta Biologics, Atlanta, GA), supplemented with 200 mmol/L of L-glutamine (Sigma, St. Louis, MO), penicillin (100 U/ml), streptomycin (100 μg/ml), and 10% fetal bovine serum. Hepatocytes were then kept at 37C in humidified air with 5% CO_2. The medium was replaced, and nonadherent cells were removed in preparation for treatment.

Kupffer Cell Tissue Cultures

Freshly isolated rat Kupffer cells were provided by Dr. Hide Tsukamoto at the Non-Parenchymal Liver Cell Isolation Core in the USC Research Center for Liver Disease and USC-UCLA Research Center for Alcoholic Liver and Pancreatic Diseases. Briefly, the cells were isolated from male Sprague-Dawley rats (350 to 450 g) by in situ sequential digestion of the liver with pronase and collagenase, low-speed centrifugation to separate parenchymal and nonparenchymal cells, and subsequent separation of a Kupffer cell–enriched fraction by discontinuous arabinogalactin gradient centrifugation.[10] Kupffer cells were incubated in DMEM (Atlanta Biologics) supplemented with 200 mmol/L-glutamine (Sigma), penicillin (100 U/ml), streptomycin (100 μg/ml), and 10% fetal bovine serum. Cells were kept for 24 hours at 37C in humidified air with 5% CO_2 before any treatment, and nonadherent cells were discarded. Kupffer cell viability was assessed by exclusion of trypan blue.

Kupffer Cell Fas Ligand Production

Kupffer cells (purity >98%) were seeded in 24-well plates (5×10^5 cells/well), The supernatant was collected from each well 2 hours after treatment with elastase (1 U/ml; Sigma) and stored in −80C. FasL protein was determined by using a commercially available human enzyme-linked immunosorbent assay (ELISA; Alexis Biochemical, San Diego, CA). In other experiments, 7×10^7 Kupffer cells were treated with elastase (1 U/ml), and FasL was measured in cell lysates by Western inmmuoblotting. We have validated this dose of elastase in multiple previous experiments as the optimal dose to stimulate various kinds of macrophages without inducing cell injury.[2–4]

Kupffer Cell Fas Ligand Gene Expression (RT-PCR)

Kupffer cells (2×10^7) were seeded in 100 mm tissue culture dishes and were treated with elastase (1 U/L) for 1 hour. FasL mRNA was measured by semiquantitative differential reverse transcription–polymerase chain reaction (RT-PCR). Briefly, the total Kupffer cell RNA was isolated by guanidium thiocyanate/acid phenol extraction and primed using oligo(dT) (Gibco, Gaithersburg, MD) and subsequently reversed transcribed with reverse transcriptase (Superscript II; Gibco). The cDNA products were coamplified in the presence of rat-specific FasL and BMG primers for 20 to 25 cycles of PCR in a UNO-Thermoblock (Biometra, Tampa, FL). The sequence for the FasL primer[7] was sense 5′ATGGAACTGCT TTGATCTCTGG3′ and antisense 5′AGATTCC TCAAAATTGATCAGAG3′ (Gibco BRL Products; Grand Island, NY). The BMG primer sequence

was sense 5′CTCCCCAAATTCAAGTGTACTCT CG3′ and antisense 5′GAGTGACGTGTTTAACT CTGCAAGC3′ (Ransom Hill Biosciences, Ramona, CA). All primers are known to span at least one intron. The reaction products were separated with electrophoresis in 2.5% metaphor gel agarose containing ethidium bromide and photographed digitally under ultraviolet light with the UV Gel Documentation System (UVP, Upland, CA). Band intensity of each sample was determined using GDS image analysis software (UVP), and individual Fas/BMG cDNA ratios were calculated for analysis.

In Vitro Kupffer Cell Medium–Induced Hepatocyte Injury

Freshly isolated rat hepatocytes (2×10^6) were seeded in 24-well Falcon cell culture plates. Twenty-four hours later, the culture medium was carefully replaced with pooled supernatant from elastase-treated Kupffer cells. Hepatocyte culture medium was harvested at 2, 4, 6, and 8 hours, respectively, and then assayed for aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) as a measure of hepatocyte injury by means of a Kodak Ektachen 700 automated analyzer (Kodak, Rochester, NY).

Cocultures of Kupffer Cells and Hepatocytes

Kupffer cells (5×10^5/well) and hepatocytes (1.0×10^6/well) were seeded in Falcon cell culture inserts and the 12-well companion plates (Becton Dickinson Labware, Franklin Lakes, NJ), respectively. The cell culture inserts have incorporated polyethylene terephthalate trac-etched membranes with a pore size of 0.4μ that prevents cell migration but allows bilateral access to nutrients, cytokines, hormones, and other media contents. Cocultures were treated with pancreatic elastase (1 U/ml) for 2, 4, and 6 hours. Empty cell culture inserts were used in the control group. The supernatant was collected at different time points and stored at −80C. Liver parenchymal enzymes (AST, LDH) were determined as a measure of Kupffer cell–induced hepatocyte injury.

Hepatocyte Viability

MTT Assay. Hepatocytes (2×10^4/well) were seeded in 96-well plates with DMEM in a total volume of 100 μl. Cells were allowed to rest overnight and were then treated with increasing doses of FasL (5 ng to 2.0 μg/ml; Alexis Biochemicals, San Diego, CA) or pooled supernatant from elastase-treated Kupffer cell cultures. Hepatocyte viability was determined using a nonradioactive proliferation assay (Promega Corp., Madison, WI). Briefly, a dye solution containing 3-[4,5-dimethylthiazol-2-yl]-2,3-diphenyltetrazolium bromide (MTT) was added to each well, and incubated at 37C for 2 hours. The absorbance was determined at 570 nm using a plate reader (Dynatech Laboratories, Inc., Chantilly, VA). The number of viable cells was calculated from a standard curve.

Hepatocyte Apoptosis

Flow Cytometry. Hepatocytes (5×10^5/well) were seeded in six-well plates and treated with FasL (5 ng/ml) with or without FasL antibody Fas:Fc (1 μg/ml; Alexis Biochemicals). FasL enhancer (1 μg/ml) was added to augment the activity of FasL as per the manufacturer's recommendations (Alexis Biochemicals). Hepatocytes were washed with ice cold phosphate-buffered saline solution (pH 7.6) twice and suspended in staining buffer (Clontech, Palo Alto, CA) before labeling with Annexin-V–FITC (5 μL, Clontech) and 7-amino–actinomycin D (7-AAD;10 μL, PharMingen International, San Diego, CA) following the manufacturer's protocol. Peak emission of 7-AAD is approximately 685 nm; hepatocyte apoptosis was measured by multiparameter flow cytometry utilizing an FL3 photomultiplier tube with a 670 nm long-pass filter.

Activation of Hepatocyte p38–Mitogen-Activated Protein Kinase and Caspase-3

Hepatocytes (10^7cells/60 mm dish) were incubated with FasL (10 ng/ml) and either with or without Fas:Fc (1 μg/ml) or with pooled supernatant from elastase-treated Kupffer cell cultures. Phosphorylated p38–mitogen-activated protein kinase (p38-MAPK) and caspase-3 activity were determined by immunoblotting. Protein extracts from hepatocytes were separated by sodium dodecylsulfate–polyacrylamide gel electrophoresis and electrotransferred to a nitrocellulose membrane. Nonspecific binding was blocked with 5% of bovine serum albumin (Sigma) for 2 hours at room temperature. The membrane was then immunoblotted overnight at 4C with 1:3000 dilutions of rabbit polyclonal phosphospecific p38-MAPK (Cell Signaling Technology) or caspase-3 antibodies (PharMingen International). Subsequently, the membrane was washed and incubated with horseradish peroxidase–conjugated antirabbit antibody for 2 hours at room temperature. The immunoblot was washed, and the bands were detected with an enhanced chemiluminescence kit (LumiGlo; New England Biolabs, Beverly, MA). Phosphorylated p38-MAPK, caspase-3, and its cleavage subunit were quantified by densitometry (UVP gel documentation system; UVP, Upland, CA).

Statistical Analysis

Experiments were repeated in triplicate (except gels) and averaged. Data are mean ± standard error of the mean (SEM). Student's *t* test was used. Significance was set at $P < 0.05$.

RESULTS

Kupffer Cell Medium–Induced Hepatocyte Injury

Elastase-treated Kupffer cell medium induced release of parenchymal enzymes from tissue cultures of rat hepatocytes as compared to control specimens; AST: 407 ± 4 vs. 42 ± 1 U/L (Fig. 1, *A*; $P < 0.001$ 2 hours vs. control); and LDH: 310 ± 13 vs. 252 ± 10 U/L (Fig. 1, *B*; $P < 0.001$, 2 hours vs. control). In Chang cell line-13 cells, elastase-treated Kupffer cell medium reduced the number of viable cells from 11,000 ± 300 cells to 6000 ± 233 cells ($P = 0.001$; MTT assay).

Cocultures of Hepatocytes and Kupffer Cells

Similarly, elastase induced a time-dependent and significant increase in AST and LDH in cocultures of hepatocytes and Kupffer cells as compared to monocultures of hepatocytes; AST: 676 ± 15 vs. 466 ± 48U/L (Fig. 2; $P = 0.04$, 2 hours vs. control); LDH: 1778 ± 31 vs. 1263 ± 5U/L; ($P < 0.001$, 2 hours vs. control).

Elastase-Induced Fas Ligand Production and Gene Expression From Kupffer Cells

Elastase increased FasL production from Kupffer cells as compared to control values; FasL: 0.29 ± 0.01 ng/ml vs. 0.21 ± 0.01 ng/ml (Fig. 3, *A*, $P = 0.03$; 4 hours elastase vs. control ELISA, and elastase/control = 3× by immunoblot densitometry). In addition, elastase induced significant upregulation of FasL mRNA as compared to control values; FasL/BMG: 0.23 ± 0.03 vs. 0.11 ± 0.003 (Fig. 3, *B*; $P = 0.04$; elastase vs. control).

FasL-Induced Hepatocyte Death

FasL significantly reduced hepatocyte viability in tissue cultures to a similar extent in doses ranging from 5 ng/ml to 2 μg/ml. Viability was reduced to 54 ± 4%, 62 ± 2%, 58 ± 3%, and 50 ± 7% of baseline by 5, 25, 50, and 100 ng/ml of FasL, respectively, as determined by MTT assay (Fig. 4; $P < 0.02$; FasL: 5ng/ml and 100 ng/ml).

FasL-Induced Hepatocyte Apoptosis

Similarly FasL induced a significant increase in hepatocyte apoptosis. Dual-labeled cells with Annexin-V and 7-AAD were significantly increased 4 hours after treatment with FasL (5 ng/ml) as compared to control (38 ± 1 vs. 30 ± 1%, $P = 0.036$, FasL vs. control, Fig. 5). FasL antibody (Fas:Fc) significantly attenuated the increase in FasL-induced apoptosis and reduced the number of dually labeled cells to control levels (29 ± 1 vs. 38 ± 1%, $P = 0.02$, Fas:Fc vs. FasL, Fig. 5).

Activation of Caspase-3 and Phosphorylation of p38-MAPK in Hepatocytes

FasL increased phosphorylated p38-MAPK and cleavage of caspase-3 (Fig. 6). Fas:Fc attenuated the FasL-induced activation of p38-MAPK and cleavage of caspase-3 (see Fig. 6).

DISCUSSION

The mortality and morbidity of acute pancreatitis is largely attributed to its systemic manifestations and the subsequent distant organ injury.[1] We previously demonstrated that pancreatic enzymes, which may gain access to the systemic circulation as a result of inflammatory changes in the pancreas, induce production of proinflammatory cytokines within distant organs such as the lungs and liver.[1–4] Work from our own laboratory has demonstrated that resident macrophages within the lungs or liver produce large amounts of TNF in response to stimulation with pancreatic enzymes, namely, elastase.[1–4]

The prognostic importance of liver injury is supported by its incorporation into clinical scoring systems that predict the severity of acute pancreatitis such as Ranson's criteria and APACHE-II. In addition, the liver houses the largest population of resident macrophages (i.e., Kupffer cells). Kupffer cell–derived cytokines and TNF induce morphologic and biochemical liver injury indistinguishable from that of acute pancreatitis, yet blocking TNF did not abolish liver injury.[2–4,11]

We investigated the possibility that FasL is produced by Kupffer cells because of the pivotal role that FasL plays in the pathogenesis of various diseases and cellular apoptosis.[7,12] Although FasL is ubiquitously produced by lymphocytes, we sought to determine whether FasL could be produced within Kupffer cells by pancreatic elastase. Indeed, elastase upregulated the gene expression of FasL within Kupffer cells. Because there are no commercially available ELISA kits for rodent FasL, we used a human FasL

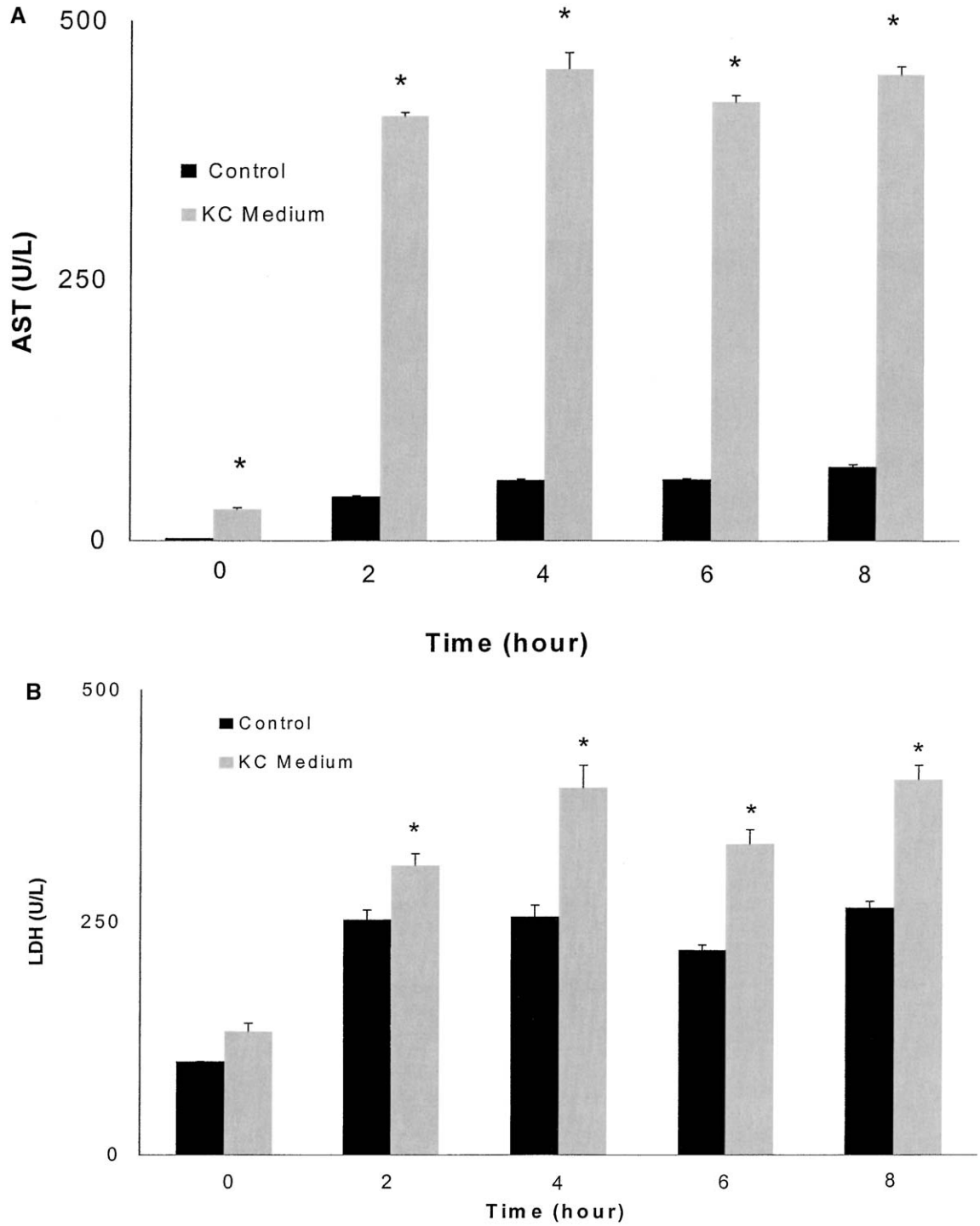

Fig. 1. A, Treatment of tissue cultures of hepatocytes with supernatant of elastase-treated Kupffer cells significantly increased AST (*$P = 0.001$ vs. control, all time points). **B**, Treatment of tissue cultures of hepatocytes with supernatant of elastase-treated Kupffer cells significantly increased LDH (*$P = 0.001$ vs. control, all time points).

kit, which may explain why there is only a small increment of FasL production after treatment with elastase and relatively high levels of FasL in untreated cells. However, we confirmed the production of FasL within Kupffer cells by immunoblotting, which utilizes a polyclonal antibody with reactivity to rat FasL (see Fig. 3, *A*), and by upregulation of FasL-mRNA by RT-PCR (see Fig. 3, *B*).

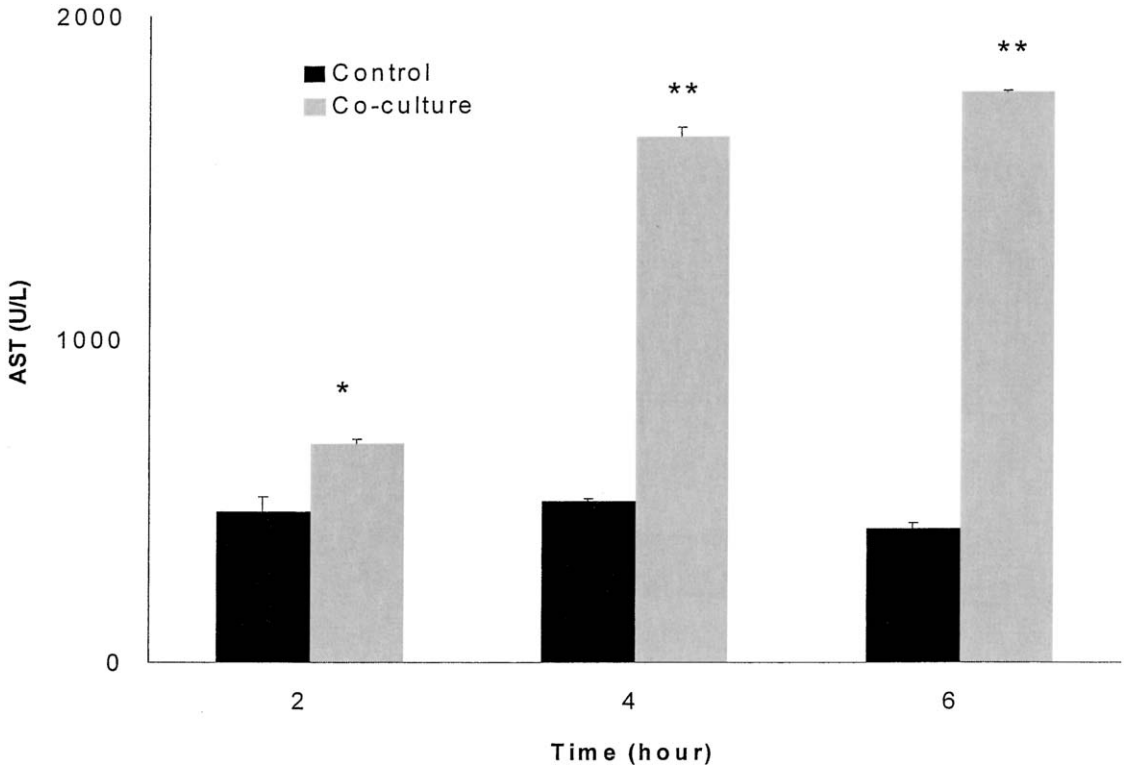

Fig. 2. Treatment of cocultures of hepatocytes and Kupffer cells with elastase (1 U/L) significantly increased levels of AST in the supernatant at 2, 4, and 6 hours (*$P = 0.04$; **$P < 0.001$).

Elastase-treated Kupffer cell medium induced a significant increase in the levels of AST and LDH, a marker of hepatocyte injury. We previously demonstrated that elastase does not directly induce hepatocyte injury; therefore these data suggest that Kupffer cell–derived mediators, including FasL, induce direct hepatocyte injury.[2,8]

Elastase-treated Kupffer cell medium contains FasL, as reported herein, as well as other cytokines, specifically TNF, as per our previous work.[2,3] Because it would not be practical or feasible to isolate and investigate all of the cytokine and byproducts that are present in elastase-treated Kupffer cell medium, we chose to evaluate FasL because of its well-defined role in hepatocyte apoptosis. Therefore and subsequent to demonstrating that FasL is produced by Kupffer cell, we undertook in vitro experiments that used FasL and its antibody, thereby avoiding the myriad confounding factors associated with the use of elastase-treated Kupffer cell medium. In our model, FasL reduced hepatocyte viability and significantly increased the number of apoptotic hepatocytes. Moreover, antibody to FasL, Fas:Fc, attenuated the FasL-induced apoptosis.

These findings are consistent with published literature regarding the pivotal role of FasL in hepatocyte apoptosis.[12] The source of FasL production is the Kupffer cell; our isolates contain more than 98% Kupffer cells, which makes the relative contribution of other potential sources of FasL such as lymphocytes and endothelial cells, miniscule.[7] The liver contains very small amounts of lymphocytes; any lymphocytes that would have contaminated hepatocytes or Kupffer cell cultures would have been removed while discarding all nonadherent cells prior to treatment, because lymphocytes adhere poorly to culture plates.

Further evidence that FasL plays a role in hepatocyte injury is supported by our observations with the use of an antibody to FasL (Fas:Fc), which inhibits the activity of mouse and human soluble FasL, and prevents FasL-induced cell lysis and death. Fas:Fc attenuated the FasL-induced apoptosis as well as the upregulation of p38-MAPK and caspase-3 in our model.

The TNFreceptor family includes TNFR1 (receptor for TNF) and Fas (receptor for FasL). Activation of Fas by FasL recruits FADD (Fas-associated protein with death domain) and unmasks its DED (death effector domain), which activates the caspase cascade leading to cell death.[13,14] Our experiments demonstrate that FasL mediates activation and cleavage of

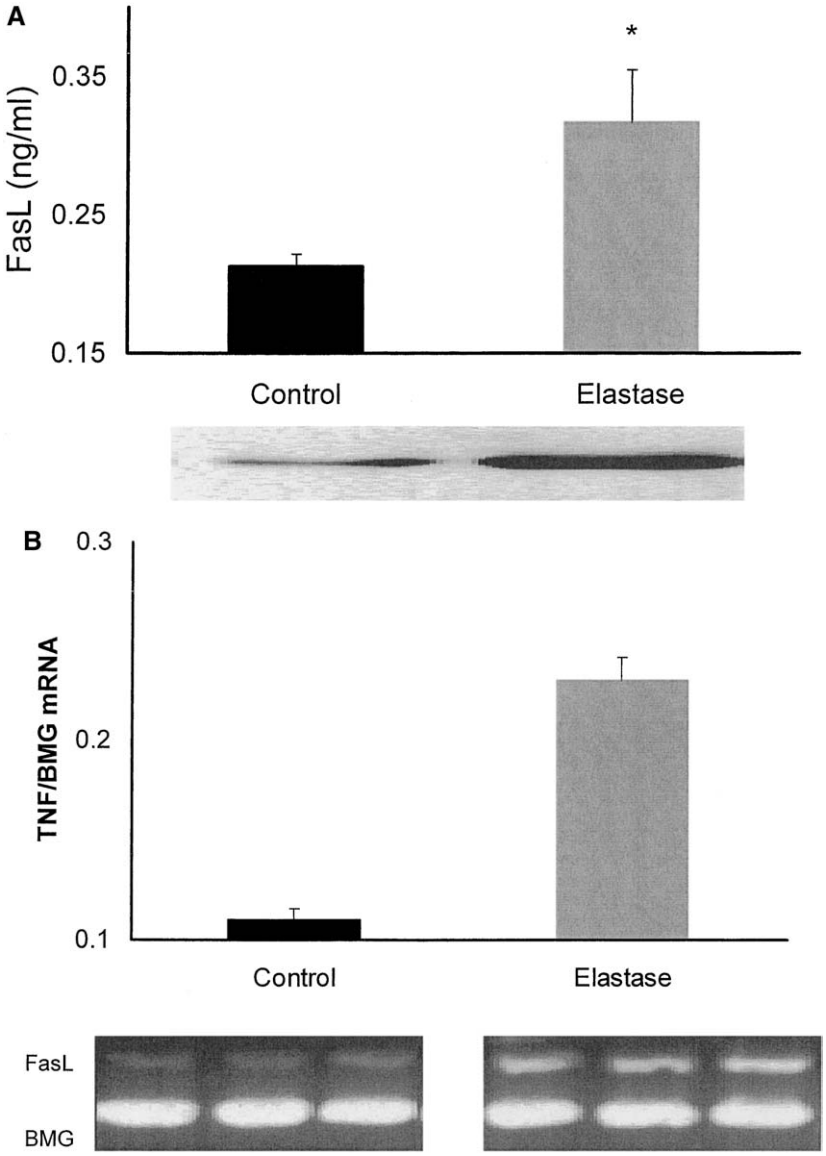

Fig. 3. A, Treatment of tissue cultures of Kupffer cells with elastase significantly increased levels of FasL in the supernatant (*P = 0.03) by ELISA, and in cell lysates by immunoblotting (gel: elastase/control = 3×). **B**, Elastase increased expression of FasL-mRNA in tissue cultures of Kupffer cells (*P = 0.04, Fas vs. control). BMG = beta 2-macroglobulin.

caspase-3 in hepatocytes, which precedes disruption of mitochondrial membrane integrity and eventual cell death. The significance of phosphorylation of p38-MAPK, which is an upstream regulator of cytokine production, is not clear in this model and warrants further investigation.

Other macrophage-derived cytokines can result in liver injury as demonstrated by our data from cocultures of hepatocytes and Kupffer cells. Although we have demonstrated that TNF reduces hepatocyte viability, we continued to question the validity of that conclusion.[2,8] Because actinomycin D is needed for TNF-mediated apoptosis, which makes our previous findings clinically irrelevant, we chose to study the role of FasL because of its well-defined role in hepatocyte apoptosis. More important, the concept that macrophage-derived cytokines induce liver injury is worth noting and is consistent with our previous findings[2,3] and those of other investigators.[5,15] These data suggest that pancreatitis-associated liver injury is mediated by tissue resident macrophages and cytokines that originate within the liver itself. Further investigation of the complex interaction of Kupffer cells and hepatocytes is warranted and may have important therapeutic implications.

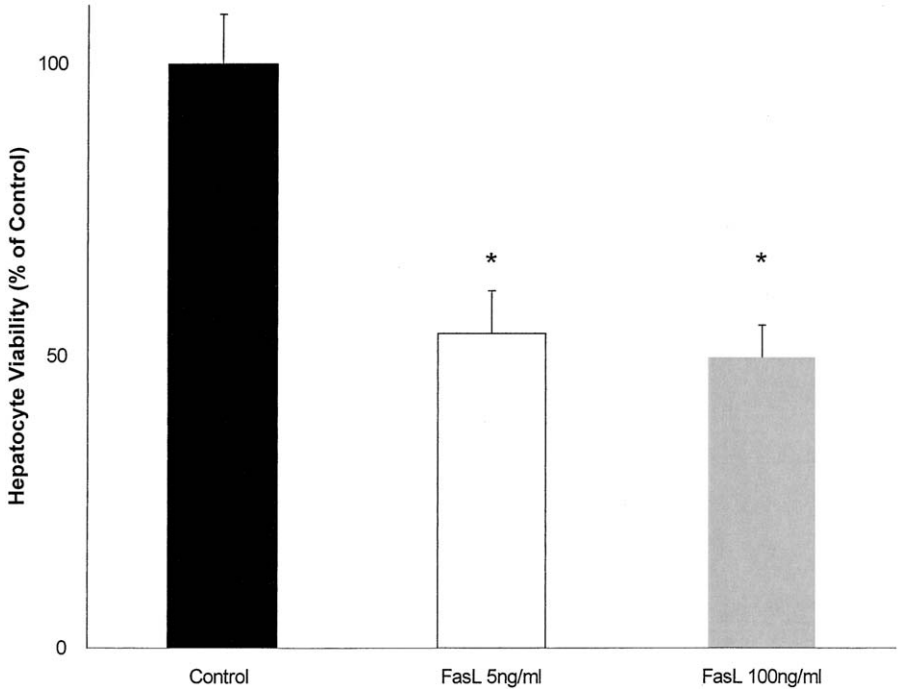

Fig. 4. FasL significantly reduced the viability of hepatocytes independent of its dose as measured by MTT assay (*$P < 0.02$ vs. control).

We acknowledge some weaknesses in our study; the reported levels of FasL from Kupffer cells are low, but we are satisfied with the reproducibility of detecting FasL protein by immunoblots and its mRNA by RT-PCR and the clear effect of FasL on hepatocyte viability and apoptosis. The difference in the proportional increase in AST/LDH is difficult to explain but control cells exhibit the same trend; perhaps some of the variation could be explained by dedifferentiation of hepatocytes kept in culture for

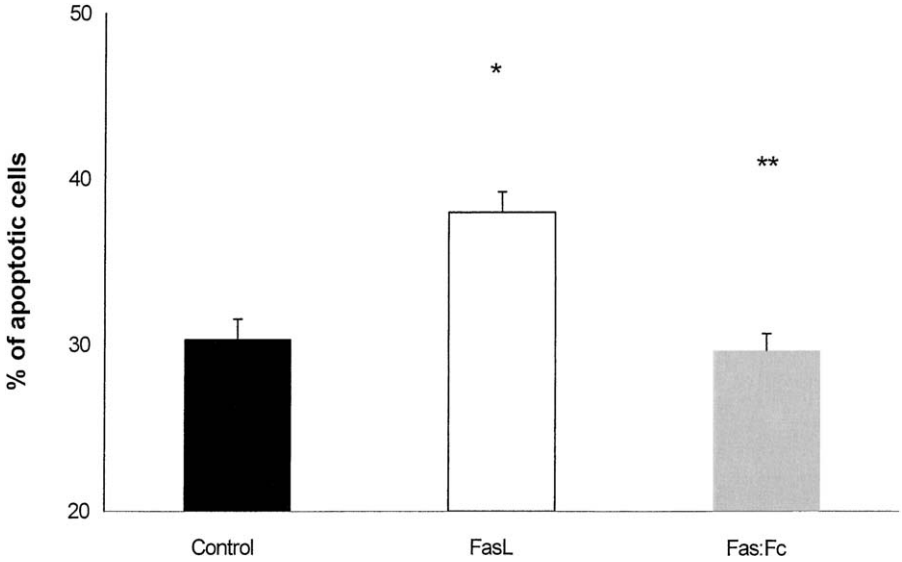

Fig. 5. FasL (5 ng/ml) with FasL enhancer significantly increased the percentage of dual labeled hepatocytes with Annexin-V/7AAD as compared to control (*$P < 0.03$ FasL + FasL enhancer vs. FasL enhancer). Fas:Fc significantly attenuated the FasL-induced increase in dual-labeled cells (**$P < 0.02$, Fas:Fc vs. FasL + FasL enhancer).

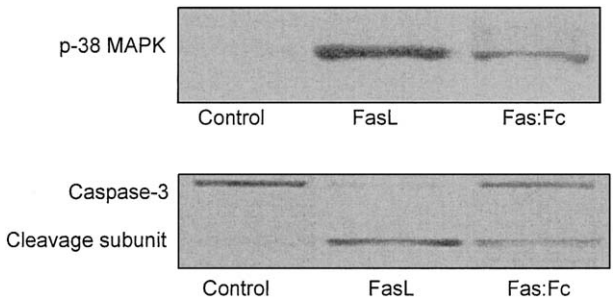

Fig. 6. Fas:Fc attenuated the FasL-induced phosphorylation of p38-MAPK and the cleavage of caspase-3 in tissue cultures of hepatocytes.

24 hours. Nevertheless, we consider the increase in AST/LDH a maker of hepatocyte injury and not an end point by itself. These data should be evaluated in view of the subsequent experiments that demonstrated hepatocyte apoptosis.

CONCLUSION

Kupffer cell–derived FasL gene expression is upregulated by pancreatic elastase. FasL induces hepatocyte injury and apoptosis in addition to activating p38-MAPK and caspase-3. Kupffer cell–hepatocyte interactions are important in the pathogenesis of liver injury.

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REFERENCES

1. Zyromski N, Murr MM. Evolving concepts in the pathophysiology of acute pancreatitis. Surgery 2003;133:235–237.
2. Murr MM, Yang J, Fier A, Kaylor P, Masteroides S, Norman JG. Pancreatic elastase induces liver injury by activating cytokine production within Kupffer cells via NF-kB. J Gastrointest Surg 2002;6:474–480.
3. Murr MM, Yang J, Fier A, Gallagher S, Carter G, Gower W, Norman JG. Regulation of TNF gene expression in Kupffer cells during acute pancreatitis: The role of p38-MAPK, ERK1/2, SPAK/JNK and NF-kB. J Gastrointest Surg 2003;7:20–25.
4. Jaffray C, Yang J, Norman JG. Elastase mimics pancreatitis-induced hepatic injury via inflammatory mediators. J Surg Res 2000;90:95–101.
5. Gloor B, Todd K, Lane J, Lewis M, Reber H. Hepatic Kupffer cell blockade reduces mortality of acute pancreatitis in mice. J Gastrointest Surg 1999;2:430–435.
6. Zhu X, Zellweger R, Ayala A, Chaundry I. Cytokine gene expression in Kupffer cells following hemorrhage. Cytokine 1996;8:430–435.
7. Muschen M, Warskulat U, Douillard P, Gilbert E, Haussinger D. Regulation of CD95 (APO-1/Fas) receptor and ligand expression by lipopolysaccharide and dexamethasone in parenchymal and nonparenchymal rat liver cells. Hepatology 1998;27:200–208.
8. Murr MM, Yang J, Fier A, Kaylor P, Fier A, Norman JG. Pancreatic-associated ascites induces hepatocyte death independent of local cytokine production. J Surg Res 2002;106: 308–313.
9. Yang J, Fier A, Carter G, Liu G, Epling-Burnette PK, Bai F, Loughran T, Masteroides S, Norman JG, Murr MM. Liver injury during acute pancreatitis: The role of pancreatitis-associated ascitic fluid (PAAF), p38-MAPK and caspase-3 in inducing hepatocyte apoptosis. J Gastrointest Surg 2003;7:200–208.
10. Kamimura S, Tsukamoto H. Cytokine gene expression by Kupffer cells in experimental alcholic liver disease. Hepatology 1995;21:1304–1309.
11. Yang J, Denham W, Carter G, Tracey KJ, Norman JG. Macrophage pacification reduces pancreatitis-induced hepatocellular injury through downregulation of hepatic TNF and IL-1. Hepatology 1998;28:1282–1288.
12. Ken-ichiro S, Yashiro S, Takashi O, Nobuhiko K, Hisaya A, Hiroyasu N. Protection against Fas-mediated and tumor necrosis factor receptor 1-mediated liver injury by blockade of FADD without loss of nuclear factor-kB activation. Ann Surg 2001;234:681–688.
13. Muzio M, Chinnaiyan A, Kischkel F, O'Rourke K, Shevchenko A, Ni J, Scaffidi C, Bretz J, Zhang M, Gentz R, Mann M, Krammer P, Peter M, Dixit V. FLICE, a novel FADD-homologous ICE/CED-3-like protease, is recruited to the CD95 (Fas/ APO-1) death-inducing signaling complex. Cell 1996;85:817–827.
14. Deaciuc IV, Fortunato F, D'Souza NB, Hill DB, Schmidt J, Lee EY, McClain CJ. Modulation of caspase-3 activity and Fas ligand mRNA expression in rat liver cells in vivo by alcohol and lipopolysaccharide. Alcohol Clin Exp Res 1999;23:349–356.
15. Hori Y, Takeyama Y, Udea T, Shinkai M, Takase K, Kuroda Y. Macrophage-derived transforming growth factor-betal induces hepatocelluar injury via apoptosis in rat severe acute pancreatitis. Surgery 2000;127:641–649.

Dendritic Cells Pulsed With Pancreatic Cancer Total Tumor RNA Generate Specific Antipancreatic Cancer T Cells

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RNA-based dendritic cell immunotherapy with the use of total tumor RNA provides the potential to generate a polyclonal immune response to multiple known and unknown tumor antigens without HLA restriction. Our study evaluated this approach as potential immunotherapy for patients with pancreatic cancer. Dendritic cells were generated using adherent monocytes isolated from peripheral blood of patients with pancreatic cancer and evaluated phenotypically by flow cytometry to determine whether dendritic cells could be generated from the blood of patients with pancreatic cancer. Immature dendritic cells were transfected with mRNA encoding full-length carcinoembryonic antigen (CEA) or pancreatic cancer total tumor messenger RNA, and then matured. Matured dendritic cell phenotypes were also analyzed by flow cytometry. Transfected, matured dendritic cells were used to stimulate autologous T cells, and the resultant antigen-specific effector T cells were analyzed by interferon-γ Elispot assay. Immature dendritic cells with characteristic phenotypic markers CD40, CD80, and CD86 were successfully isolated from the blood of patients with pancreatic cancer. Incubation with maturation agents increased expression of CD80 and CD83, demonstrating the induction of a mature antigen-presenting phenotype. Dendritic cells transfected with a pancreatic cancer–associated antigen (CEA) generated antigen-specific T cells ($P < 0.05$). Dendritic cells transfected with autologous total tumor pancreatic cancer RNA generated T cells that specifically recognized HLA-matched pancreatic cancer cell lines ($P < 0.05$ compared to control cell lines). Dendritic cells from patients with pancreatic cancer maintain the ability to translate and process transfected RNA and serve as mature antigen-presenting cells. These RNA-transfected dendritic cells from pancreatic cancer patients successfully generate specific T cells against the pancreatic cancer–associated antigen CEA as well as T cells that specifically recognize pancreatic cancer cells. These data suggest that total tumor RNA–pulsed dendritic cells may have potential as an adjuvant immunotherapy for patients with pancreatic cancer. (J GASTROINTEST SURG 2004;8:175–182)

KEY WORDS: Dendritic cells, pancreatic cancer, total tumor RNA, immunotherapy, carcinoembryonic antigen

Pancreatic cancer is the fifth leading cause of cancer-related death in the United States.[1] Complete surgical resection remains the cornerstone of care, with adjuvant chemotherapy providing marginal survival benefit.[2] Despite best surgical and medical efforts, overall prognosis is poor and less than 5% of patients are alive 5 years after diagnosis.[1,3] Given such dismal results, novel therapeutic options for patients with pancreatic cancer are desperately needed.

Recent advances in the basic understanding of immunology and tumor biology have sparked renewed interest in active immunotherapy as a treatment for various cancers including pancreatic adenocarcinoma.[4,5] One approach to developing immunotherapy strategies is the use of professional antigen-presenting cells such as dendritic cells, loaded with tumor antigens, as a vaccine to stimulate an antitumor immune response. Animal models in which dendritic

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cells pulsed with peptide tumor antigens were used have demonstrated generation of cytotoxic T-cell responses protective against implanted tumors.[6,7] Furthermore, antigen-specific T-cell responses have been generated against the tumor-associated antigen carcinoembryonic antigen (CEA) in vitro using human dendritic cells pulsed with CEA peptide or transfected with mRNA-encoding CEA.[8,9] In addition, dendritic cells pulsed with CEA mRNA have been shown to be a feasible immunotherapy strategy in vivo for patients after resection of pancreatic cancer.[10]

Our laboratory has focused on the use of RNA-transfected dendritic cells as an immunologic stimulant. Unlike peptide-based vaccines, mRNA vaccines are not limited to specific HLA haplotypes. Autologous dendritic cells present tumor antigen within the context of their own HLA type and would thus expand the patient populations that would be eligible to receive treatment. Furthermore, an RNA-based approach is not limited to known tumor antigens. The ability to generate total tumor mRNAs from pathologic specimens, as opposed to defined established tumor antigen mRNA, expands the range of potential unknown antigens that might elicit more of a polyclonal immune response. Thus the entire tumor antigenic repertoire, both known and unknown, is potentially represented and presented on the dendritic cell surface. This is particularly important in a disease such as pancreatic cancer in which there are few known tumor-associated antigens that could serve as immunologic targets. Last, total tumor mRNA can be isolated and amplified from only a few cancerous cells or from image-guided biopsy material. Thus this RNA-based approach is not usually limited by size or surgical accessibility of the tumor.

Despite the theoretical potential of this approach and the technical ability to use total tumor RNA, it must first be determined whether the biology of patients with pancreatic cancer allows for an appropriate immune response. Cancer has been known to have systemic immunosuppressive effects. The mechanism of these effects is unknown, but questions have been raised as to whether dendritic cells from patients with pancreatic cancer function normally.[10–12] To appropriately evaluate the feasibility of a dendritic cell–based immunotherapy in patients with pancreatic cancer, it must be determined whether functional dendritic cells can be generated from the peripheral blood of these patients. In other words, dendritic cells from these patients with pancreatic cancer must be able to take up, process, and present antigen to naive T cells in order to be considered as a potential form of immunotherapy.

Thus the first goal of this study was to evaluate the phenotypic and functional abilities of dendritic cells derived from patients with pancreatic adenocarcinoma. Second, we incorporated an approach using autologous pancreatic cancer total tumor RNA to generate an antipancreatic cancer T-cell response to determine the feasibility of adjuvant RNA-based immunotherapy in patients with pancreatic cancer.

METHODS

Pancreatic Cancer Patients and Healthy Volunteers

After informed consent to participate in a protocol approved by the Duke University Institutional review board was obtained, 13 patients with pathologically proved pancreatic adenocarcinoma donated tumor tissue and/or blood. As part of another research protocol, most of these patients had undergone neoadjuvant chemotherapy consisting of continuous infusion of 5-fluorouracil with concurrent external beam radiotherapy over 5 weeks to 4500 cGy. Ten healthy volunteers underwent phlebotomy or leukapheresis for generation of dendritic cells as a control population. Samples were not pooled, and each patient or volunteer sample was treated individually for experiments.

Generation of Dendritic Cells

Healthy volunteers or patients with pancreatic cancer underwent peripheral phlebotomy or leukapheresis. Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-Hypaque (Amersham Pharmacia Biotech, Piscataway, NJ) density gradient separation. Cells were either used immediately or cryopreserved in autologous serum containing 10% dimethyl sulfoxide (Sigma, St. Louis, MO).

PMBCs were cultured in serum-free X-vivo 15 media (BioWhittaker, Walkerville, MD) in a 150 cm^2 polystyrene flask at 37C and 5% CO_2. After 2 hours, nonadherent cells were removed by gentle washing with phosphate-buffered saline solution. Adherent cells were replenished with 30 ml X-vivo 15 media containing 800 U/ml granulocyte macrophage-colony stimulating factor (GM-CSF; Immunex, Seattle, WA) and 500 U/ml interleukin-4 (IL-4; R & D Systems, Minneapolis, MN) and incubated for 7 days at 37C in 5% CO_2.

Total Tumor RNA Isolation and In Vitro Transcribed mRNA

Pancreatic cancer specimens were obtained at the time of surgery and were stored in RNAlate (Ambion,

Austin, TX) at 4C until processing. Total cellular RNA from pancreatic tissues was extracted and isolated using the Qiagen RNAeasy kit (Qiagen, Valencia, CA). All RNA extraction was carried out in a designated hood with Rnase-free labware. Purified RNA was quantified by spectrophotometry (Beckmann Instruments, Fullerton, CA). Samples were stored at −80C until used.

mRNA for carcinoembryonic antigen (CEA), influenza peptide M1, melanoma-associated antigen Mart-1/Melan A, and green fluorescent protein (GFP) was isolated according to methods previously described.[13]

Dendritic Cell Transfection

After 7 days in culture, dendritic cells were harvested and suspended in serum-free media at a concentration of 5×10^7 cells/ml. One hundred microliters of cells were placed in a 2 mm cuvette with 20 μg of mRNA. The cuvette was then placed in the electroporator (Electro Square Porator ECM 830; BTX), and a 300 V current was delivered for 500 μs. The transfected cells were immediately removed from the cuvette and placed in serum-free media containing 800 U/ml GM-CSF and 500 U/ml IL-4 in six-well plates. A subset of dendritic cells were left untreated and were analyzed by flow cytometry. For the remaining dendritic cells, a maturation cocktail consisting of tumor necrosis factor-α (5 ng/ml), recombinant human (rh) IL-1-β (5 ng/ml), rhIL-6 (150 ng/ml), and prostaglandin E_2 (1 μg/ml) was added, and the dendritic cells were cultured for 24 hours. Phenotypic changes in expression of several cell surface molecules were analyzed by flow cytometry for both untreated and treated dendritic cells.

Flow Cytometry

Dendritic cells (2×10^5 cells) were washed and resuspended in phosphate-buffered saline solution containing 0.02% sodium azide and 1% bovine serum albumin, and incubated with various fluorochrome-conjugated monoclonal antibodies at 4C for 20 minutes in the dark. Immunoglobulin G_{2a} subclass antibodies conjugated with phytoerythrin and specific against CD3, CD14, CD56, major histocompatibility complex (MHC) class I (Caltag, Burlingame, CA), MHC class II (Sigma), as well as an isotype control, were used. Immunoglobulin G_1 subclass antibodies conjugated with fluorescein isothyocyanate and specific against CD40, CD58, CD80, CD83, (Pharmingen Becton Dickson, San Jose, CA), CD 54 (Immunotech, Beckman Coulter), and CD 86 (Caltag, Burlingame, CA), as well as an isotype control, were also used. The cells were washed twice in phosphate-buffered saline solution containing 0.02% sodium azide and 1% bovine serum albumin, and fixed in phosphate-buffered saline solution containing 1% formaldehyde. Standard two-color fluorescence-activated cell sorting (FACS) was performed using an FACS caliber cytometer (Pharmingen Becton Dickson). Data analysis was performed using CellQuest software (Pharmingen Becton Dickson). Live cells were gated according to forward and side light scatter.

T-Cell Cultures

PBMCs obtained from leukapheresis were used as a source of naive T cells. These cells were suspended in RPMI containing 10% fetal calf serum, 25 mmol/L HEPES, L-glutamine, and antibiotics. Dendritic cells were harvested 24 hours after transfection and treated with maturation cocktail and plated at a ratio of 1:10 with the effector T cells (2×10^5 dendritic cells:2×10^6 effectors) in a total volume of 2 ml in 24-well tissue culture plates and cultured for 7 days at 37C and 5% CO_2. After 7 days, the effector T cells were harvested, washed, counted, and restimulated with newly transfected and matured dendritic cells. The effector cells were serially stimulated a total of four times. Five days after the fourth stimulation, the effector cells were evaluated by interferon (IFN)-γ release Elispot assay.

TIL 1235 is a CD8+ T-cell clone that recognizes the immunodominant HLA-A_2–restricted Mart-1/Melan-A epitope ELAGIGILTV. It was generously supplied by Tim Clay at Duke University Medical Center and cultured in AIM V media containing 6000 IU/ml IL-2 (NCI Biological Resources Branch, Frederick, MD) and supplemented with 10% human antibody serum (Valley Biomedical, Inc., Winchester, VA). It was maintained at 37C in a humidified atmosphere containing 5% CO_2 and used as an effector population in dendritic cell coculture experiments (Elispot assay).

IFN-γ Release Elispot Assay

IFN-γ release Elispot assay was performed as previously described.[13] Each assay sample was tested in triplicate. Spots were imaged and counted by an ImmunoSpot Series 1 analyzer system (Cellular Technology, Ltd., Cleveland, OH). Statistical analysis was performed using Student's *t* test at a 5% significance level.

RESULTS

Dendritic Cell Phenotype and Maturation

Cells isolated from both healthy volunteers and patients with pancreatic cancer were evaluated by flow

cytometry for expression of particular cell surface markers that define dentritic cell phenotype. Cell surface marker profiles were consistent with dendritic cells and were similar for both groups. Dendritic cells from both groups expressed CD40, CD80, CD83, CD86, and MHC class I and II molecules as shown in Fig. 1. These cell populations were negative for CD14 (B cells) and CD56 (natural killer cells).

In addition, dendritic cells from pancreatic cancer patients were capable of further differentiation into mature dendritic cells after stimulation with maturation agents. After maturation, there was an increase in the expression of these markers as indicated in Fig. 1. Mature dendritic cells exhibit a phenotypic and functional change toward antigen presentation. CD83 is a known dendritic cell maturation marker. Antigenic peptides are expressed at the cell surface in the context of MHC class I or class II molecules, which are upregulated in mature dendritic cells. Similarly, CD40, CD80, and CD86 are important costimulatory molecules essential for generation of the immune response and are also increased appropriately in mature dendritic cells from patients with pancreatic cancer.

There were no significant differences in the number of dendritic cells generated, dendritic cell phenotypic profiles, or the ability to differentiate into mature dendritic cells for patients with pancreatic adenocarcinoma compared to those of healthy volunteers.

Functional Antigen-Presention

The T-cell clone TIL 1235 specifically recognizes the melanoma-associated antigen Mart-1/Melan A. We therefore transfected Mart-1 RNA into dendritic cells from pancreatic cancer patients. Thus functional dendritic cells would be capable of mRNA processing and place peptide antigen on the cell surface for presentation to T cells. Activation of the Mart-1–specific T-cell clone by dendritic cells expressing Mart antigen results in the release of IFN-γ, which is captured as a spot in the Elispot assay. Fig. 2 demonstrates the successful processing and presentation of Mart-1/Melan A antigen by dendritic cells from pancreatic cancer patients with specific activation of the T-cell clone ($P < 0.01$).

Generation of Antigen-Specific Effector T Cells

Dendritic cells from patients with pancreatic cancer were transfected with mRNA for the pancreatic cancer–associated antigen, CEA, and used to stimulate naive autologous T cells. T-cell cultures were tested for antigen-specific recognition by IFN-γ release Elispot assay. Stimulator targets in the Elispot assay were dendritic cells pulsed with CEA mRNA or pulsed without antigen as a control specimen. Although there was a high background of activity against dendritic cell stimulators alone, specific T-cell activation by CEA antigen was nearly twice that of controls (Fig. 3; $P < 0.05$). These data demonstrate

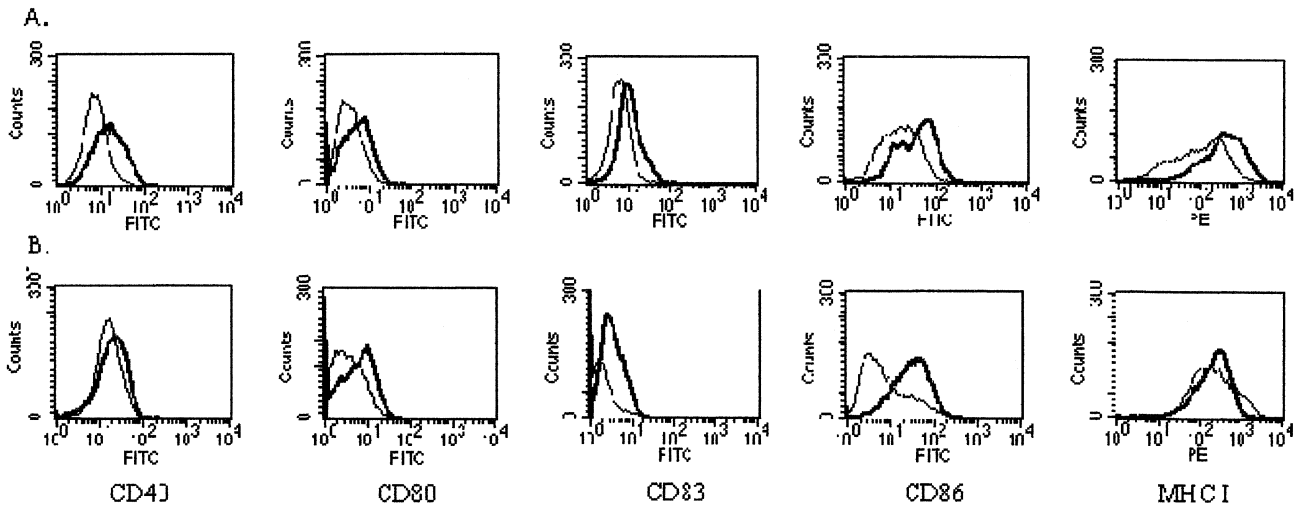

Fig. 1. Dendritic cell profiles of cell surface markers as measured by flow cytometry. Monoclonal antibodies specific for CD40, CD80, CD83, and CD86 were labeled with FITC and MHC. Class I molecules were labeled with PE. The thin line in each histogram represents the profile of dendritic cells derived from peripheral blood mononuclear cells. The thicker lines represent further differentiation and phenotypic changes following stimulation with maturation agents. The profiles and differentiation were similar for both healthy volunteers (**A**) and patients with pancreatic cancer (**B**).

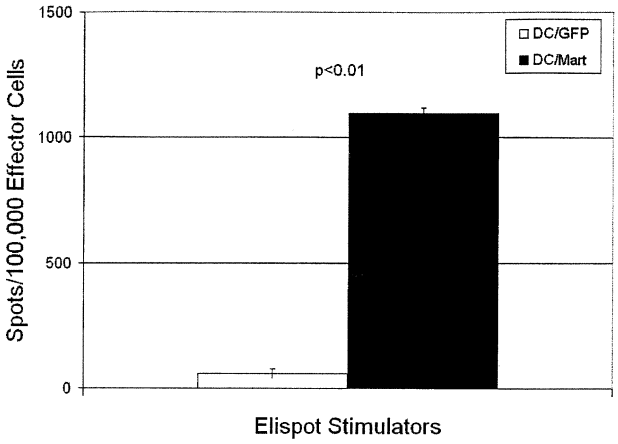

Fig. 2. Interferon-γ release Elispot assay measuring activation of Mart-1/Melan A T-cell clone TIL1235 by dendritic cells from pancreatic cancer patients transfected with mRNA for Mart-1/Melan A (*DC/Mart*). Control stimulators in this assay were dendritic cells transfected with mRNA for green fluorescent protein (DC/GFP).

that dendritic cells from patients with pancreatic cancer are capable of translating RNA into antigenic protein with resultant antigen processing and presentation on the cell surface. These dendritic cells are then functionally able to generate antigen-specific response from naive T cells.

Dendritic Cells Pulsed With Pancreatic Cancer Total Tumor RNA

Human pancreatic tumor specimen was obtained and total tumor RNA was isolated, then transfected into autologous dendritic cells. The transfected dendritic cells were matured, then used as stimulators in culture with autologous naive T cells. After four stimulations, the resultant T cells were isolated and tested in an IFN-γ release Elispot assay. The stimulators in the assay were HLA-matched pancreatic cancer lines as well as control cell line K562.

Dendritic cells from pancreatic cancer patients transfected with autologous pancreatic adenocarcinoma total tumor were able to generate T cells that specifically recognize pancreatic cancer cell lines (Fig. 4). The data represented here are from samples run in triplicate from one patient with pancreatic cancer and repeated in a separate experiment. The in vitro–generated T cells were tested against two separate pancreatic cancer cell lines. The Hs766T cell line was derived from human primary pancreatic adenocarcinoma, whereas the CFPAC-1 line was derived from a pancreatic adenocarcinoma metastatic liver lesion. Generated T cells recognized and were activated by both cell lines with significant specificity compared to control values ($P < 0.05$).

DISCUSSION

This study demonstrates that dendritic cells from patients with pancreatic cancer retain normal immunologic function. Despite concern about immunosuppression and decreased immune function, we were able to isolate similar numbers of dendritic cells with the same phenotype as those from healthy volunteers. In addition, the dendritic cells were capable of further

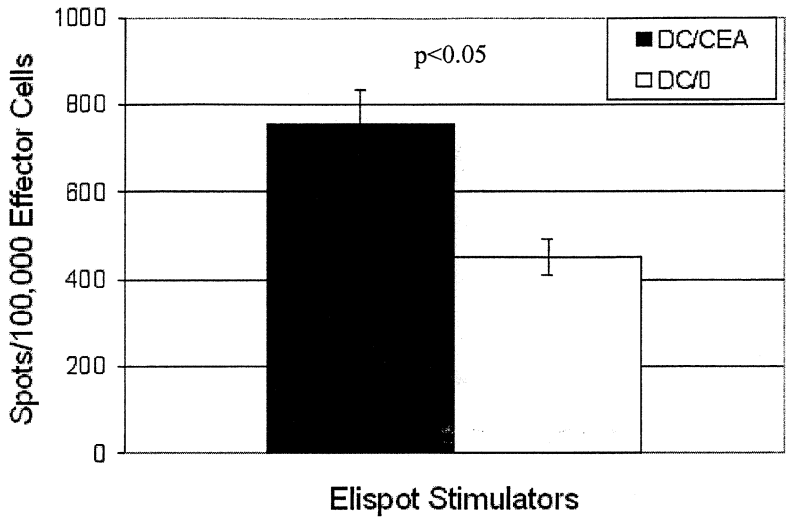

Fig. 3. Interferon-γ release Elispot assay measuring T-cell specificity against carcinoembryonic antigen (CEA). Naive T cells stimulated by autologous dendritic cells (*DC*) pulsed with CEA RNA specifically recognize CEA presented by dendritic cells (*DC/CEA*), causing interferon-γ release in the Elispot assay. Control stimulator used for the Elispot assay was dendritic cells pulsed without antigen (*DC/0*). $P < 0.05$.

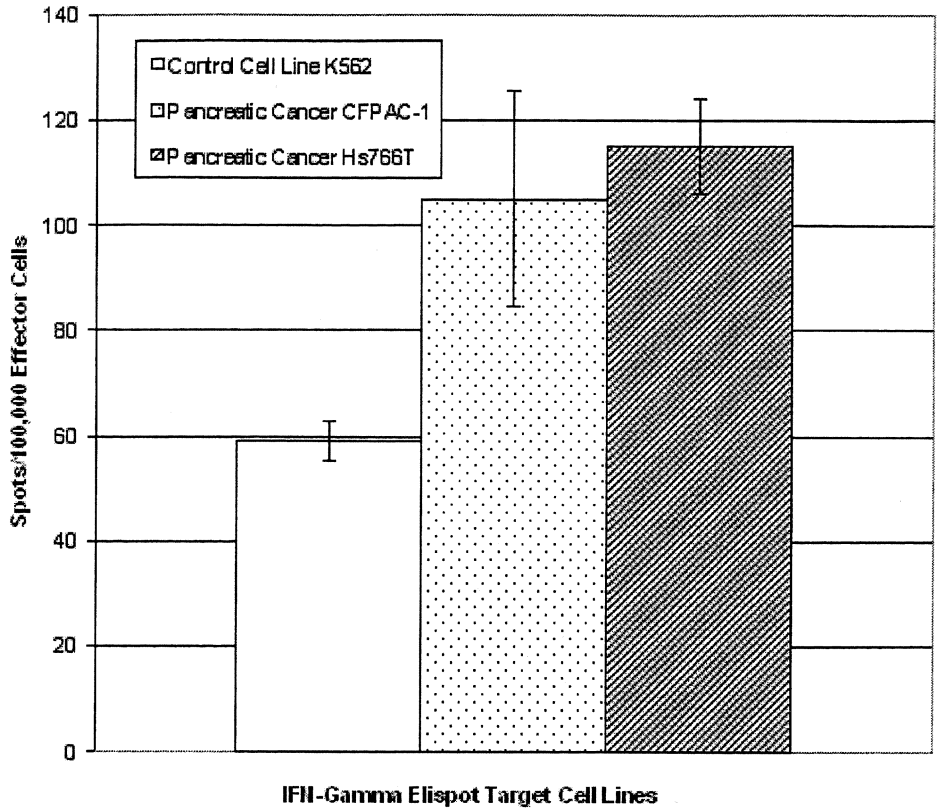

Fig. 4. Interferon-γ release Elispot assay measuring ability of generated T cells to recognize pancreatic cancer cell lines. Naive T cells stimulated by autologous dendritic cells pulsed with autologous pancreatic tumor specifically recognize pancreatic adenocarcinoma cell lines *CFPAC-1* and *Hs766T*. Control cell line stimulator in the Elispot assay was the leukemia cell line K562. $P < 0.05$ for generated T-cell recognition of pancreatic cancer cell lines vs. control cells.

differentiation into mature dendritic cells that are capable of antigen processing and presentation. Piemonti et al.[12] have reported a similar experience.

A unique aspect of our pancreatic cancer patient population in this study is the high incidence of neoadjuvant chemoradiation therapy. Nearly all patients underwent preoperative treatment prior to acquisition of blood or tissue samples. Thus one might expect decreased immunologic function. However, dendritic cells seem to maintain their function in the setting of both cancer and chemotherapy, as shown by effective antigen presentation and generation of CEA-specific and pancreatic cancer–specific effector T cells. In fact, recent work suggests that 5-fluorouracil actually enhances CEA expression and increases susceptibility to tumor lysis by cytotoxic T cells in colon and breast cancer.[14] This is particularly relevant because chemotherapy remains the mainstay of adjuvant therapy after surgical resection. Thus immunotherapy used as an additional adjuvant might be a clinically feasible option.

Host antigen-presenting cells are the key elements responsible for the in vivo priming of CD4+ and CD8+ T-cell responses leading to a systemic antitumor response.[15] The scarcity of dendritic cells within the local tumor environment in patients with pancreatic cancer[11] may be one explanation for the proposed decreased immune function in pancreatic cancer patients. Our group has previously demonstrated that patients with pancreatic cancer can generate appropriate numbers of dendritic cells to undergo successful RNA-based dendritic cell vaccination after neoadjuvant chemoradiation and tumor resection.[10] In vitro isolation and manipulation of dendritic cells to express tumor antigen, as described in the present study, may provide a means to circumvent the problem of decreased dendritic cells in the local environment. Thus this technique has potentially large implications for individual patient responses.

We have taken human dendritic cells from patients with cancer and pulsed them with autologous pancreatic adenocarcinoma total tumor mRNA and successfully generated T cells specific against pancreatic cancer in vitro. The paucity of well-characterized pancreatic cancer–specific tumor antigens underscores the necessity and advantages of a total tumor mRNA

approach. Theoretically, the broadest and strongest immune response will be generated through inclusion of all defined and undefined tumor antigens. Allogenic tumor lysate–based vaccines provide a similar approach[5] but may never have the full complement of antigens because of the heterogeneity of each tumor. Another disadvantage of tumor cell vaccines is the difficulty in establishing generic pancreatic cancer cell lines because of the low cellularity in relation to fibroblasts and noncancerous stromal cells.[16] By using autologous tumor, mRNA is directly isolated and cell lines need not be established. Given that this approach would be utilized in the setting of adjuvant therapy following surgery, tissue would always be available. Only small amounts of tissue are required to isolate RNA, which can be amplified by reverse transcriptase–polymerase chain reaction.

In summary, pancreatic cancer remains a fatal disease without effective treatment options for locally advanced or metastatic disease. No single treatment has been successful in improving survival outcomes, and immunotherapy has a potential adjuvant role in surgery and chemoradiation. This work provides preclinical evidence that further investigation into total tumor RNA–based pancreatic cancer immunotherapy is warranted.

REFERENCES

1. Greenlee R, Murray T, Bolden S, Wingo P. Cancer statistics, 2000. CA Cancer J Clin 2000;50:7–33.
2. Yeo CJ, Abrams RA, Grochow LB, Sohn TA, Ord SE, Hruban RH, Zahurak ML, Dooley WC, Coleman J, Sauter PK, Pitt HA, Lillemoe KD, Cameron JL. Pancreaticoduodenectomy for pancreatic adenocarcinoma: Postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. Ann Surg 1997;225:621–633; discussion 633–636.
3. National Cancer Institute SEER Cancer Statistics Review 1973–1990. Bethesda, MD: National Institutes of Health, 1993.
4. Jaffee EM, Hruban RH, Biedrzycki B, Laheru D, Schepers K, Sauter PR, Goemann M, Coleman J, Grochow L, Donehower RC, Lillemoe KD, O'Reilly S, Abrams RA, Pardoll DM, Cameron JL, Yeo CJ. Novel allogeneic granulocyte-macrophage colony-stimulating factor-secreting tumor vaccine for pancreatic cancer: A phase I trial of safety and immune activation. J Clin Oncol 2001;19:145–156.
5. Schnurr M, Galambos P, Scholz C, Then F, Dauer M, Endres S, Eigler A. Tumor cell lysate-pulsed human dendritic cells induce a T-cell response against pancreatic carcinoma cells: An in vitro model for the assessment of tumor vaccines. Cancer Res 2001;61:6445–6450.
6. Mayordomo JI, Zorina T, Storkus WJ, Zitvogel L. Bone marrow-derived dendritic cells pulsed with synthetic tumour peptides elicit protective and therapeutic antitumor immunity. Nature Med 1995;1:1297–1302.
7. Celluzzi CM, Mayordomo JI, Storkus WJ, Lotze MT, Falo LD Jr. Peptide-pulsed dendritic cells induce antigen-specific CTL-mediated protective tumor immunity. J Exp Med 1996; 183:283–287.
8. Nair SK, Hull S, Coleman D, Gilboa E, Lyerly HK, Morse MA. Induction of carcinoembryonic antigen (CEA)-specific cytotoxic T-lymphocyte responses in vitro using autologous dendritic cells loaded with CEA peptide or CEA RNA in patients with metastatic malignancies expressing CEA. Int J Cancer 1999;82:121–124.
9. Eppler E, Horig H, Kaufman H, Groscurth P, Filgueira L. Carcinoembryonic antigen (CEA) presentation and specific T cell-priming by human dendritic cells transfected with CEA-mRNA. Eur J Cancer 2002;38:184–193.
10. Morse M, Nair S, Boczkowski D, Tyler D, Hurwitz H, Proia A, Clay T, Schlom J, Gilboa E, Lyerly H. The feasibility and safety of immunotherapy with dendritic cells loaded with CEA mRNA following neoadjuvant chemoradiotherapy and resection of pancreatic cancer. Int J Gastrointest Cancer 2002; 32:1–6.
11. Dallal RM, Christakos P, Lee K, Egawa S, Son YI, Lotze MT. Paucity of dendritic cells in pancreatic cancer. Surgery 2002;131:135–138.
12. Piemonti L, Monti P, Zerbi A, Balzano G, Allavena P, Di Carlo V. Generation and functional characterisation of dendritic cells from patients with pancreatic carcinoma with special regard to clinical applicability. Cancer Immunol Immunother 2000;49:544–550.
13. Kalady M, Onaitis M, Emani S, Padilla K, Tyler D, Pruitt S. Enhanced dendritic cell antigen presentation in RNA-based immunotherapy. J Surg Res 2002;105:17–24.
14. Correale P, Aquino A, Giuliani A, Pellegrini M, Micheli L, Cusi MG, Nencini C, Petrioli R, Prete S, De Vecchis L, Turriziani M, Giorgi G, Bonmassar E, Francini G. Treatment of colon and breast carcinoma cells with 5-fluorouracil enhances expression of carcinoembryonic antigen and susceptibility to HLA-A(*)02.01 restricted, CEA-peptide-specific cytotoxic T cells in vitro. Int J Cancer 2003;104:437–445.
15. Huang AY, Bruce AT, Pardoll DM, Levitsky HI. In vivo cross-priming of MHC class I-restricted antigens requires the TAP transporter. Immunity 1996;4:349–355.
16. Jaffee EM, Schutte M, Gossett J, Morsberger LA, Adler AJ, Thomas M, Greten TF, Hruban RH, Yeo CJ, Griffin CA. Development and characterization of a cytokine-secreting pancreatic adenocarcinoma vaccine from primary tumors for use in clinical trials. Cancer J Sci Am 1998;4:194–203.

Invited Discussion—Expert Commentator

Dr. Sean J. Mulvihill (Salt Lake City, UT): Dr. Kalady and his colleagues are studying immunotherapy of pancreatic cancer, priming dendritic cells to act as antigen-presenting cells through transfection with pancreatic cancer mRNA followed by stimulation of effector T cells shown to recognize HLA-matched pancreatic cell lines. Immunotherapy generally has been an ineffective strategy in gastrointestinal tract malignancy, although efficacy has been shown in patients with melanoma and renal cell carcinoma. Dendritic cells are important antigen-presenting cells and are central to the induction of

antigen-specific T-cell responses. Because of this, dendritic cells have become the focus of laboratory investigations in recent years as potential vehicles for active specific immunization against cancer. Although laboratory effects have been observed, the limited clinical applications of dendritic cells as immunostimulants have to date been disappointing. It remains to be seen whether this strategy will produce substantial clinical benefit.

Discussion

Dr. J. Moser (Pittsburgh, PA): Have you been able to identify any new pancreas cancer–specific sequences using total tumor-derived RNA that might be useful for all patients with pancreatic cancer, rather than having to extract RNA from one patient's tumor, transfect dendritic cells, and then reinfuse them in a patient-specific manner?

Dr. M. Kalady: That is a good point. The identification of new cancer antigens using this RNA-based technique is definitely something of interest. When we isolate total tumor RNA, we do not actually analyze the RNA and go back to see what those sequences were. We do not test them in any way. We simply use the total RNA from that patient's tumor. So, no, we have not actually searched for or identified any new antigens.

Dr. M. Dauer (Munich, Germany): Were the cell lines that you used for the Elispot assay, when you used the total RNA, from the patient or allogeneic cell lines?

Dr. Kalady: We used allogeneic pancreatic cancer cell lines.

Dr. Dauer: Have you used any cytotoxicity assays to prove that the T cells are really functioning with respect to tumor cell lysis?

Dr. Kalady: We have not done that for this particular set of experiments. We have used chromium 51 in other experiments but not yet in this study.

Treatment Outcomes Associated With Surgery for Gallbladder Cancer: A 20-Year Experience

Hiromichi Ito, M.D., Evan Matros, M.D., David C. Brooks, M.D., Robert T. Osteen, M.D., Michael J. Zinner, M.D., Richard S. Swanson, M.D., Stanley W. Ashley, M.D., Edward E. Whang, M.D.

The aim of this study was to evaluate contemporary outcomes associated with the management of gallbladder cancer. The medical records of 48 consecutive patients with gallbladder cancer treated at our institution from January 1981 through November 2001 were reviewed. Survival was analyzed using the Kaplan-Meier method (mean follow-up period 24 months) and the log-rank test. Prognostic factors were analyzed using Cox regression. Mean patient age was 68 years. Sixty percent of patients were female. Thirty-nine patients (81%) underwent laparotomy or laparoscopy. Eighteen patients (38%) underwent complete resection (10 simple cholecystectomies and 8 radical cholecystectomies). There were no procedure-related deaths. The overall 5-year survival rate was 13%. Patients who underwent complete resection had a higher 5-year survival rate (31%) than patients who underwent palliative surgery or no surgery (0%; $P < 0.05$). For patients who underwent radical cholecystectomy, the 5-year survival rate was 60%. For the 18 patients who underwent curative resection, positive lymph node metastasis and patient age over 65 were factors predictive of significantly worse survival. Overall survival rates for patients with gallbladder cancer remain poor. Although radical surgery can be performed safely, it is associated with long-term survival only in a highly select subset of patients with gallbladder cancer. (J GASTROINTEST SURG 2004;8:183–190)

KEY WORDS: Gallbladder cancer, cholecystectomy

Gallbladder cancer represents 1% of all cancers and is the most common among the estimated 6800 cases of biliary tract cancer diagnosed in the United States each year.[1] Patients with gallbladder cancer usually have advanced disease at the time of diagnosis. As a result, curative resection is rarely possible, and long-term survival is unusual. Indeed, reported overall 5-year survival rates for cohorts of patients diagnosed with gallbladder cancer only range from 5% to 12%.[2–4] Because of the low incidence of these cancers and the low frequency with which they are resected, information with respect to prognostic factors is limited. Therefore we analyzed the treatment-associated outcomes for 48 consecutive patients with gallbladder cancer managed at our institution. Our goal was to identify specific prognostic factors predictive of survival.

MATERIAL AND METHODS

The medical records of all patients with gallbladder cancer admitted to the inpatient unit of Brigham and Women's Hospital during the period spanning January 1981 through November 2001 were analyzed. Patients were identified using the International Classification of Disease-9 (ICD-9) code for gallbladder cancer (code 156.0) and the computer-assisted hospitalization analysis for the study of efficacy (CHASE) management system.

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Parameters obtained from the medical records included demographic data (patient age and sex), signs and symptoms present at the time of diagnosis, the preoperative diagnosis, the operation performed and whether it was curative (complete resection with no gross residual cancer present at the completion of surgery) or palliative (gross residual cancer present at the completion of surgery), and pathologic findings. Pathologic parameters analyzed were histologic differentiation, depth of tumor invasion (T), regional lymph node status (N), margin status, and overall stage according to the American Joint Committee on Cancer (AJCC) staging system.[5]

Patient survival data were obtained from the United States Social Security Administration Death Master File. Survival duration was calculated from the time of operation, or time of diagnosis for patients who did not undergo any surgery, through the time of death. The survival curves for selected patient groups were determined using the method of Kaplan and Meier.[6] Survival durations for these groups were derived from the corresponding Kaplan-Meier curves and compared using the log-rank test. Potential prognostic factors were evaluated using Cox univariate and multivariate analyses.[7]

RESULTS

Patients

During the study period, 48 patients with gallbladder cancer were admitted to our hospital. The median age of this patient cohort was 66 years (range 37 to 96 years). Twenty-nine patients (60%) were female.

Presenting Symptoms and Signs

The frequencies with which symptoms and signs were present at the time of diagnosis in study patients are summarized in Table 1. Sixty-seven percent of patients presented with right upper quadrant abdominal pain, 27% had jaundice, 19% had weight loss, and 13% had fever. One patient had ascites.

Diagnostic and Therapeutic Procedures

Nine patients (19%) underwent endoscopic or percutaneous tumor biopsy but no operative intervention because of the presence of metastases or locally advanced disease precluding surgical resection, as detected on imaging studies.

Thirty-nine patients (81%) underwent laparotomy or laparoscopy (Table 2); among these patients the preoperative diagnosis was gallbladder mass in 44%, cholelithiasis in 28%, and acute cholecystitis in 28%. Eighteen patients underwent complete resection (10 underwent simple cholecystectomy and 8 underwent radical cholecystectomy including regional lymph node dissection and wedge resection of the gallbladder fossa of the liver). Of the patients who underwent complete resection, 11 patients (61%) underwent surgery with the preoperative diagnosis of cholecystitis or cholelithiasis. Seven of these patients were diagnosed with gallbladder cancer intraoperatively on the basis of operative findings; four were diagnosed postoperatively on the basis of pathologic findings (T1 through T3 tumors were found in their specimens). The remaining 21 patients underwent nontherapeutic or palliative procedures (3 underwent intraoperative tumor biopsy alone, 10 underwent biliary-enteric bypass, and 8 underwent simple cholecystectomy). There were no procedure-related deaths among study patients.

Stage and Pathologic Findings

The stage distribution among study patients is shown in Table 3. Sixty-nine percent of patients were found to have stage IV disease at the time of diagnosis.

Table 1. Symptoms and signs at presentation

Symptoms and signs	No. of patients
Abdominal pain	32 (67%)
Jaundice	13 (27%)
Weight loss	9 (19%)
Fever	6 (13%)
Acute abdomen	3 (6%)

Table 2. Diagnostic and therapeutic procedures

Therapeutic procedure	No. of patients
None	9 (19%)
Curative	18 (38%)
Simple cholecystectomy	10 (21%)
Radical cholecystectomy	8 (17%)
Noncurative	21 (44%)
Laparotomy/laparoscopy with biopsy	3 (6%)
Biliary bypass, or drainage	10 (21%)
Simple cholecystectomy	8 (17%)

Table 3. Overall stage

Stage	No. of patients
1	4 (8)
2	7 (15)
3	4 (8)
4	33 (69)

Table 4. Pathologic parameters of tumors from patients who underwent curative resection

Pathologic parameters	No. of patients; total n = 18
Tumor	
1	4 (22%)
2	9 (50%)
3	3 (17%)
4	2 (11%)
Node	
0	4 (22%)*
1	5 (28%)*
N/A	9 (50%)
Grade (differentiation)	
Well	4 (22%)
Moderate	8 (44%)
Poor	6 (33%)
Positive margin	4 (22%)

*Including specimens obtained from simple cholecystectomy without formal lymph node dissection.

The pathologic findings for patients who underwent curative operations are summarized in Table 4. All tumors were adenocarcinomas except for one adenosquamous carcinoma. Forty-four percent were moderately differentiated, and 33% were poorly differentiated. In four cases (22%), microscopic residual cancer at the resection margins was detected. Fifty percent were T2 tumors, and 50% of specimens contained identifiable lymph nodes (55% of these specimens were positive for lymph node metastasis). The probability of lymph node metastasis being detected was greater with higher T stage: 33% for T2 tumors, 75% for T3 tumors, and 100% for T4 tumors.

Survival and Prognostic Factors

Mean follow-up period was 28 months. Overall 1-year and 5-year survival rates for our entire patient cohort were 40% and 13%, respectively (Fig. 1). Patients who underwent complete resection had higher 1-year and 5-year survival rates (73% and 31%, respectively) than patients who underwent palliative surgery or no surgery (12% and 0%, respectively; $P < 0.05$; Fig. 2).

Patients with T1/T2 tumors had better survival rates than those with T3/T4 tumors (92% vs. 50% at 1-year, 46% vs. 0% at 5-years; $P < 0.05$) (Fig. 3). The presence of lymph node metastases and high tumor grade (poor differentiation) were adverse prognostic factors among these patients (0% vs. 75% 2-year survival rates for patients with positive lymph nodes vs. negative lymph nodes, respectively; $P < 0.05$ and 27% vs. 74% 2-year survival rates for patients with poorly differentiated tumors vs. well to moderately differentiated tumors, respectively; $P < 0.05$) (Fig. 4). For patients who had undergone

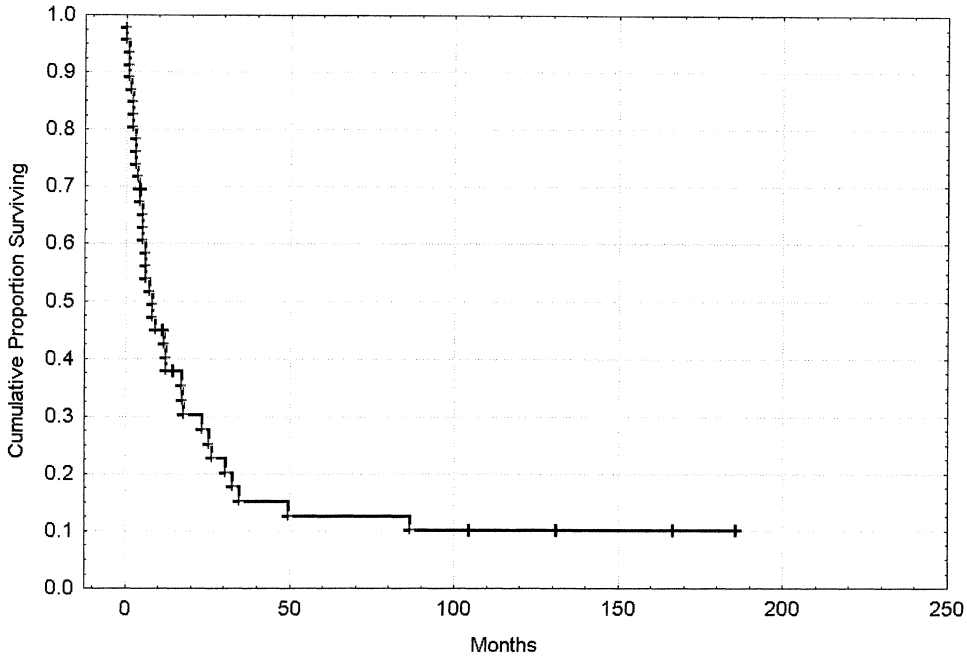

Fig. 1. Kaplan-Meier estimates of overall survival for the entire cohort of patients with gallbladder cancer. The estimated median survival was 8.0 months, and 5-year survival was 13%.

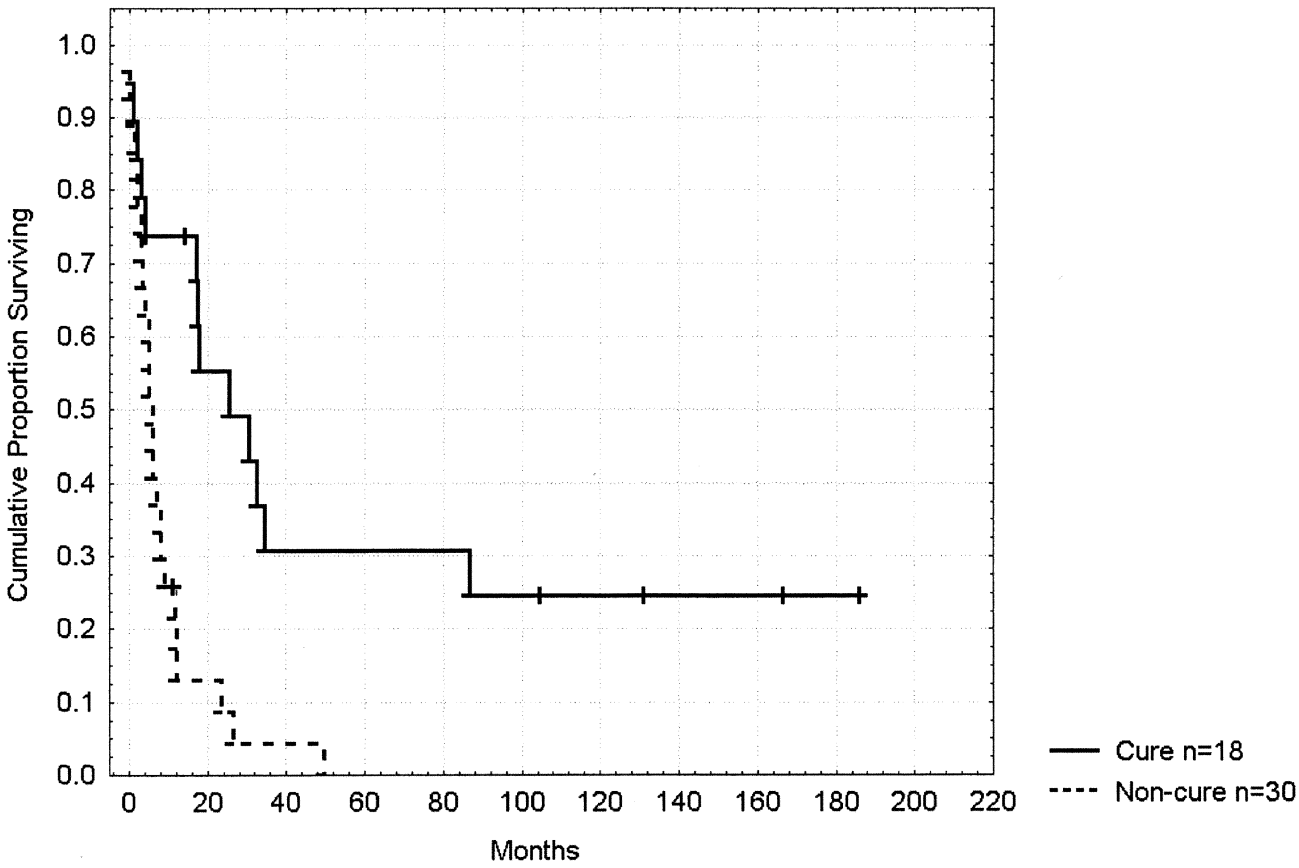

Fig. 2. Kaplan-Meier estimates of overall survival for patients who underwent curative resection and those who did not undergo such resection. Five-year survival rates for these patient groups were 31% and 0%, respectively ($P < 0.05$ by log-rank test).

simple cholecystectomy, 1- and 5-year survival rates were 60% and 20%, respectively. For patients who had undergone radical cholecystectomy, 1- and 5-year survival rates were 100% and 60%, respectively (Fig. 5). The distributions of the overall stages among patients who underwent simple cholecystectomy or radical cholecystectomy were similar (50% stage I or II and 50% stage III or IV in both groups); the difference in overall survival between patients in these groups did not reach statistical significance ($P = 0.27$, log-rank test).

Of the 30 patients who did not undergo curative surgery, 37% underwent biopsy alone, 27% had a simple cholecystectomy, and 33% had a biliary bypass or drainage. Median durations of survival for these groups were 5.6, 8.0, and 5.6 months, respectively.

We analyzed potential prognostic factors predictive of survival in the 18 patients who underwent curative resection using Cox regression. The factors included in this analysis were patient age and sex, pain, jaundice, or weight loss at the time of diagnosis, and pathologic factors, including margin involvement, depth of tumor invasion (T stage), lymph node involvement (N stage), tumor grade (differentiation), the presence of distant metastasis (M), and overall stage. Univariate analysis showed that patient age over 65, preoperative jaundice, T stage higher than 3, lymph node metastasis, poor differentiation, and overall stage higher than III were associated with significantly worse survival. On multivariate analysis, patient age over 65 and lymph node metastasis were associated with significantly worse survival. The prognostic factors analyzed, *P* values, and relative risks on Cox regression analysis are summarized in Table 5.

DISCUSSION

Gallbladder cancer is uncommon but not rare. Indeed, gallbladder cancer is the fifth most common gastrointestinal cancer and the most common biliary tract cancer.[1] In our institution's 20-year experience with this cancer, 38% of patients were able to undergo complete resection, and those who underwent complete resection achieved a 31% 5-year survival rate.

In previously reported series of patients with gallbladder cancer, the resectability rates have ranged

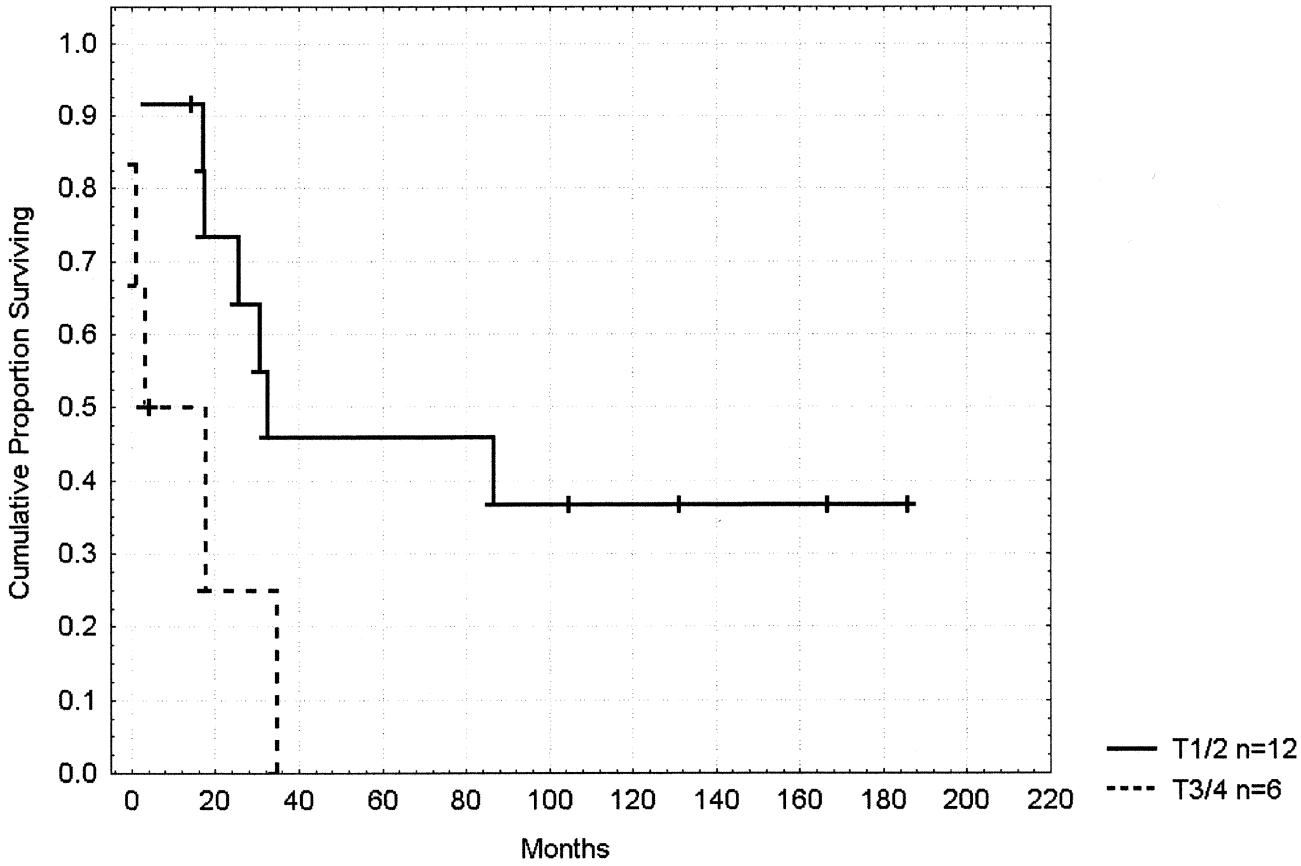

Fig. 3. Kaplan-Meier estimates of overall survival for patients with T1/2 tumors and those with T3/4 tumors. Five-year survival rates for these patient groups were 46% and 0%, respectively ($P < 0.05$ by log-rank test).

from 17% to 47%, and the 5-year survival rates for patients having undergone complete resection have ranged from 18% to 58%[8–15] (Table 6). Consistent with our results, the factor most consistently reported to be associated with prognosis has been N stage. In the series reported by Benoist et al.,[9] no patient with lymph node metastases survived 1 or more years. Similarly, in the series reported by Bartlett et al.,[8] no patients with T2 (or greater) tumors with lymph node metastases survived 2 or more years. In our series, no patient with positive lymph nodes survived for more than 2 years.

Available data on which to base therapeutic recommendations are limited to those derived from retrospective analyses. Is radical surgery a better treatment for the gallbladder cancer? For T1 cancers, procedures of magnitude greater than simple cholecystectomy appear unlikely to be associated with improved survival. In our study, none of the patients with T1 tumors had lymph node metastasis detected. In the study reported by Wakai et al.,[16] 143 lymph nodes from 12 patients with T1 gallbladder cancer treated with radical resection were examined. None of these lymph nodes contained metastatic cancer. These investigators also reported that survival of patients with T1 tumors who underwent simple cholecystectomy was similar to that of patients with T1 tumors who underwent radical resection.[16]

Available data suggest that radical cholecystectomy may have its greatest utility in the treatment of T2 tumors. The incidence of lymph node metastasis associated with T2 tumors was 33% in our study and has been reported to range from 28% to 63%.[8,10,11,13,17] In the study reported by Chijiwa et al.,[18] radical resection of T2 tumors was associated with a 59% 5-year survival rate, whereas simple cholecystectomy was associated with only a 17% 5-year survival rate. Similarly, Fong et al.[10] reported better survival for patients with T2 tumors who underwent radical resection than those who underwent simple cholecystectomy.

Much controversy with respect to the value of radical cholecystectomy in the treatment of T3 and T4 tumors exists. Five-year survival rates among patients with T3 or T4 tumors have been reported to range from 0% to 36%.[8,10,11,19] In our series, no patients

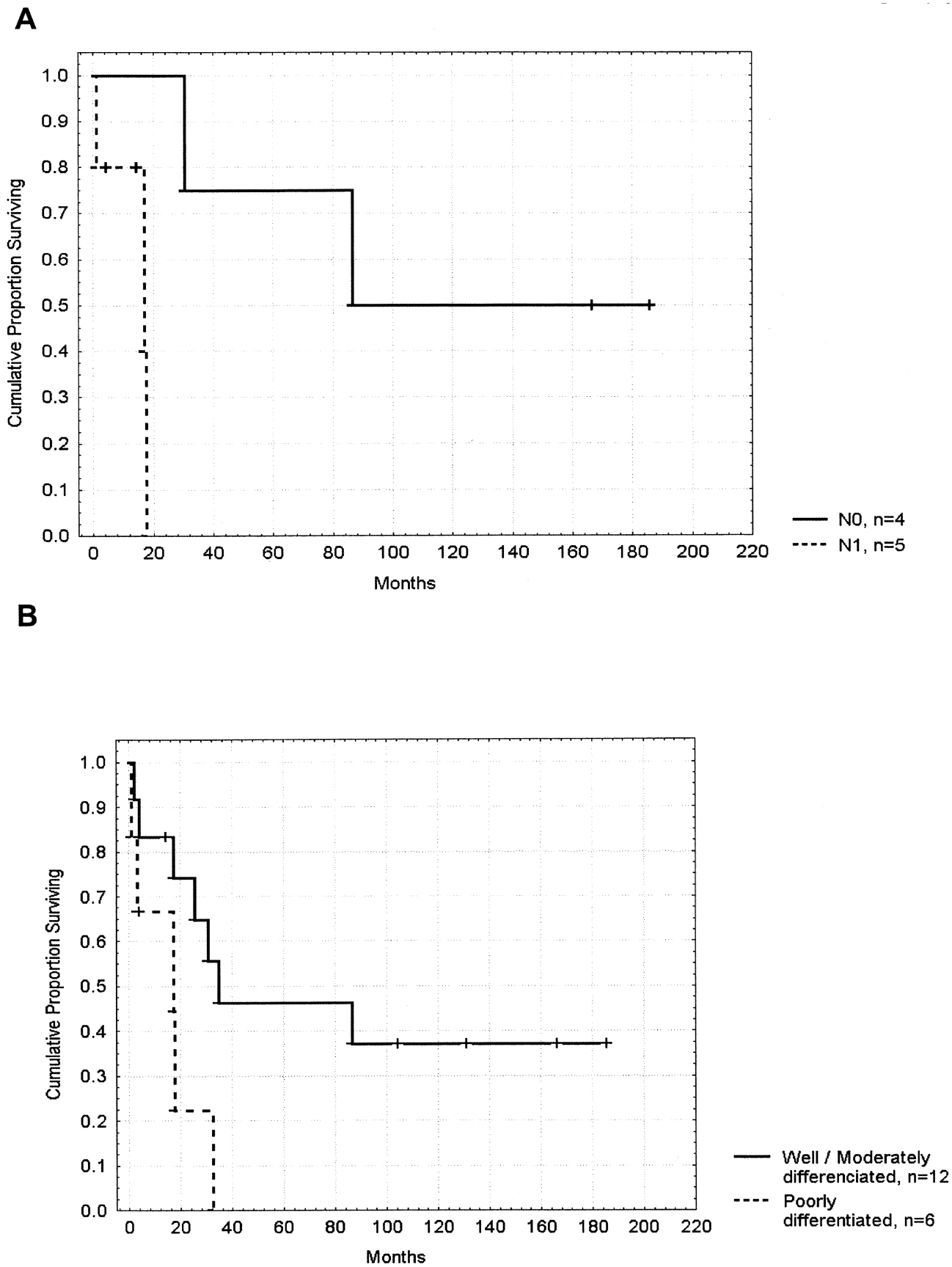

Fig. 4. **A**, Kaplan-Meier estimates of overall survival for patients with positive lymph node metastasis and those with negative nodes. Two-year survival rates for these patient groups were 75% and 0%, respectively ($P < 0.05$ by log-rank test). **B**, Kaplan-Meier estimates of overall survival for patients with grade 1/2 tumors and those with grade 3 tumors. Two-year survival rates of these patient groups were 74% and 27%, respectively ($P < 0.05$ by log-rank test).

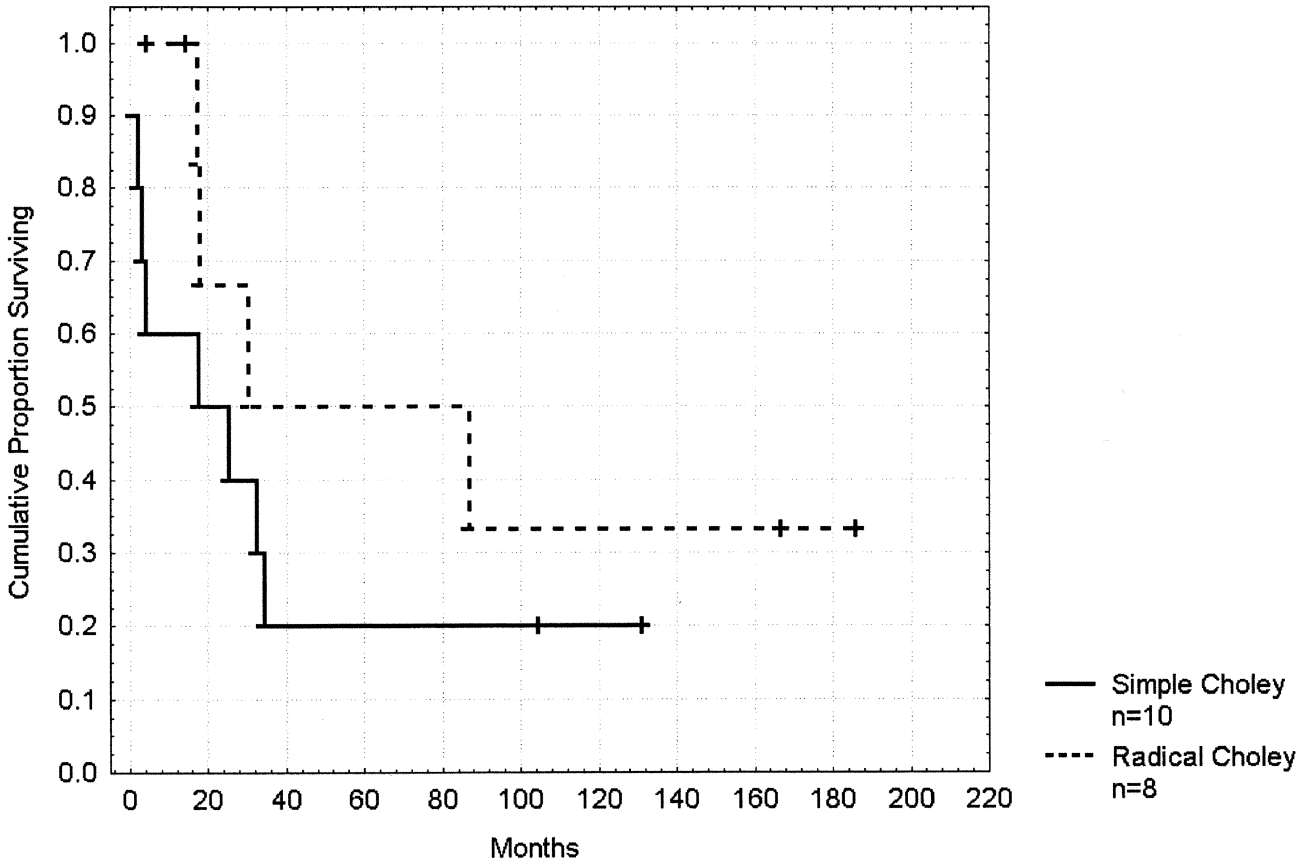

Fig. 5. Kaplan-Meier estimates of overall survival for patients who underwent simple cholecystectomy (*choley*) and those who underwent radical cholecystectomy. Five-year survival rates for these patient groups were 60% and 20%, respectively ($P > 0.05$ by log-rank test).

with T3 or T4 tumors survived for 5 years. In a series of 41 patients who had undergone radical resection for gallbladder cancer reported by Shimada et al.,[20] 81.3% of patients with T3 or T4 tumors had lymph node metastasis; yet 84% of these patients had N2 or para-aortic lymph node involvement. None of these patients survived for 5 years. Some studies do suggest improved survival with radical resection among patients with T3/4 tumors, however.[10,14,21]

Table 5. *P* values and relative risk for Cox regression analysis of potential prognostic factors predicting survival after curative resection

Prognostic factors	Univariate analysis	Multivariate analysis	Relative risk
Age >65 yr	0.008	0.02	6.9
Male Sex	0.06		
Pain at presentation	0.22		
Jaundice at presentation	0.08		
Weight loss at presentation	0.24		
Positive margin	0.71		
T (higher than 3)	0.04	0.35	2.1
N1	0.009	0.039	13.8
Poor differentiation	0.04	0.9	0.92
M1	0.5		
Stage higher than 3	0.03	0.42	0.54

Because of the low incidence of gallbladder cancer, information on the relative efficacy of operations for this disease has been limited to that derived from single-institution case series. Resolution of the existing controversies will require multi-institutional collaborative efforts. However, improvements in outcomes for patients with advanced gallbladder cancers with modifications of surgical technique alone are likely to be only incremental. For these patients, improved understanding of the mechanisms driving gallbladder cancer initiation and progression based on fundamental investigations will be required.

CONCLUSION

The overall survival for patients with gallbladder cancer remains poor. Although radical surgery is safe,

Table 6. Recently reported series of gallbladder cancer and predictive indicators documented

Reference	Year	N	Resectability (%)	5 yr survival after curative resection	Identified prognostic factor
Bartlett et al.[8]	1996	149	15.4	58	T, N*, M, H, B, stage
Ruckert et al.[14]	1996	81	22		N, stage
Benoist et al.[9]	1998	86	100	26	N, stage
North et al.[12]	1998	162	22	57	Margin, stage
Muratore et al.[11]	2000	70	47	27.4	T*, N, stage*
Fong et al.[10]	2000	248	25	38	T, N, stage
Schauer et al.[15]	2001	127	35.5	20	T, N, M*, resectability*, G, stage*
Puhalla et al.[13]	2002	267	17	18.2	T, N, grade*, margin*, stage
Present series		48	38	38	Patient age*, T, N*, G, stage

*Significant in multivariate analysis.

it is associated with long-term survival only in a highly select subset of patients with gallbladder cancer.

REFERENCES

1. Jemal A, Murray T, Sammuels A, et al. Cancer statistics, 2003. CA Cancer J Clin 2003;53:5–26.
2. Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer 1995;75(1 Suppl):171–190.
3. Cubertafond P, Gainant A, Cucchiaro G. Surgical treatment of 724 carcinomas of the gallbladder. Results of the French Surgical Association Survey. Ann Surg 1994;219:275–280.
4. Wilkinson DS. Carcinoma of the gall-bladder: An experience and review of the literature. Aust N Z J Surg 1995;65:724–727.
5. American Joint Committee on Cancer Gallbladder. AJCC Cancer Staging Manual, 5th ed. Philadelphia: Lippincott-Raven, 1997.
6. Kaplan F, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;63:475–481.
7. Cox D. Regression models and life tables. J R Stat Soc 1972; 34:197–219.
8. Bartlett DL, Fong Y, Fortner JG, et al. Long-term results after resection for gallbladder cancer. Implications for staging and management. Ann Surg 1996;224:639–646.
9. Benoist S, Panis Y, Fagniez PL. Long-term results after curative resection for carcinoma of the gallbladder. French University Association for Surgical Research. Am J Surg 1998; 175:118–122.
10. Fong Y, Jarnagin W, Blumgart LH. Gallbladder cancer: Comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. Ann Surg 2000;232:557–569.
11. Muratore A, Polastri R, Bouzari H, et al. Radical surgery for gallbladder cancer: A worthwhile operation? Eur J Surg Oncol 2000;26:160–163.
12. North JH Jr, Pack MS, Hong C, Rivera DE. Prognostic factors for adenocarcinoma of the gallbladder: An analysis of 162 cases. Am Surg 1998;64:437–440.
13. Puhalla H, Wild T, Bareck E, et al. Long-term follow-up of surgically treated gallbladder cancer patients. Eur J Surg Oncol 2002;28:857–863.
14. Ruckert JC, Ruckert RI, Gellert K, et al. Surgery for carcinoma of the gallbladder. Hepatogastroenterology 1996;43: 527–533.
15. Schauer RJ, Meyer G, Baretton G, et al. Prognostic factors and long-term results after surgery for gallbladder carcinoma: A retrospective study of 127 patients. Langenbecks Arch Surg 2001;386:110–117.
16. Wakai T, Shirai Y, Yokoyama N, et al. Early gallbladder carcinoma does not warrant radical resection. Br J Surg 2001; 88:675–678.
17. Kondo S, Nimura Y, Hayakawa N, et al. Regional and paraaortic lymphadenectomy in radical surgery for advanced gallbladder carcinoma. Br J Surg 2000;87:418–422.
18. Chijiiwa K, Nakano K, Ueda J, et al. Surgical treatment of patients with T2 gallbladder carcinoma invading the subserosal layer. J Am Coll Surg 2001;192:600–607.
19. Arnaud JP, Casa C, Georgeac C, et al. Primary carcinoma of the gallbladder—review of 143 cases. Hepatogastroenterology 1995;42:811–815.
20. Shimada H, Endo I, Togo S, et al. The role of lymph node dissection in the treatment of gallbladder carcinoma. Cancer 1997;79:892–899.
21. Miyazaki M, Itoh H, Ambiru S, et al. Radical surgery for advanced gallbladder carcinoma. Br J Surg 1996;83:478–481.

Management of Complex Biliary Tract Calculi With a Holmium Laser

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The difficulty in managing complex biliary tract calculi is exemplified in patients with primary intrahepatic calculi. Standard surgical and endoscopic approaches often fail to clear calculi in these patients who have recurrent episodes of cholangitis. The success of the holmium laser for urologic calculi led us to adapt treatment strategies for primary and secondary biliary tract calculi where standard treatments had been unsuccessful. Our goals were to remove all calculi, prevent recurrent sepsis, and preserve hepatic parenchyma. Thirty-six patients with complex biliary calculi were treated. After sepsis was controlled and the extent of calculi was evaluated, appropriate access to and drainage of the biliary tract was achieved. Holmium laser lithotripsy was performed under video guidance using flexible choledochoscopes and a 200 μ laser fiber generating 0.6 to 1.0 joules at frequencies of 6 to 10 Hz. Lithotripsy procedures were repeated until cholangiography and cholangioscopy confirmed the clearance of calculi. Twenty-two patients of Asian descent with primary intrahepatic calculi and 14 patients with secondary intrahepatic calculi were treated. Access to the biliary tract could be accomplished through percutaneous catheter tracts, T-tube tracts, or the cystic duct during laparoscopic cholecystectomy. Biliary drainage was by biliary enteric anastomosis or endoscopic sphincterotomy. Complete stone clearance required an average of 3.9 procedures (range 1 to 15) for patients with primary intrahepatic calculi and 2.6 procedures (range 1 to 10) for patients with secondary intrahepatic calculi regardless of stone composition. No patient required hepatic resection and no complications or deaths were attributed to the holmium laser. Clearance of calculi can reliably and safely be achieved with a holmium laser regardless of stone composition or location while preserving hepatic parenchyma and preventing recurrent sepsis. (J Gastrointest Surg 2004;8:191–199)

KEY WORDS: Bile duct, hepatolithiasis, cholangiohepatitis, bile duct calculi, cholangitis, laser lithotripsy

The management of complex intrahepatic and extrahepatic biliary lithiasis is fraught with complications and treatment failures.[1–3] The etiology of biliary tract calculi differs in Asia and the West.[4] The majority of biliary calculi in Asia result from infectious or parasitic disease arising in the biliary ducts. This disease process has been referred to as hepatolithiasis, cholangiohepatitis, or recurrent pyogenic cholangitis; we prefer the term primary intrahepatic calculi. In contrast, biliary tract calculi in the West develop as a secondary result of calculi originating in the gallbladder or primary stones resulting from benign strictures, sclerosing cholangitis, choledochal cysts, or malignant biliary tumors.[1] Regardless of the origination of the calculi, the net result is biliary obstruction and cholangitis.

Advances in laparoscopic and endoscopic techniques allow for safe expeditious removal of calculi confined to the gallbladder and common bile duct in most patients.[5] However, when these methods have been exhausted, standard surgical approaches such as common bile duct exploration, biliary enteric bypass, and hepatic resection may be indicated but carry increased morbidity.[6] Failure to clear calculi from the entire biliary tree results in recurrent episodes of cholangitis and ultimately liver failure. Several investigators have advocated hepatic resection for patients with primary intrahepatic calculi. In some

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patients, where the bulk of the stone burden involves the liver to left of the umbilical fissure (segments II and III), resection can be accomplished with minimal morbidity. However, when calculi are found throughout the biliary tree, hepatic resection is no longer an option.[7,8]

The goal of managing patients with complex biliary lithiasis is to remove obstructing calculi, maintain free flow of bile, preserve hepatic parenchyma, and provide access to the biliary tree for treatment of recurrent calculi. The methods for meeting these goals have evolved through combining skills from surgical, endoscopic, and radiologic specialties.[1,5,9] The striking success of the holmium laser for complex urinary calculi prompted us to investigate its use as a lithotrite for biliary tract calculi.[10] Our initial focus was to apply the existing technologies of holmium laser lithotripsy to patients with primary intrahepatic calculi located throughout the biliary tree with no adequate treatment options. After the successful treatment of patients with primary intrahepatic calculi, we then used the same techniques for clearing calculi in patients who presented with secondary biliary calculi where treatment by standard methods had failed. We present our experience in managing these difficult clinical challenges.

METHODS

Patient Characteristics

From April 1996 through February 2003, treatment of 36 patients with complex biliary tract calculi at the New York University Medical Center and Bellevue Hospital Medical Center included use of the holmium laser. Diagnostic evaluation included CT scanning, ultrasonography, magnetic resonance imaging with cholangiography, percutaneous cholangiography, and endoscopic cholangiography where indicated. Patients received antibiotics and ursodeoxycholic acid at the discretion of the treating physician. Demographic data are presented in Tables 1 and 2. There were 23 women and 13 men ranging in age from 28 to 88 years. Patients were classified into two groups: primary intrahepatic calculi (n = 22) and secondary intrahepatic calculi (n = 14).

Patients considered as having primary intrahepatic calculi presented with a history and symptoms that have been referred to as hepatolithiasis, cholangiohepatitis, or recurrent pyogenic cholangitis. All 22 patients presenting with primary intrahepatic calculi (patients P1 to P22; see Table 1) immigrated to the United States from either mainland China or Hong Kong, and the gallbladder was secondarily involved in the disease process.

Fourteen patients were assigned to the group designated the secondary intrahepatic calculi group (patients S1 to S14; see Table 2). Because none of these patients were of Asian descent, it was initially assumed that calculi found in the bile duct originated in the gallbladder. Ten patients had a history or evidence of gallbladder calculi. In the remaining four patients, calculi were a result of disease processes originating within the bile ducts. Two patients had a diagnosis of sclerosing cholangitis (S7 and S10), one patient had a history of congenital bile duct atresia (S11), and one patient developed intrahepatic calculi after liver transplantation, complicated by hepatic artery occlusion (S4; see Table 2). Although these patients could be considered to have primary intrahepatic calculi, they did not have the endemic form of the disease and were therefore grouped separately. Patients in this report were referred for management, and the holmium laser was employed after standard techniques had failed to clear bile duct calculi.

Technique of Laser Lithotripsy

Before laser lithotripsy could be performed, patients required access to the biliary tract and establishment of adequate biliary tract drainage. The method of access—percutaneous transhepatic catheter or T tube—was determined at the time of patient presentation according to previous treatment. In patients who presented with cholangitis or who had previous cholecystectomy, the percutaneous transhepatic catheter was used, whereas those requiring elective cholecystecomy had a T tube placed at the time of surgery.

Biliary tract drainage was either by choledochoenterostomy or endoscopic sphincterotomy. Patients presenting with previous choledochoenterostomy or endoscopic sphincterotomy were considered to have adequate drainage. Endoscopic sphincterotomy was performed in patients who had previously undergone cholecystectomy. Our preference was to perform a Roux-en-Y-hepaticojejunostomy with subfascial placement of the Roux limb for future access in patients who required open surgery for cholecystectomy. In two patients (S2 and S8; see Table 2) the common bile duct was accessed via cystic ductotomy during laparoscopic cholecystectomy; biliary drainage was previously established in these patients by endoscopic sphincterotomy. Percutaneous access was not possible in patient P4 (see Table 1) because of large intrahepatic cysts. This patient was managed by converting a choledolchoduodenostomy to a Roux-en-Y hepaticojejunostomy with a T tube. Access to the bile duct was through the T-tube tract. When the patient developed recurrent calculi, the biliary tree was accessed though the blind end of the Roux limb, which had been placed subfacially.

Table 1. Patients with primary biliary tract calculi

Patient	Age (yr)	Sex	Presentation	Previous surgery	Initial procedure	Access	Drainage	No. of LLTs	Follow-up (mo)
P1	61	F	pain, fever	None	CCX, HJ/RY	TT	HJ	4	50
P2	44	F	pain, fever	CCX, LHRXN, CDD	R-PTC	R-PTC	CDD	1	49
P3	41	M	cholangitis	CCX, ESX	B-PTC	B-PTC	ES	15	Died of progressive liver failure at 24 mo
P4	58	F	pain, fever	CCX, CDD	HJ/RY	TT	HJ	5	Recurrent calculi at 33 mo
P5	49	M	pain	CCX, HJ/RY	R-PTC	TT/R-PTC	HJ	7	50
P6	49	M	pain	CCX	HJ/RY	TT	HJ	3	78
P7	61	F	cholangitis	None	CCX, HJ/RY	TT	HJ	2	75
P8	52	F	cholangitis	CCX, CDD	B-PTC	B-PTC	CDD	5	Recurrent calculi at 45 mo
P9	43	M	cholangitis	CCX, LHRXN, ESX	None	TT	ES	1	47
P10	44	F	pain, fever	CCX, CDD	B-PTC	B-PTC	CDD	3	Died of cholangiocarcinoma at 58 mo
P11	63	M	cholangitis	None	CCX, HJ/RY	TT	HJ	1	Died of cholangiocarcinoma at 44 mo
P12	79	F	pain, fever	CCX, HJ/RY	B-PTC	B-PTC	HJ	2	47
P13	47	M	pain	None	CCX, HJ/RY	TT	HJ	2	40
P14	54	F	pain	CCX, ES	B-PTC	B-PTC	ES	3	51
P15	57	F	pain, fever	None	CCX, HJ/RY	TT	HJ	4	36
P16	63	F	pain, fever	CCX	HJ/RY	TT	HJ	5	20
P17	41	F	pain	CCX	ES, L-PTC	B-PTC	ES	7	16
P18	70	F	cholangitis	CCX, HJ/RY	B-PTC	B-PTC	HJ	4	17
P19	64	F	pain	CCX	R-PTC, HJ/RY	TT/R-PTC	HJ	3	14
P20	28	M	cholangitis	CCX	R-PTC, HJ/RY	TT/R-PTC	HJ	3	8
P21	28	F	pain, fever	None	CCX, HJ/RY	TT	HJ	2	8
P22	36	F	pain, fever	CCX, HJ/RY	B-PTC	PTC	HJ	3	6

PTC = percutaneous transhepatic cholangiocatheter; L = left hepatic; R = right hepatic; B = bilateral; LLT = laser lithotripsy; HJ/RY = hepatico-jejunostomy/Roux-en-Y; ES = endoscopic sphincterotomy; LHRXN = left hepatic resection; TT-T = T tube; CCX = cholecystectomy; CDD = choledolchoduodenostomy.

Table 2. Patients with secondary biliary tract calculi

Patient	Age (yr)	Sex	Cholecystectomy	Access	Drainage	Presentation	No. of LLTs	Notes	Follow-up
S1	43	M	Open/remote CBDE/remote	T tube	ES	Jaundice	3	Failed open CBDE, failed ERC/SE	60 mo, uneventful
S2	42	F	Laparoscopic	Cystic duct	ES	Pancreatitis	1	Failed ERC/SE	58 mo, uneventful
S3	68	M	Open/remote	R-PTC	ES/remote	Cholangitis	1	Refused ERC/SE	55 mo, uneventful
S4	88	F	Open/remote	R-PTC	ES	Cholangitis	1	Failed ERC/SE	52 mo, uneventful
S5	57	F	Open/TXPLT	B-PTC	ES	Cholangitis	10	Post-transplantation hepaticolithiasis	Recurrent calculi at 22 mo, died at 55 mo of progressive liver failure
S6	68	M	Open/remote	R-PTC	ES	Cholangitis	1	Failed ERC/SE	50 mo, uneventful
S7	76	M	Open/remote	B-PTC	HJ/RY	Cholangitis	8	Sclerosing Cholangitis	Recurrent calculi at 18 mo progressive sclerosing cholangitis colon cancer associated with ulceritive colitis
S8	29	F	Laparoscopic	Cystic duct	ES	Jaundice	1	Failed ERC/SE	38 mo, uneventful
S9	62	F	Open/remote	R-PTC	ES	Cholangitis	1	Failed ERC/SE	37 mo, uneventful
S10	38	F	Open/remote	T tube/L-PTC	HJ/RY	Pain, fever	5	Left hepatic duct stricture	Recurrent calculi at 31 mo, progressive sclerosing cholangitis
S11	33	F	Open/remote	R-PTC	HJ/RY	Cholangitis	1	Congenital atresia with late stricture	10 mo, uneventful
S12	80	F	Open/remote CBDE/remote	R-PTC	ES	Cholangitis	1	Failed open CBDE failed ERC/SE	6 mo, uneventful
S13	74	M	Laparoscopic/remote CBDE/remote	R-PTC	ES	Cholangitis	1	Failed open CBDE, failed ERC/SE	9 mo, uneventful
S14	60	M	Open/remote CBDE/remote	T tube	ES	Jaundice	1	Failed open CBDE, failed ERC/SE	1 mo, uneventful

LLT = Laser lithotripsy; ES = endoscopic sphincterotomy; PTC = percutaneous transhepatic cholangiocatheter; R = right hepatic; B = bilateral; CBDE = common bile duct exploration; ERC/SE = endoscopic retrograde cholangiogram with stone extration; HJ/RY = hepaticojejunostomy/Roux-en-Y.

For patients undergoing cholecystectomy or biliary surgery, laser lithotripsy was performed at the time of surgery through a standard bile ductotomy. Percutaneous access tracts were allowed to mature for 4 to 6 weeks prior to laser lithotripsy procedures. In order to prevent the laser fiber from inadvertently contacting the bile duct during laser lithotripsy, patients required general endotracheal anesthesia to prevent sudden movements and controlled ventilation with low tidal volumes to limit diaphragmatic excursion. Intraoperative cholangiography was performed through existing catheters, which were subsequently removed over guidewires. We preferred to use a 7.5 F outside diameter endoscope (Karl Storz Endoscopy, Tuttlingen, Germany) with a 3.6 F working channel, which was inserted through the established tract under video guidance to access the biliary tree. Continuous warm (33 to 37C) 0.9% saline irrigation through the working channel of the choledochoscope was used to distend the biliary ducts, remove debris, and provide a medium to transfer laser energy. The laser energy was generated from a 60-watt solid-state holmium:YAG unit (Boston Scientific, Natick, MA). The laser fiber was introduced through the working channel of the choledochoscope. Our preference is to use a 200 mm fiber to allow maximal deflection of the choledochoscope. As calculi were encountered, they were fragmented with a laser frequency of 6 to 10 Hz and energy of 0.5 to 1.0 joules. During the course of cholangioscopy when strictures were encountered, we found that the laser could divide strictures and thus allow us to gain access to the obstructed segment of the liver and remove the calculi. Procedures were limited to 2 to 3 hours' duration to prevent hypothermia and abdominal distention from the irrigation solution. Laser lithotripsy was repeated as often as necessary until the biliary tree was free of calculi and obstructing strictures.

RESULTS

Presenting Symptoms

For the patients in the primary intrahepatic calculi group (see Table 1), presenting symptoms included pain and fever without cholangitis (anicteric) in nine patients, cholangitis in seven patients, and isolated right upper quadrant pain in six patients. None of these patients presented with pancreatitis, and jaundice was always accompanied by additional symptoms. Presenting symptoms for the group with secondary intrahepatic calculi included cholangitis (n = 9), pain and fever (n = 2), jaundice (n = 1), pain (n = 1), or pancreatitis (n = 1).

Procedures Performed Before Laser Lithotripsy

Six of the 22 patients with primary intrahepatic calculi were not previously treated for biliary tract disease before referral to our center (see Table 2). The remaining 16 patients received a variety of treatments in an attempt to rid them of calculi. Four patients had previously undergone cholecystectomy alone. Ten had cholecystectomy with a drainage procedure (choledochoduodenostomy in 4, endoscopic sphincterotomy in 2, and hepaticojejunostomy in 4). Two patients had a combined procedure consisting of cholecystectomy, left hepatic resection, and a drainage procedure (endoscopic sphincterotomy in 1 and choledochoduodenostomy in 1).

Twelve of the 14 patients with secondary intrahepatic calculi underwent cholecystectomy prior to referral, 11 by open technique and one laparoscopically. Two patients had no previous biliary tract procedures and underwent laparoscopic cholecystectomy at the time of laser lithotripsy for biliary tract calculi. In four patients, removal of calculi had been attempted by open common bile duct exploration and endoscopic retrograde cholangiopancreatography (ERCP). Six patients had previously undergone ERCP that did not completely remove bile duct calculi. One patient refused ERCP because after a previous ERCP he had had an episode of life-threatening pancreatitis that required operative necrosectomy. Patient S5 underwent orthotopic liver transplantation with primary bile duct anastomosis that was complicated by hepatic artery thrombosis. Although the transplant survived, there was sloughing of the biliary mucosa and subsequent calculi formation that could not be cleared by ERCP. Three patients had previous hepaticojejunostomy, two after extrahepatic bile duct resection for sclerosing cholangitis. Patient S11 had a hepaticojejunostomy created to treat a congenital biliary stricture shortly after birth.

Access for Laser Lithotripsy

In order to perform laser lithotripsy, there must be adequate access to the biliary tree so that a 7 to 10 F choledochoscope can be passed with ease. Access to the biliary tree in patients with primary intrahepatic calculi was via surgically placed T tubes in 10 patients, percutaneous transhepatic catheters in nine patients, and a combination in three patients. For patients with secondary intrahepatic calculi, access to the biliary tree was by means of surgically placed T tubes in four patients, percutaneous transhepatic catheter in nine, and a combination in one.

Drainage for Laser Lithotripsy

Biliary tract drainage must be sufficient for small stone fragments to pass unimpeded and must also be

able to provide adequate biliary flow such that stasis does not develop and contribute to calculi formation in the future. Biliary drainage in patients with primary intrahepatic calculi was by biliary-enteric anastomosis in 18 patients (choledochoduodenostomy in 3 and hepaticojejunostomy in 15), or endoscopic sphincterotomy in four patients. Not surprisingly, the majority of patients with secondary intrahepatic bile duct calculi had endoscopic sphincterotomy (n = 11) as drainage procedures and only three had biliary enteric anastomosis (hepaticojejunostomy).

Outcome

Laser Performance. Samples of calculi from both groups of patients were retrieved and subjected to mineral analysis. The retrieved fragments contained mixed combinations of cholesterol, calcium bilirubinate, and mixed bile pigments. The holmium laser was able to fragment stones irrespective of the composition.

Elimination of Intrahepatic Calculi by Holmium Laser Lithotripsy. Bile ducts were considered cleared if no calculi could be identified by cholangiography (Fig. 1) or cholangioscopy, and transcutaneous catheters could be removed without the development of infections complications. Clearance of calculi was achieved in patients with primary intrahepatic calculi, requiring an average of 3.9 treatments per patient (range 1 to 15). Secondary intrahepatic calculi required an average of 2.6 treatments per patient (range 1 to 10) for clearance of calculi. Clearly the majority of these patients required one treatment for calculi located in the common bile duct.

Complications. The most common complication was brief, self-limiting febrile episodes after treatments. Procedure-related complications included hepatic subcapsular hematoma (due to a guidewire in patient P1), infected hepatic cyst (patient P4), supraventricular tachycardia (3), and post-procedure pneumonia (patient S12). No patients in either group developed septic shock despite the presence of bactobilia. No complications or deaths were a direct result of using the holmium laser. Inadvertent firing of the laser in direct contact with the bile duct mucosa did not cause irreversible injury that could be identified on subsequent cholangioscopy. This observation led us to use the laser to divide strictures under direct vision with good success.

Follow-Up. The follow-up data in Table 1 include the length of time (based on follow-up visit or phone contact) the patient was know to be symptom free (range 6 to 78 months). It is difficult to ascertain for sure how the patients in the groups with primary intrahepatic calculi fared in the long term because some patients left the New York metropolitan area shortly after their treatments. Two patients returned with recurrent intrahepatic calculi, which were successfully treated by means of a percutaneous transhepatic catheter for access (patient P8) or by accessing the blind end of the Roux limb (patient P4). Three patients died, one from progressive liver failure (patient P3) and two from cholangiocarcinoma (patients P10 and P11).

More complete follow-up information is available for patients with secondary intrahepatic calculi (see Table 2). One patient (S5) died of progressive hepatic failure; this patient was unable to undergo retransplantation because of hepatic artery thrombosis and recurrent calculi 22 months after treatment. Patients S7 and S10 have been diagnosed with sclerosing cholangitis. As the disease progresses, new strictures form leading to stasis and recurrent stone formation, which can be successfully retreated to minimize their symptoms.

DISCUSSION

Faced with the challenge of managing patients with complex biliary calculi, we adapted the techniques of biliary endoscopy and holmium laser lithotripsy, and have demonstrated that the holmium laser is a safe and effective method to clear biliary tract calculi. This is true regardless of the location or composition of the calculi. When planning treatment for patients with complex biliary calculi, careful evaluation must be made of stone location, biliary anatomy, and previous biliary tract procedures performed on the patient. Successful outcome can be assured if there is adequate access to the biliary tree for complete evaluation and treatment. Sufficient enteric drainage of the bile ducts will allow stone fragments to enter the gastrointestinal tract during lithotripsy procedures, and prevent future stasis and recurrent calculi formation after stone clearance.

Persistent or recurrent stones from inadequately treated primary intrahepatic calculi can cause recurrent cholangitis and can eventually lead to hepatic failure and death.[2,6] Standard therapy includes endoscopic, percutaneous, and surgical approaches. ERCP provides access to the common bile duct for diagnoses. When combined with endoscopic sphincterotomy (ES), ERCP allows for drainage of the common bile duct and in skilled hands can be used for extraction of intrahepatic calculi.[11] Although ERCP/ES can provide access to the common bile duct, strictures and stones beyond the secondary biliary radicals may be out of reach. Percutaneous transhepatic cholangiography can be used for the

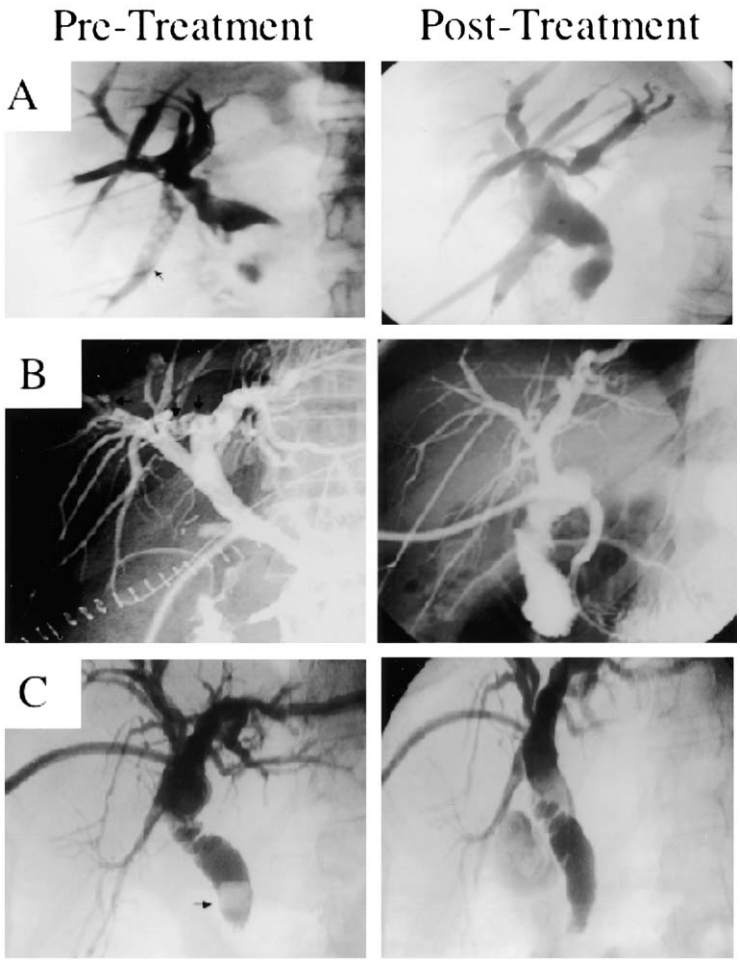

Fig. 1. A, Radiologic studies of patient P2 who had a previous cholecystectomy, choledochoduodenostomy, and left hepatic resection (segments II and III) and presented with recurrent right upper quadrant pain and fever. Pretreatment percutaneous cholangiogram demonstrates calculi in the right hepatic ducts (*arrow*), accessed by a percutaneous catheter. After treatment with Holmium laser lithotripsy, all calculi are fragmented and cleared from the biliary tree. **B**, Patient S1 was referred for treatment following failed attempts to clear calculi by ERCP and open common bile duct exploration. After Holmium laser lithotripsy through the T-tube tract, all calculi were cleared. **C**, A common scenario is a single common bile duct stone after cholecystectomy, as demonstrated by percutaneous cholangiography in patient S9 (arrow). After a failed attempt to clear the calculi with ERCP and endoscopic sphincterotomy, a choledochoscope was passed through the percutaneous transhepatic catheter tract, and the Holmium laser was used to fragment the stone. A completion cholangiogram demonstrates free flow of contrast medium into the duodenum without filling defects.

diagnosis of primary intrahepatic calculi and may be used for dilation of strictures and extraction of intrahepatic calculi.[1,12] Surgical therapy includes biliary enteric bypass and hepatic resection.[3,8,13] From our experience it is apparent that standard modalities are not sufficient for clearing intrahepatic calculi in all patients. Holmium laser lithotripsy does not replace any of these modalities but complements them. In fact, holmium laser lithotripsy relies on these traditional modalities for diagnosis of biliary calculi, localization of stones, and stricture, providing access for lithotripsy and drainage of the biliary tree. The best results are achieved when these modalities are used in a multidisciplinary approach that leads to complete clearance of stones, elimination of strictures, adequate drainage of the biliary system, and preservation of hepatic parenchyma.[1]

The inadequacy of standard techniques of stone removal through ERCP, percutaneous transhepatic cholangiography, and surgery has been previously reported, and several methods of lithotripsy have been applied to this disease in order to eliminate intrahepatic calculi.[14–16] A major advantage of the holmium laser is that it is capable of delivering sufficient energy

to fragment biliary stones, regardless of composition, through probes that are flexible and small in caliber (200 μ). The small fiber diameter does not impede deflection of the biliary endoscope while it is being manipulated through the biliary tree.[10]

This is the largest and most comprehensive report on the use of the holmium laser to treat biliary calculi. Several types of laser lithotripters (e.g., YAG, coumarin dye) have been applied to primary intrahepatic calculi.[8,16] The disadvantages of these energy sources for laser lithotripsy are that energy delivered is determined by fiber diameter and lithotripsy must be performed under direct vision to prevent inadvertent injury to the bile ducts. The therapeutic approach we report here overcomes these disadvantages of laser lithotripsy by combining advances in biliary endoscopy with a holmium laser. The safety and efficacy of holmium laser lithotripsy in the treatment of urinary tract calculi has been clearly demonstrated.[10] The holmium laser is a thermal laser that provides pulsatile delivery of high energy.[17] The mechanism of stone fragmentation is by superheating surrounding water and creating a vaporization bubble. The thermal effect is localized to an area within 3 mm of the probe and is minimized by continuous irrigation. Sufficient energy to fragment biliary calculi can be delivered through 200 and 365 μ fibers that are easily accommodated in the working channels of 7.5, 10, or 15 F flexible endoscopes.

The importance of planning access and drainage for holmium laser lithotripsy cannot be overemphasized. In general, access to the biliary tract for laser lithotripsy can be achieved through either a T-tube tract, right or left percutaneous transhepatic cholangiography catheters, or the blind end of a Roux limb. The common bile duct can be reached from any of these approaches. When accessing the intrahepatic ducts through a percutaneous transhepatic cholangiography tract, it is technically easiest to approach them from the contralateral side. For example, a right-sided PTC access is best to approach the left hepatic ducts. Bilateral intrahepatic calculi would require bilateral percutaneous transhepatic cholangiography (PTC), or access to the common bile duct by a T tube or Roux limb. The catheter used for access should be 10 to 12 F, which allows formation of a tract large enough for manipulation without causing undue discomfort for the patient. Catheters used for access should be left in place for 4 to 6 weeks to allow a tract to mature. Without sufficient time to mature, excess bleeding can result from manipulation of the tract, or the tract can rapidly contract making insertion of the biliary endoscope difficult.

The most appropriate form of biliary drainage, biliary-enteric bypass or endoscopic sphincterotomy, remains controversial.[13] A larger diameter drainage site can be achieved by biliary enteric anastomosis, and we believe that a Roux-en-ɣ hepaticojejunostomy has less potential morbidity and more options for reaccess than choledochoduodenostomy. We have also found that because of inflammation in the porta hepatis, it is often difficult to isolate the bile duct from surrounding vascular structures. Therefore we recommend a side-to-side biliary-enteric anastomosis because it is not necessary to divide the bile duct when constructing the anastomosis. Endoscopic sphincterotomy provides a sufficient channel to allow drainage in patients with primary or secondary intrahepatic calculi. We were initially skeptical that endoscopic sphincterotomy as a drainage procedure for patients with primary intrahepatic calculi would be sufficient, but our experience demonstrated that the fragments created by the holmium laser are small enough to pass. Most patients with secondary bile duct calculi have stones confined to the common bile duct, and prior to referral many of these patients have had endoscopic sphincterotomy in an attempt to clear bile duct stones. This scenario is likely to increase in frequency as the reliance on endoscopic techniques for removal of residual calculi after laparoscopic cholecystectomy increases. Patients in whom this approach is unsuccessful can be referred for laser lithotripsy that would require a right-sided PTC catheter followed by lithotripsy, thus maintaining the goal of providing a minimally invasive approach. The holmium laser can also be used for clearing stones during laparoscopic common bile duct exploration through the cystic duct. Finally, we recently used the holmium laser as a lithotrite through a "daughter scope" passed into the common bile duct during ERCP for common bile duct stones. This approach provided adequate access to the hepatic duct bifurcation. Access to the secondary ducts using this strategy would depend on the anatomy of each individual patient.

Although many clinicians experienced in the management of primary intrahepatic calculi advocate liver resection, we believe that the use of holmium laser lithotripsy will significantly reduce or eliminate the need for resection in these patients.[17,18] All patients with primary intrahepatic calculi in this series had evidence of stones and/or strictures in both the right and left hepatic ducts, either by imaging, by direct biliary endoscopy, or by history of previous hepatic resection (see Fig. 1). Therefore hepatic resection would not have benefited any of these patients. Resection should be reserved for those patients with abscess and atrophy after repeated episodes of cholangitis, when resection would not compromise functional hepatic parenchyma.

Laser lithotripsy with a holmium laser can be safely performed in patients with complex biliary calculi using a multidisciplinary approach of surgery, ERCP, and PTC. Patients could be treated with minimal morbidity and complications regardless of stone location or composition. We found that with the use of these techniques the need for open bile duct exploration and hepatic resection can be eliminated.

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REFERENCES

1. Pitt HA, Venbrux AC, Coleman J, Prescott CA, Johnson MS, Osterman FA, Cameron JL. Intrahepatic stones. The transhepatic team approach. Ann Surg 1994;219:527–535.
2. Cheung KL, Lai EC. The management of intrahepatic stones. Adv Surg 1995;29:111–129.
3. Stain SC, Incarbone R, Guthrie CR, Ralls PW, Rivera-Lara S, Parekh D, Yellin AE. Surgical treatment of recurrent pyogenic cholangitis. Arch Surg 1995;130:527–532.
4. Hanau LH, Steigbigel NH. Cholangitis: Pathogenesis, diagnosis, and treatment. Curr Clin Topics Infect Dis 1995;15: 153–178.
5. Hunter JG, Soper NJ. Laparoscopic management of bile duct stones. Surg Clin North Am 1992;72:1077–1097.
6. Liu CL, Fan ST, Wong J. Primary biliary stones: Diagnosis and management. World J Surg 1998;22:1162–1166.
7. Sun WB, Han BL, Cai JX. The surgical treatment of isolated left-sided hepatolithiasis: A 22 year experience. Surgery 2000; 27:493–497.
8. Uchiyama K, Onishi H, Tani M, Kinoshita H, Ueno M, Yanaue H. Indication and procedure for treatment of hepatolitiasis. Arch Surg 2002;173:149–153.
9. Choi S, Choi TK, Wong J. Intraoperative flexible cholangioscopy for intrahepatic and extrahepatic biliary calculi. Surgery 1987;101:571–576.
10. Grasso M. Experience with the holmium laser as an endoscopic lithotrite. Urology 1996;48:199–206.
11. Lee JG, Leung JW. Endoscopic management of difficult common bile duct stones. Gastrointest Endosc Clin North Am 1996;6:43–55.
12. Stokes KR, Clouse ME. Biliary duct stones: Percutaneous transhepatic removal. Cardiovasc Intervent Radiol 1990;13: 240–244.
13. Panis Y, Fagniez PL, Brisset D, Lacaine F, Levard H, Hay JM. Long term results of choledochoduodenostomy versus choledochojejunostomy for choledocholithiasis. The French Association for Surgical Research. Surg Gynecol Obstet 1993; 177:33–37.
14. Shaw MJ, Mackie RD, Moore JP, Dorsher PJ, Freeman ML, Meier PB, Potter T, Hutton SW, Vennes JA. Results of a multicenter trial using a mechanical lithotripter for the treatment of large bile duct stones. Am J Gastroenterol 1993;88:730–733.
15. Sheen-Chen SM, Chou FF. Intraoperative choledochoscopic electrohydraulic lithotripsy for difficulty retrieved impacted common bile duct stones. Arch Surg 1995;130:430–432.
16. Sullivan KL, Bagley DH, Gordon SJ, Soulen MC, Grasso M, Bonn J, Shapiro MJ. Transhepatic laser lithotripsy of choledocholithiasis: Initial clinical experience. J Vasc Intervent Radiol 1991;2:387–391.
17. Blomley MJ, Nicholson DA, Bartal G, Foster C, Bradley C, Myers M, Man W, Li S, Banks LM. Holmium-YAG laser for gall stone fragmentation: an endoscopic tool. Gut 1995;36: 442–445.
18. Jeng KS, Ohta I, Yang FS. Reappraisal of the systematic management of complicated hepatolithiasis with bilateral intrahepatic biliary strictures. Arch Surg 1996;131:141–147.

Treatment of Patients With Unresectable Primary Hepatic Malignancies Using Hyperthermic Isolated Hepatic Perfusion

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Primary hepatocellular carcinoma is one of the most common malignancies worldwide. Isolated hepatic perfusion (IHP) is a regional treatment technique that isolates the organ to allow delivery of high-dose chemotherapy, biological agents, and hyperthermia directly to unresectable cancers confined to the liver. This study presents our experience using IHP with melphalan with or without tumor necrosis factor (TNF) to treat patients with hepatocellular carcinoma or adenocarcinoma of hepatobiliary origin. Nine patients with unresectable primary hepatic malignancies underwent a 60-minute IHP with 1.5 mg/kg melphalan with or without 1.0 mg TNF. Four patients failed one or more previous treatment regimens, and the mean hepatic replacement by tumor was 41% (range 10% to 75%). Patients were monitored for response, toxicity, time to recurrence, and survival. Six (67%) of nine patients experienced greater than 50% regression of tumor by objective radiographic imaging and an additional patient had a 45% reduction in tumor burden. Mean time to progression was 7.7 months for those who responded to treatment. Patients who had a response to therapy had an average overall survival of 16.3 months. IHP can be performed safely and has significant antitumor activity in patients with unresectable primary hepatic malignancies. Hepatic progession continues to be the dominant factor influencing survival in this group of patients. (J GASTROINTEST SURG 2004;8:200–207)

KEY WORDS: Regional perfusion, hyperthermia, liver neoplasms

Primary hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. Although it is more common in Asia and Africa, its incidence is rising in Western countries.[1] Most commonly, it develops in the setting of chronic inflammatory liver disorders such as chronic hepatitis B or C. The stage of disease at the time of diagnosis dictates the type of treatment offered. With early diagnosis, curative surgical resection is possible. More commonly, however, individuals are diagnosed at an advanced, incurable stage.

Surgical resection is considered the treatment of choice for early-stage HCC in both cirrhotic and noncirrhotic patients. Although the overall 5-year survival rate approaches 50%,[2] only 9% to 27% of patients are suitable for resection at the time of diagnosis because of advanced tumor stage, tumor location, multifocality, or poor hepatic reserve.[3] Liver transplantation is considered an alternative treatment for patients with HCC; however, the limited availability of donor organs restricts this option to a select group of patients.[4]

Systemic chemotherapy has not yielded promising results for unresectable HCC. The objective response rate for most single agents is less than 10%.[5] A recent study reviewing combination therapies has produced objective response rates of only 26% with median survivals of 8.9 months and no apparent improvement in overall survival.[6] In addition, toxicities have been considerable including myelosuppression and death secondary to neutropenic sepsis. A follow-up study demonstrated an overall response rate of 16.8%, which is considerably lower than those previously reported.[7]

Multiple locoregional therapies have been proposed for the treatment of primary liver cancers.

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Transarterial chemoembolization (TACE) is a regional therapy widely used despite conflicting clinical data with respect to survival. Although Lo et al.[8] demonstrated a significant survival benefit of TACE over symptomatic treatment, two randomized trials from France demonstrated no survival benefit over palliation alone.[9,10] A meta-analysis of multiple randomized controlled trials did report an overall survival benefit for TACE, but the magnitude of the benefit was modest.[11] A recent study demonstrated a survival benefit for patients treated with percutaneous intratumor ethanol injection with small lesions and good hepatic reserve.[12] However, it requires multiple treatments and is limited in its applicability to patients with superficial lesions, less than 30% neoplastic volume, or limited disease. Radiofrequency ablation has been explored for the treatment of small unresectable tumors, but follow-up data are not mature.[13]

The concept of hyperthermic isolated hepatic perfusion (IHP) was introduced more than 40 years ago as an alternative means to achieve high concentrations of cytotoxic anticancer drugs or biological agents in the liver for patients with unresectable metastases confined to the organ.[14] In recent years it has been demonstrated that IHP using melphalan alone or in combination with tumor necrosis factor (TNF) is technically feasible and can result in regression of hepatic metastases in patients with colorectal carcinoma or ocular melanoma.[15–18] In this paper we present our initial clinical experience with IHP using melphalan alone or with TNF in patients with primary hepatic malignancies.

MATERIAL AND METHODS

Patient Selection

Between November 1995 and June 1999, 9 patients were enrolled in two related clinical protocols approved by the institutional review board and, when TNF was used, the Cancer Therapy Evaluation Program of the National Cancer Institute. All patients had measurable, biopsy-proven unresectable primary malignancies confined to the liver. Preoperatively, all patients underwent multiple staging studies including CT scan of the chest, abdomen, and pelvis to evaluate for extrahepatic disease, MRI of the liver and, as clinically indicated, MRI of the brain and bone scan. Additionally, all patients had celiac and superior mesenteric arteriography performed to assess vascular anatomy.

Eligibility criteria were defined as Eastern Cooperative Oncology Group performance status of 0 or 1, serum bilirubin level less than 2 mg/dl, platelet count greater than 150,000/ml, serum creatinine $\leq$1.5 mg/dl, and normal coagulation profile including prothrombin time and partial thromboplastin time assays. Patients with biopsy-proven cirrhosis with evidence of significant portal hypertension by history, endoscopy, or radiologic studies were excluded. Patients over the age of 65 or with risk factors for coronary disease had a complete cardiac evaluation prior to therapy. All patients gave informed consent prior to participation in these trials.

Isolated Hepatic Perfusion

The technique of IHP has been previously reported.[19] Briefly, the abdomen is entered via laparotomy incision and inspected for the presence of extrahepatic disease. The liver is extensively mobilized. The right lobe is retracted anteriorly and medially, and the inferior vena cava is completely dissected free from the retroperitoneum from the level of the renal veins to the diaphragm. All minor branches of the inferior vena cava are ligated and divided to eliminate potential sources of perfusate leakage during the procedure. The structures of the porta hepatis are skeletonized and a cholecystectomy is performed. All lymph node–bearing tissue around the porta hepatis is removed. The portal vein and common bile duct are mobilized from the head of the pancreas to the inferior border of the liver. A 2-cm segment of the gastroduodenal artery is dissected and serves as the arterial cannulation site. Saphenous and left axillary venous cutdowns are performed.

After systemic anticoagulation, cannula are inserted into the inferior vena cava via the saphenous vein and into the axillary vein, and connected to a venovenous bypass circuit. The suprarenal inferior vena cava is occluded, and venous cannula are inserted into the retrohepatic inferior vena cava and distal portal vein. The portal venous flow is shunted to the axillary vein via venovenous bypass. An arterial cannula is placed in the gastroduodenal artery and connected to the arterial inflow of the perfusion circuit. The retrohepatic inferior vena cava cannula is connected to the venous outflow tract to complete the circuit. The common hepatic artery is occluded. Finally, the suprahepatic inferior vena cava is cross-clamped just below the diaphragm, and IHP is initiated.

The liver is perfused for 60 minutes at 39.5 to 40.0C with flow rates ranging from 600 to 1200 ml/min using a centrifugal pump (Biomedicus, Eden Prairie, MN) to maintain line pressures less than 200 mm Hg and a stable reservoir volume. Melphalan, 1.5 mg/kg (Burroughs-Glaxo, Research Triangle Park, NC), with or without 1.0 mg TNF (Knoll Pharmaceuticals, Whippany, NY), is administered into the

perfusate once stable perfusion parameters are obtained. Perfusate temperature is controlled with a Hemotherm cooler-heater (Cincinnati SubZero Products, Cincinnati, OH), and hepatic temperatures are monitored with temperature probes. For patients treated with TNF, perfusate leakage into the systemic circulation is continuously monitored and quantitated using ^{131}I-labeled human serum albumin in patients who receive TNF as previously described.[20] At the conclusion of the perfusion, the liver is flushed with 1500 ml of crystalloid followed by 1500 ml of colloid, and the proximal portal vein is flushed with 1 L of normal saline solution. After decannulation and repair of the venotomies, normal physiologic blood flow is returned to the liver. Patients are monitored in the intensive care unit for at least 48 hours postoperatively.

Toxicity

Systemic and regional toxicities are graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Systemic toxicity is defined as all toxicity that is not reversed within 24 hours of the operative procedure. Regional (hepatic) toxicities are graded as elevations in hepatic transaminases that persist for more than 7 days from the procedure.

Response

All patients were followed with physical examination, laboratory tests, CT scans of the chest, abdomen, and pelvis, and MRI of the liver every 3 months for the first year, every 4 months for the second year, and every 6 months thereafter until disease progression. A complete response is defined as complete disappearance of all radiographically established tumors without evidence of new lesions for a period of 30 days after therapy. A partial response is defined as $\geqslant$50% reduction in the sum of the product of the perpendicular diameters of all measurable lesions in the liver for at least 30 days without progression of any single lesion or development of new hepatic lesions. Each patient was followed until he or she demonstrated progression of hepatic disease or systemic failure.

Statistics

All data are presented as mean ± standard deviation or median followed by range.

RESULTS

Patient demographics are outlined in Table 1. The mean age was 54 years (range 32 to 72 years). Five of 9 patients (3 women and 2 men) had a pathologic diagnosis of HCC, whereas the remaining 4 patients (1 woman and 3 men) had primary intrahepatic cholangiocarcinoma or adenocarcinoma of unknown origin but was presumed to arise from hepatobiliary elements. Each of the 4 patients bearing the latter diagnosis had undergone extensive evaluation including both upper and lower endoscopy to eliminate the possibility of an extrahepatic primary lesion. Four patients had previous therapy including either chemotherapy or chemoembolization prior to enrollment in this trial. The remaining 5 patients had no treatment prior to IHP.

Tumor burden was variable among the 9 patients. The average number of metastatic lesions in the liver was 13 and ranged from 1 to more than 100 lesions. The lesions ranged in size in terms of greatest diameter from 5 to 16 cm with a mean of 10 cm. The percentage of hepatic replacement by tumor ranged from 10% to 75% with a mean value of 41%.

The perfusion data, operative parameters, and recovery data are reviewed in Table 2. Perfusion flow rates ranged from 750 to 900 ml/min. Three of 9 patients received 1.0 mg TNF, and all 9 patients received melphalan, 1.5 mg/kg based on ideal body weight. All patients were treated with a central liver temperature of greater than 39ºC. The remainder of the perfusion data are listed in Table 2. The mean

Table 1. Patient and disease parameters: Primary hepatic malignancies

No. of patients	9
Age (yr)	54 (range 32–72)
Female:Male	3:6
Diagnosis	
Hepatocellular carcinoma	5
Cholangiocarcinoma	4
Prior chemotherapy	4 (45%)
Prior surgery	0
Time between diagnosis and intrahepatic perfusion	1–44 mo
Median	5 mo
Mean	10 mo
Mean no. of hepatic lesions	13 (range 1–100+)
Mean diameter of largest lesion (cm)	10 (range 5–16)
Percentage hepatic replacement by tumor	
<25%	2
25–50%	5
>50%	2

Table 2. Perfusion and operative data

Melphalan dose (mg)	101 (range 84–117)
No. of patients receiving TNF	3
Perfusion flow rate (ml/min)	814 (range 750–900)
Perfusion pressure (mm Hg)	162 (range 127–194)
Bypass flow rate (ml/min)	2011 (range 1500–2500)
Central liver temperature (ºC)	39.9 (range 39.3–41.8)
Estimated blood loss (L)	2.4 (range 1.2–4.5)
Operative time (hr)	8.7 (range 7–10)
ICU stay (days)	4 (range 3–6)
Hospital stay (days)	12.0 (range 7–17)

All values are given as mean with ranges in parentheses.

operative time of 8.5 to 9 hours reflects the considerable time necessary to prepare the liver for perfusion and did not vary despite increased experience with the procedure. The average estimated blood loss was 2400 ml but ranged from 1200 to 4500 ml. All 9 patients remained in the intensive care unit between 3 and 6 days with a mean of 4.3 days. Total length of hospital stay ranged from 7 to 17 days.

Toxicity data are presented in Table 3. There were no operative or treatment-related deaths. The majority of patients experienced grade II fever and weight gain. Six of the 9 patients experienced a grade IV hyperbilirubinemia, all levels peaking between days 1 and 7, with a mean of 3.6 days, and returning to the normal range by their first clinic visit at 6 weeks. Five patients developed grade IV hepatic transaminase levels, which returned to the normal range within 7 days.

Treatment response was determined by comparing follow-up MRI scans of the liver to pretreatment studies. As demonstrated in Table 4, six (67%) of the nine patients experienced a partial response ranging from 53% to 91% tumor reduction. One additional patient had a minor response with a 45% decrease in tumor burden. All patients experienced hepatic disease progression with the exception of one patient in whom tumor first metastasized to lung. In 6

Table 3. Treatment-related toxicities

Toxicity	Grade 1–2	%	Grade 3–4	%
Systemic				
Fever	9	100	—	—
Hypotension	2	22	—	—
Weight gain	8	89	1	11
Thrombocytopenia	7	78	1	11
Neutropenia	1	11	—	—
PT/PTT	8	89	—	—
Hepatic				
Bilirubin	2	22	6	67
Transaminases	4	44	5	56
Alkaline phosphatase	7	78	—	—

PT/PTT = prothrombin time/partial thromboplostin time.

Table 4. Primary hepatic malignancies: Results of isolated hepatic perfusion

Complete response	0
Partial response	6 (67%)
Duration (mo)	7.7 (range 3–13)
Site of first recurrence	
Hepatic	6 (67%)
Systemic	1 (11%)
Both	2 (22%)
Overall survival (mo)	
Mean	15
Range	6–29
1-year survival	22%

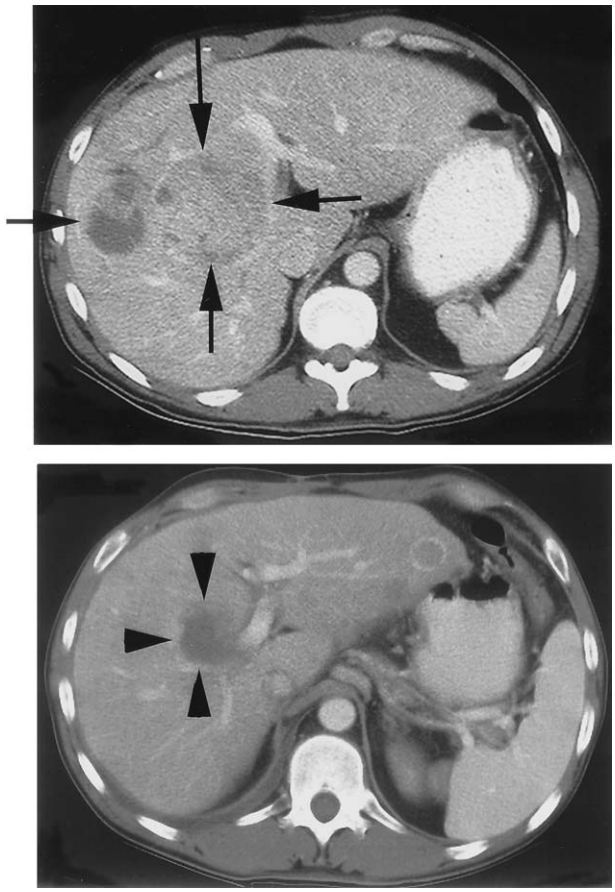

Fig. 1. Pre- and post-treatment contrast-enhanced CT scans from a patient with unresectable HCC. The patient received a 60-minute IHP. The patient achieved a partial response to therapy for approximately 10 months with initial recurrence in lung and liver. *Top panel* demonstrates the appearance of representative lesion before treatment. *Bottom panel* represents a comparable tumor 5 months after treatment. *Arrows* delineate the extent of the tumor in the top panel; *arrowheads* depict it in the bottom panel.

patients, tumor in the liver was the sole site of disease at death. In 2 of the 3 remaining patients, hepatic progression was concurrent with pulmonary metastases. For patients who had a partial response to IHP, the mean time to any site of disease progression was 7.7 months. Mean overall survival time was 16.3 months with a range of 6.4 to 23.5 months for patients who responded initially. Two patients were lost to follow-up, as they left the United States after their disease progressed. The two patients who did not respond died of tumor progression at 9.4 and 29.1 months, respectively, after perfusion. Figs. 1 and 2 demonstrate the radiographic appearance of 2 patients who responded to IHP. Fig. 3 shows hepatic progression–free and overall survival curves of all evaluable patients until the time of their last follow-up.

DISCUSSION

As the incidence of HCC rises, the development of novel treatment strategies such as IHP are clearly warranted.[21] Many regional treatment strategies that deliver anticancer agents directly to the liver in concentrations much greater than those tolerated systemically are under clinical evaluation.[22] The technique of IHP was developed in the late 1950s and was first reported in humans in 1961 by Ausman.[14] The technique of IHP has clearly evolved over the past 30 years. The technique used in this study has been previously described, and the efficacy associated with this treatment in patients with metastatic disease to the liver from ocular melanoma and colorectal carcinoma has been reported.[15–18]

The initial phase I trial conducted by the Surgery Branch at the National Cancer Institute used TNF and low-dose interferon-gamma in the perfusate.[23] Subsequently, multiple additional trials have been designed to determine the maximum tolerated dose of TNF with and without melphalan.[19,24,25] Response rates as high as 77% have been reported with the use of both agents.[16] The available data suggest that melphalan alone has comparable initial antitumor activity to TNF plus melphalan in patients with colorectal cancer or ocular melanoma, but the most durable responses to IHP have been associated with the use of TNF.[19] TNF is no longer available in the United States for IHP trials.

This paper presents the data from our experience with IHP and primary hepatic malignancies. The patients represented in this study had very advanced hepatic disease, as demonstrated by the large diameter and number of metastatic lesions as well as the mean percent hepatic replacement of 41%. In addition, 4 of 9 patients were refractory to other therapies before IHP. Despite this, 6 of 9 patients experienced a radiographic partial response to treatment, and one additional patient had a 45% reduction in tumor burden. Clearly there was clinically significant regression of

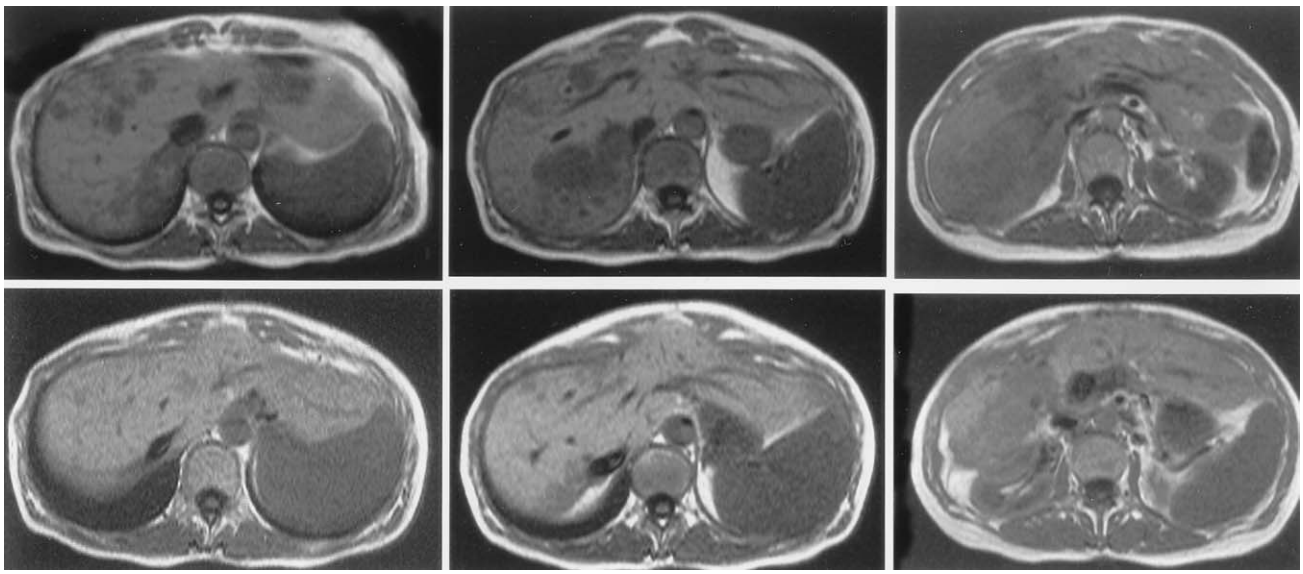

Fig. 2. Pre- and post-treatment T1-weighted MRI from a patient with unresectable HCC. The patient received a 60-minute IHP. This patient achieved a partial response to therapy for 8 1/2 months. *Top three panels* are images at different levels of the liver before treatment. *Bottom three panels* demonstrate comparable areas of the liver 7 months after treatment. Note the decrease in the overall size of the liver after treatment as well as the measurable lesions.

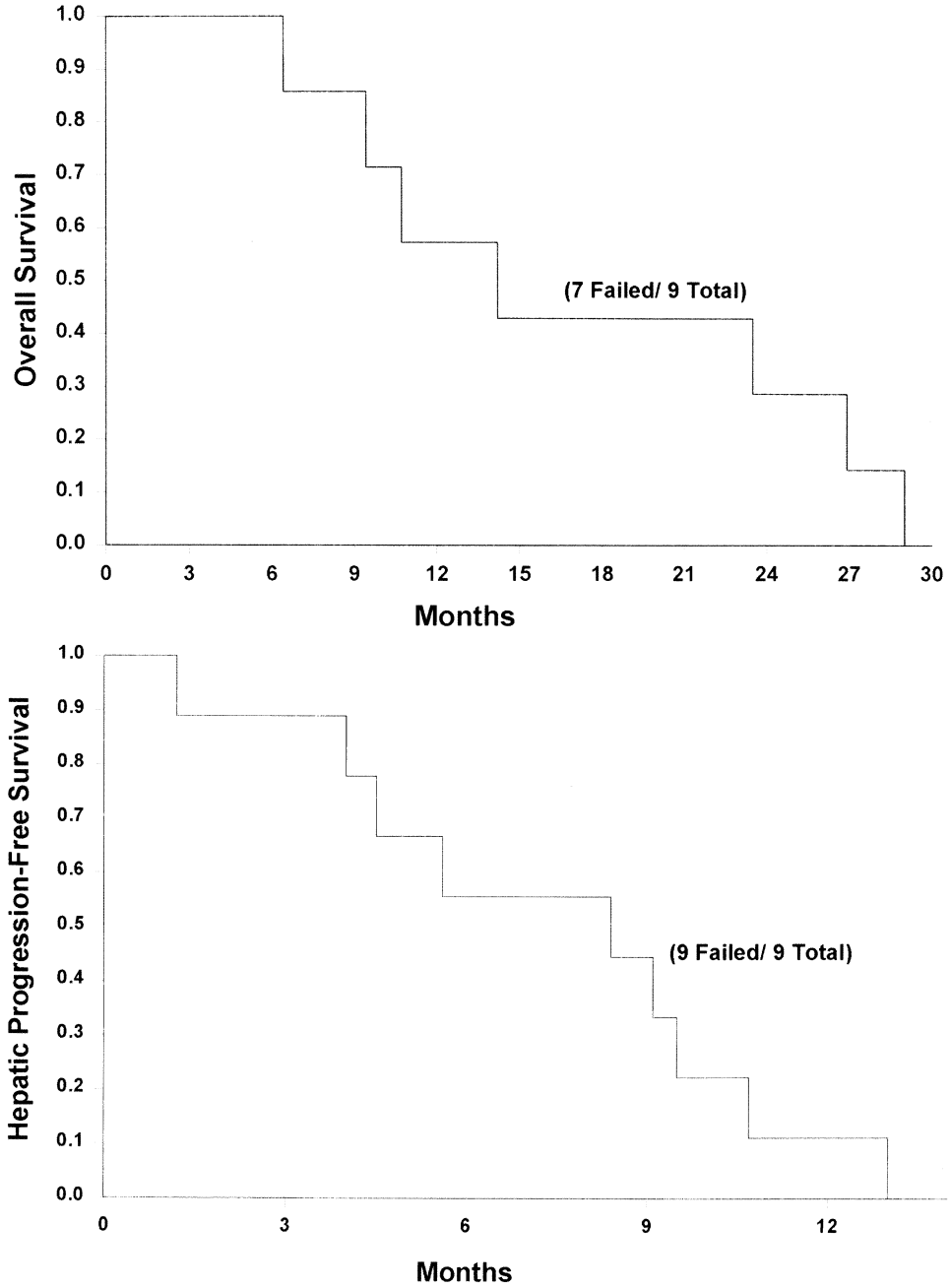

Fig. 3. Kaplan-Meier survival curves for overall survival and hepatic progression–free survival after treatment with melphalan with or without TNF. Two patients were censored from the overall survival curve because of loss to follow-up. All 9 patients were included in the hepatic progression–free survival curve. Median hepatic progression–free survival is 8 months, and median overall survival is 13 months.

tumor after a 60-minute perfusion with melphalan with or without TNF.

The hepatic toxicities (hyperbilirubinemia and transaminitis) experienced by the majority of patients were self-limited and completely reversible typically within 7 days. These did not prolong hospitalization or result in significant clinical morbidity.

IHP is under clinical investigation at a limited number of institutions worldwide, but has not gained widespread clinical application because of its technical complexity and potential morbidity.[26,27] With respect to possible toxicity associated with the treatment, the use of a standardized operative technique results in consistent and complete vascular

isolation of the liver.[28,29] The advantage of complete separation of hepatic and systemic vasculature is that it allows for higher doses of therapeutic agents. In fact, the limitation to dose escalation of melphalan in IHP relates to the intolerance of normal hepatic parenchyma to higher concentrations of the drug. In addition, IHP uses hyperthermia, which has known synergistic tumoricidal effects with chemotherapy[30,31] and biological agents, such as TNF, in experimental models.[32] Various centers have gained experience with isolated limb perfusion using TNF and melphalan for unresectable sarcoma or in transit melanoma of an extremity demonstrating a complete obliteration of tumor neovasculature within days of treatment.[33,34] The efficacy of TNF with melphalan administered via isolated limb perfusion vs. the use of melphalan alone for achieving regression of advanced or bulky lesions has not been established in prospective randomized trials.

The major limitation of IHP is that, by virtue of its regional nature, no microscopic metastatic systemic disease is treated, so patients are at risk for developing lesions at distant sites. It is controversial whether regional control will influence overall survival despite the fact that the primary tumor is hepatic in origin. Systemic failure may prevent regional therapy from ever having a significant impact on overall survival. However, in patients with extensive hepatic replacement and no radiographic evidence of disease outside the liver, it seems reasonable that a treatment resulting in substantial reduction in tumor burden in the liver may prolong survival. Indeed, in 8 of 9 patients hepatic tumor burden was an important ($n = 2$), if not the only ($n = 6$), site of disease at death. Therefore further study of the use of IHP in patients with primary hepatic malignancies is warranted.

CONCLUSION

We demonstrated that IHP with melphalan, with or without TNF, can be performed safely in patients with unresectable advanced lesions of hepatocellular or hepatobiliary origin and may result in meaningful regression of tumor burden.

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REFERENCES

1. Bosch FX, Ribes J, Borras J. Epidemiology of primary liver cancer. Semin Liver Dis 1999;19:271–825.
2. Poon RT, Fan ST, Lo CM, et al. Improving survival results after resection of hepatocellular carcinoma: A prospective study of 377 patients over 10 years. Ann Surg 2001;234:63–70.
3. Lee NW, Wong J, Ong GB. The surgical management of primary carcinoma of the liver. World J Surg 1982;6:66–75.
4. Levinsky NG. Organ donation by unrelated donors. N Engl J Med 2000;343:430–432.
5. Okada S. Chemotherapy for Hepatocellular Carcinoma. In Okuda K, Tabor E, eds. Liver Cancer. New York: Churchill Livingstone; 1997, p 8.
6. Leung TW, Patt YZ, Lau WY, et al. Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. Clin Cancer Res 1999;5:1676–1681.
7. Leung TW, Tang AM, Zee B, et al. Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. Cancer 2002;94:421–427.
8. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164–1171.
9. Pelletier G, Roche A, Ink O, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 1990;11:181–184.
10. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 1995;332:1256–1261.
11. Camma C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: Meta-analysis of randomized controlled trials. Radiology 2002;224:47–54.
12. Livraghi T. Role of percutaneous ethanol injection in the treatment of hepatocellular carcinoma. Dig Dis 2001;19: 292–300.
13. Seidenfeld J, Korn A, Aronson N. Radiofrequency ablation of unresectable primary liver cancer. J Am Coll Surg 2002; 194:813–828.
14. Ausman RK. Development of a technic for isolated perfusion of the liver. N Y State J Med 1961;61:3393–3397.
15. Alexander HR, Bartlett DL, Libutti SK. Isolated hepatic perfusion: A potentially effective treatment for patients with metastatic or primary cancers confined to the liver. Cancer J Sci Am 1998;4:2–11.
16. Alexander HR, Bartlett DL, Libutti SK, et al. Isolated hepatic perfusion with tumor necrosis factor and melphalan for unresectable cancers confined to the liver. J Clin Oncol 1998; 16:1479–1489.
17. Oldhafer KJ, Lang H, Frerker M, et al. First experience and technical aspects of isolated liver perfusion for extensive liver metastasis. Surgery 1998;123:622–631.
18. Hafström LR, Holmberg SB, Naredi PLJ, et al. Isolated hyperthermic liver perfusion with chemotherapy for liver malignancy. Surg Oncol 1994;3:103–108.
19. Alexander HR, Libutti SK, Bartlett DL, et al. A phase I-II study of isolated hepatic perfusion using melphalan with or without tumor necrosis factor for patients with ocular melanoma metastatic to liver. Clin Cancer Res 2000;6:3062–3070.
20. Barker WC, Andrich MP, Alexander HR, Fraker DL. Continuous intraoperative external monitoring of perfusate leak using I-131 human serum albumin during isolated perfusion of the liver and limbs. Eur J Nucl Med 1995;22:1242–1248.
21. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745–750.
22. Alexander HR, Bartlett DL, Fraker DL, Libutti SK. Regional treatment strategies for unresectable primary or metastatic cancer confined to the liver. In DeVita VT Jr, Hellman S,

Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. 4th ed. Philadelphia: JB Lippincott, 1996, pp 1–19.
23. Alexander HR, Bartlett DL, Libutti SK. Current status of isolated hepatic perfusion with or without tumor necrosis factor for the treatment of unresectable cancers confined to liver. Oncologist 2000;5:416–424.
24. Bartlett DL, Libutti SK, Figg WD, Fraker DL, Alexander HR. Isolated hepatic perfusion for unresectable hepatic metastases from colorectal cancer. Surgery 2001;129:176–187.
25. Libutti SK, Bartlett DL, Fraker DL, Alexander HR. Technique and results of hyperthermic isolated hepatic perfusion with tumor necrosis factor and melphalan for the treatment of unresectable hepatic malignancies. J Am Coll Surg 2000; 191:519–530.
26. Carroll NM, Alexander HR Jr. Isolation perfusion of the liver. Cancer J 2002;8:181–193.
27. Weinreich DM, Alexander HR. Transarterial perfusion of liver metastases. Semin Oncol 2002;29:136–144.
28. Hoekstra HJ, Naujocks T, Schraffordt-Koops H, et al. Continuous leaking monitoring during hyperthermic isolated regional perfusion of the lower limb: Techniques and results. Reg Cancer Treat 1992;4:301–304.
29. Klaase JM, Kroon BBR, van Geel AN, Eggermont AMM, Franklin HR. Systemic leakage during isolated limb perfusion for melanoma. Br J Surg 1993;80:1124–1126.
30. Kitamura K, Kuwano H, Matsuda H, Toh Y, Masuda H, Sugimachi K. Synergistic effects of intratumor administration of cis-diamminedichloroplatinum(II) combined with local hyperthermia in melanoma bearing mice. J Surg Oncol 1992; 51:188–194.
31. Miller RC, Richards M, Baird C, Martin S, Hall EJ. Interaction of hyperthermia and chemotherapy agents; cell lethality and oncogenic potential. Int J Hyperthermia 1994;10:89–99.
32. Klostergaard J, Leroux E, Siddik ZH, Khodadadian M, Tomasovic SP. Enhanced sensitivity of human colon tumor cell lines in vitro in response to thermochemoimmunotherapy. Cancer Res 1992;52:5271–5277.
33. Eggermont AMM, Schraffhorst Koops H, Klausner JM, et al. Isolated limb perfusion with tumor necrosis factor and melphalan for limb salvage in 186 patients with locally advanced soft tissue extremity sarcomas. Ann Surg 1996;224: 756–765.
34. Olieman AFT, van Ginkel RJ, Hoekstra HJ, Mooyaart EL, Molenaar WM, Koops HS. Angiographic response of locally advanced soft-tissue sarcoma following hyperthermic isolated limb perfusion with tumor necrosis factor. Ann Surg Oncol 1997;4:64–69.

Liver Transplantation for Neuroendocrine Tumors

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Liver transplantation for the treatment of metastatic neuroendocrine tumors (NETs) is radical. Although cure is not impossible, it is improbable. The reported experience with transplantation for NETs is limited to less than 150 cases with widely varying results and few 5-year disease-free survivors. We reviewed our experience with transplantation for patients with NETs. Fourteen symptomatic patients with unresectable NET liver metastases who had failed medical management were listed for transplantation. Two patients listed for transplantation underwent prior right lobectomies. Three patients were listed but did not undergo transplantation: one was lost to follow-up, one died 14 months after listing, and one remains waiting over 4 years. Eleven patients underwent liver transplantation, three with living donor grafts. There were four men (36.4%) and seven women (63.6%) who had a mean age of 51.2 ± 6.3 years. Three patients had distal pancreatectomies and one patient had a Whipple procedure at the time of transplantation. There were six nonfunctioning tumors (54.6%), three carcinoid tumors (27.3%), and two (18.2%) Vipomas. In one patient, with fulminant hepatic failure, the NET was an incidental finding in the explant. The 1- and 5-year survival among transplanted patients is 73% and 36%, respectively, with a mean follow-up of 34 ± 40 months (range 0 to 119 months). Of the three patients surviving more than 5 years, only one was disease free. In carefully selected patients with metastatic NETs, liver transplantation may be an appropriate option. (J GASTROINTEST SURG 2004;8:208–212)

KEY WORDS: Liver, transplantation, neuroendocrine, cancer

Neuroendocrine tumors (NETs) are a diverse group of rare tumors with varying biology and natural history. NET liver metastases often progress slowly but may cause significant symptoms as a result of size and/or hormone production. Confirmation of the indolent nature of this tumor is the historical data that suggest a 30% overall 5-year survival and a median survival of 3 to 4 years for metastatic liver disease without treatment.[1–3]

Treatments for metastatic liver NETs include pharmacologic therapy (e.g., somatostatin analogues, H_2 blockers, proton pump inhibitors), ablation therapy (e.g., cryoablation, ethanol injection, radiofrequency ablation), embolization (with and without chemotherapy), surgical resection (anatomic and nonanatomic including enucleation), and, in rare cases, transplantation. Liver transplantation for metastatic disease is, at best, controversial and in most cases even contraindicated. Historically, results of transplantation for metastatic malignancies have been extremely poor.[4,5] Previously we reported on our treatment strategies for patients with metastatic neuroendocrine tumors. That report included three patients who underwent liver transplantation and are also included in this series.[6] In this article we review our experience with liver transplantation in patients with metastatic NETs.

PATIENTS AND METHODS

We reviewed our electronic database at Mount Sinai Hospital to identify all patients with NET liver metastases referred for surgical evaluation between January 1992 and December 2002. Surgical resection was recommended whenever technically and medically possible. When tumors were unresectable or patients were poor surgical candidates, medical

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therapy was optimized. Patients were listed for transplantation if they had unresectable tumors, had failed medical therapy, and had persistent, uncontrollable symptoms from tumor bulk and/or hormone production.

Standard immunosuppression consisting of cyclosporine or tacrolimus and corticosteroids was used, except in one case where an identical twin was the living donor; this case was managed without immunosuppression.

Results are reported as mean ± standard deviation.

RESULTS

Between January 1992 and December 2002, a total of 1662 patients underwent liver transplantation, and 43 patients with NET liver metastases were evaluated. Fifteen (35%) were candidates only for pharmacologic therapy. Sixteen (37%) underwent hepatic resection. Seven underwent nonanatomic resection; the others underwent left lateral segmentectomy (n = 2), left lobectomy (n = 2), right lobectomy (n = 2), or right trisegmentectomy (n = 3). Two of these patients subsequently received liver transplants. At a mean follow-up of 41 months after resection, there have been three deaths.

Fourteen patients (33%) were listed for transplant, including the two who underwent prior resection. Three of the listed patients never underwent transplantation. One died 14 months after being listed, another was lost to follow-up, and the third remains listed more than 4 years later. Eleven patients underwent transplantation (Table 1) (4 males and 7 females; mean age, 51.2 ± 6.3 years). Overall, NET liver metastases accounted for 0.7% of all transplants performed at our institution.

Five of the transplant recipients had previously undergone surgery for control of locoregional tumors (distal pancreatectomy, n = 1; right lobectomy and distal pancreatectomy, n = 1; right lobectomy and pancreaticoduodenectomy, n = 1; small bowel resection, n = 1; and left hemicolectomy, n = 1). Four other patients underwent distal pancreatectomy (n = 3) or pancreaticoduodenectomy (n = 1) at the time of transplantation. In two of these patients, unknown primary lesions were identified intraoperatively within the tail of the pancreas.

Among seven patients in whom the indication for transplantation was related to bulky tumor disease, the mean explant size was 4540 g (range 3100 to 6400 g), with a mean of 85% liver replacement by tumor (range, 50% to 95%). This includes a 65-year-old woman who presented with fulminant hepatic failure originally presumed to be cryptogenic. With the explant available for analysis, it became clear that the patient's CT scan had been of extremely poor quality. In fact, the liver was nearly completely replaced by NET.

Pathologic evaluation and immunohistochemical staining showed the NETs to be non–hormone producing lesions in six patients (55%), carcinoid tumors in three patients (27%), and Vipomas in two (18%).

The mean follow-up was 34 ± 40 months (range 0 to 119 months). Eight patients (73%) have died, including two who died intraoperatively. One had undergone prior right lobectomy and, because of technical difficulties, died as a result of uncontrolled bleeding. The other patient died as a result of refractory coagulopathy. A third patient died on postoperative day 4 from a suspected pulmonary embolism. The five other deaths were due to complications related to recurrent disease at 16, 19, 41, 76, and 79 months

Table 1. Mount Sinai experience with transplantation for patients with metastatic neuroendocrine tumors

Patient	Age (yr)	Sex	Tumor type	First-degree resection	Alive	Disease free	Survival (mo)	Comments
1	40	F	N/F	Distal pancreas*	N	N	79	
2	52	M	VIP	Distal pancreas	Y	Y	123	Prior hepatectomy
3	56	M	N/F	Distal pancreas*	N	N	41	
4	51	M	N/F	Distal pancreas*	N	N	76	
5	56	F	N/F	Whipple*	N	N	0	Pulmonary embolus on postop day 4
6	57	F	Carcinoid	Appendix	N	N	0	Intraoperative death
7	24	F	N/F	Distal pancreas*	N	N	16	Living donor
8	56	F	N/F	Not identified	N	N	19	NET unrecognized before transplant
9	59	M	VIP	Distal pancreas	N	N	0	Prior hepatectomy; intraoperative death
10	56	F	Carcinoid	Ileum	Y	N	13	Living donor
11	56	F	Carcinoid	Rectum	Y	N	11	Living donor

N/F = nonfunctioning; VIP = vasoactive intestinal peptide.
*Performed at the time of transplant.

Table 2. Published single-center experiences with transplantation for metastatic neuroendocrine tumors

Reference	Year	No. of patients	Median follow-up (mo)	1-yr survival (%)	5-yr survival (%)	Actual 5-yr disease-free survivors
Mount Sinai	2003	11	30	73	36	1
Olausson et al.[7]	2002	9	22	89	—	0
Rosenau et al.[8]	2002	19	38	89	80	3
Ringe et al.[10]	2001	5	22	80	—	0
Coppa et al.[11]	2001	9	39	100	70	—
Pascher et al.[12]	2000	4	42	100	50	1
Frilling et al.[13]	1998	4	54	50	50	0
Dousset et al.[14]	1996	9	29	33	33	0
Anthuber et al.[15]	1996	4	11	25	0	0
Alessiani et al.[9]	1995	14	—	—	—	—
Routley et al.[16]	1995	11	—	82	57	—
Arnold et al.[17]	1989	4	30	50	—	0
Makowka et al.[18]	1989	5	32	60	—	0

after transplantation. Overall patient survival at 1 and 5 years is 73% and 36%, respectively.

Of the three patients who have survived more than 5 years, only one (who has survived for 123 months) remains disease free. Interestingly, this patient underwent prior right lobectomy and required retransplantation on postoperative day 3 because of primary nonfunction. For the three recipients of live donor grafts, the 1- and 2-year survival rates are 100% and 67%, respectively.

DISCUSSION

Liver transplantation for the treatment of metastatic NETs is radical. Cure, although not impossible, is improbable. Certain patients with surgically unresectable tumors and uncontrollable symptoms, in whom all other therapies have been unsuccessful, may benefit from transplantation for palliation. Long-term disease-free survival, however, is rare. The published experience with transplantation for metastatic NETs is limited to less than 150 cases.[7–20] Critical analysis of the published single-center series, which include roughly 100 cases, is remarkable for the very low number of actual 5-year disease-free survivors[7–18] (Table 2). Multicenter series report 1- and 5-year survival rates after transplantation ranging from 58% to 68% and 36% to 47%, respectively.[19,20] Although most series report 5-year survival rates, none has a median follow-up of 5 years. Collectively there are very few reports of 5-year disease-free survivors, confirming the impression that cure by transplantation is rare (see Table 2).[7–18]

In our experience with transplantation for this unusual and controversial indication, we have learned many lessons regarding patient selection that are critical for success. Excellent imaging studies are an important component of tumor evaluation for resection. Octreotide scanning is very sensitive for detecting these tumors. Many patients with NET liver metastases have extrahepatic nodal involvement. We have not considered this a contraindication to resection or transplantation for the same reason that we consider transplantation to be a viable option—namely, the indolent nature of these tumors. Scans should be reviewed with a bias for possible resection. Particularly in patients with symptoms related to hormone production, creative liver resection employing the technique of tumor enucleation without regard for the classically desired 1 cm tumor-free margin may offer long-term benefit.[1,21]

In patients with NET liver metastases, the primary tumor may be discovered before, at the time of, or after the recognition of liver involvement; in a small minority of patients, it may not be recognized at all. Certainly the liver is a "fertile field" for these tumors, and the observation that liver metastases typically grow faster and larger than their primary progenitors is supported by experimental evidence.[22,23]

The adequacy of primary tumor control should be assessed. Ideally the primary tumor will have been identified and resected in potential transplant candidates. Often, as was the case in several of our patients, additional procedures are necessary at the time of transplantation. Patients with biologically less aggressive tumors (i.e., more indolent) probably have a better chance for long-term survival. A recent study by Rosenau *et al.*[8] suggests that survival is diminished in patients with tumor immunohistochemistry demonstrating rapid proliferation, as evidenced by a high proportion of cells staining positive for Ki 67, or

increased metastatic potential, as evidenced by regular staining for the adhesion molecule E-cadherin. Tumor differentiation and hormone production can also be evaluated. Even non–hormone producing NETs will often express a variety of measurable substances (e.g., chromogranin A, pancreostatin) that can be useful as prognostic markers, particularly after resection or transplantation.[24]

Finally, the patient's physiologic status should be adequately evaluated. Careful assessment of cardiac, pulmonary, and renal function is part of every transplant evaluation.

Overall, it is probably the generally indolent nature of NETs rather than the benefit of any particular therapy that explains the relatively long survival of patients with liver metastases, as compared to those with metastases from other sources. Nevertheless, most patients with this disease eventually develop significant symptoms and die as a result. Bearing in mind that cure by any means is ultimately unlikely, it seems reasonable to withhold the most radical treatment (i.e., liver transplantation) until it is clear that treatment options less likely to result in serious complications or death have been exhausted. The number of patients transplanted with living donor grafts in this series is too small to comment on any potential survival benefit for these patients. Living donors may, however, provide a realistic chance of transplantation for these patients, who currently receive no prioritization in the Model for End-Stage Liver Disease (MELD) allocation system,[25] and allows for optimal timing and medical management. Admittedly there are legitimate ethical concerns about live donor transplantation in general and for patients with metastatic disease in particular.

CONCLUSION

The role of liver transplantation in the treatment of patients with NET metastases may be defined as follows: For patients who are physiologically capable of withstanding the transplant process, who have slowly progressive disease, who have extensive liver involvement that, despite medical and/or invasive interventions, puts their life or well-being in imminent danger, and who have no extrahepatic disease posing such a threat, a liver transplant may provide a number of years of good-quality life when no other options remain.

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REFERENCES

1. Soreide O, Berstad T, Bakka A, Schrumpf E, Hanssen LE, Engh V, Bergan A, Flatmark A. Surgical treatment as a principle in patients with advanced abdominal carcinoid tumors. Surgery 1992;111:48–54.
2. Moertel CG. Karnofsky memorial lecture: An odyssey in the land of small tumors. J Clin Oncol 1987;5:1502–1503.
3. Thompson GB, van Heerden JA, Grant CS, Carney JA, Ilstrup DM. Islet cell carcinomas of the pancreas: A twenty year experience. Surgery 1988;104:1011–1017.
4. Pichlmayr R. Is there a place for liver grafting for malignancy? Transplant Proc 1988;20:478–482.
5. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. Surgery 1991;110:726–734.
6. Curtiss SI, Mor E, Schwartz ME, Sung MW, Hytiroglou P, Thung SN, Sheiner PA, Emre S, Miller CM. A rational approach to the use of hepatic transplantation in the treatment of metastatic neuroendocrine tumors. J Am Coll Surg 1995; 180:184–187.
7. Olausson M, Friman S, Cahlin C, Nilsson O, Jansson S, Wangberg B, Ahlman H. Indications and results of liver transplantation in patients with neuroendocrine tumours. World J Surg 2002;26:998–1004.
8. Rosenau J, Bahr MJ, von Wasielewski R, Mengel M, Schmidt HHJ, Nashan B, Lang H, Klempnauer J, Manns M, Boeker KHW. Ki67, E-cadherin, and p53 as prognostic indicators of long-term outcome after liver transplantation for metastatic neuroendocrine tumors. Transplantation 2002; 73:386–394.
9. Alessiani M, Tzakis A, Todo S, Demetris AJ, Fung JJ, Starzl TE. Assessment of five-year experience with abdominal organ cluster transplantation. J Am Coll Surg 1995;180:88–89.
10. Ringe B, Lorf T, Dopkens K, Canelo R. Treatment of hepatic metastases from gastroenteropancreatic neuroendocrine tumors: Role of liver transplantation. World J Surg 2001;25:697–699.
11. Coppa J, Pulvirenti A, Schiavo M, Romito R, Collini P, Di Bartolomeo M, Fabbri A, Regalia E, Mazzaferro V. Resection versus transplantation for liver metastases from neuroendocrine tumors. Transplant Proc 2001;33:1537–1539.
12. Pascher A, Steinmullr T, Radke C, Hosten N, Wiedenmann B, Neuhaus P, Bechstein WO. Primary and secondary hepatic manifestation of neuroendocrine tumors. Langenbecks Arch Surg 2000;385:265–270.
13. Frilling A, Rogiers X, Malago M, Liedke O, Kaun M, Broelsch CE. Liver transplantation in patients with liver metastases of neuroendocrine tumors. Transplant Proc 1998;30:3298–3300.
14. Dousset B, Saint-Marc O, Pitre J, Soubrane O, Houssin D, Chapuis Y. Metastatic endocrine tumors: Medical treatment, surgical resection, or liver transplantation. World J Surg 1996; 20:908–915.
15. Anthuber M, Jauch K-W, Briegel J, Groh J, Schildberg FW. Results of liver transplantation for gastroenteropancreatic tumor metastases. World J Surg 1996;20:73–76.
16. Routley D, Ramage JK, McPeake J, Tan KC, Williams R. Orthotopic liver transplantation in the treatment of metastatic neuroendocrine tumors of the liver. Liver Transpl Surg 1995; 1:118–121.
17. Arnold JC, O'Grady JG, Bird GL, Calne RY, Williams R. Liver transplantation for primary and secondary hepatic apudomas. Br J Surg 1989;76:248–249.
18. Makowka L, Tzakis AG, Mazzaferro V, Teperman L, Demetris AJ, Iwatsuki S, Starzl TE. Transplantation of the liver for metastatic endocrine tumors of the intestine and pancreas. Surg Gynecol Obstet 1989;168:107–111.

19. Le Truet YP, Delpero JR, Dousset B, Cherqui D, Segol P, Mantion G, Hannoun L, Benhamou G, Launois B, Boillot O, Domergue J, Bismuth H. Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. Ann Sug 1997;225:355–364.
20. Lehnert T. Liver transplantation for metastatic neuroendocrine carcinoma. Transplantation 1998;66:1307–1312.
21. Chamberlain RS, Canes D, Brown KT, Saltz L, Jamagin W, Fong Y, Blumgart LH. Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg 2000;190: 432–445.
22. Havelaar IJ, Sugarbaker PH, Vermess M, Miller DL. Rate of growth of intraabdominal metastases from colorectal cancer. Cancer 1984;54:163–171.
23. Hara Y, Ogata Y, Shirouzu K. Early tumor growth in metastatic organs influenced by the microenvironment is an important factor which provides organ specificity of colon cancer metastasis. J Exp Clin Cancer Res 2000;19:497–504.
24. Stridsberg M, Öberg K, Li Q, Engstrom U, Lundqvist G. Measurements of chromogranin A, chromogranin B (secretogranin I), chromogranin C (secretogranin II) and pancreostatin in plasma and urine from patients with carcinoid tumours and endocrine pancreatic tumours. J Endocrinol 1995;144:49–59.
25. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Themeau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470.

Laparoscopic Right Hepatectomy: Surgical Technique

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The objective of this study was to demonstrate the safety of laparoscopic right hepatectomy for benign or malignant disease. Many reports document the success of minor or segmental liver resections performed laparoscopically. Major hepatic resection has rarely been reported. This report documents our experience with 12 laparoscopic right hepatectomies. Ten patients had suspected malignancy, but all had lesions well clear of the midplane of the liver. The surgery followed three distinct phases: (1) Portal dissection during which diathermy and harmonic shears are used, clips are applied to the right hepatic duct and right hepatic artery, and a vascular stapler is used to divide the right portal vein; (2) dissection of the vena cava, which is usually done by tunneling below the liver using harmonic shears, clips, and a linear stapler to divide the right hepatic vein; and (3) parenchymal division during which harmonic shears and multiple firings of linear staplers are used to divide the liver substance. In five patients the procedure was completed totally laparoscopically, five patients had a laparoscopic-assisted procedure, and two patients had to be converted to formal open hepatectomy. Four patients required blood transfusion. There were no deaths and two cases of major morbidity—bile leakage in one and wound dehiscence in one. The average hospital stay was 8 days, but for those whose operations were completed totally laparoscopically, 4 days was the average. Two of the nine patients with documented cancer have since died—one with widespread intrahepatic hepatocellular carcinoma and another with widespread metastatic melanoma after resection of a colorectal metastasis. Seven patients with colorectal cancer are alive and disease free with follow-up of 6 to 24 months. Laparoscopic right hepatectomy is feasible in selected patients. It is technically demanding but can be safely accomplished by surgeons who have experience in advanced laparoscopic procedures and open hepatic surgery. (J GASTROINTEST SURG 2004;8:213–216)

KEY WORDS: Laparoscopy, liver resection

The increase in sophistication of laparoscopic equipment has allowed the performance of many complex intra-abdominal operations. Laparoscopic hepatectomy can offer the usual advantages of minimal access surgery.[1] Most reported series of laparoscopic liver resections have documented nonanatomic or left lateral segmentectomies with only occasional major resections.[2–5] Expertise at some centers has evolved to such an extent that even living related donor hepatectomy has been performed.[6] Right hepatectomy, although first described by Huscher et al.[7] in 1997, has not been widely reported.

This report documents our experience with the technique of laparoscopic right hepatectomy. The procedure is technically demanding but is possible in selected patients.

PATIENT SELECTION

From November 1999 to September 2002, one or the other of us attempted laparoscopic right hepatectomy in 12 patients. Eight patients were females who ranged in age from 41 to 75 years (mean 56 years). Nine patients had suspected colorectal metastases, two had focal nodular hyperplasia, and one had hepatocellular carcinoma in a noncirrhotic liver.

Case selection was based on patient and lesion characteristics. Slimmer female patients with minimal previous surgery were preferred. All lesions had to be well clear of the midplane of the liver to allow adequate surgical margins. All patients underwent CT assessment; MRI and PET scans were also available for some patients toward the end of the series.

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SURGICAL PROCEDURE

All procedures were performed under general anesthesia with the patient in the supine position and the surgeon standing on the patient's right looking at a monitor over the patient's right shoulder. Epidural anesthesia was used routinely to allow the anesthesiologist to maintain a low central venous pressure.

A pneumoperitoneum was established in all cases. Open access was performed and a pressure of 14 mm Hg was maintained. Five to six trocars were used with positioning dependent on body habitus and internal adhesions. A 12 mm port is needed in the right midclavicular line at the level of the umbilicus. This allows access of a linear stapler to divide the portal and right hepatic veins. The abdominal cavity and liver are assessed visually with a 30-degree laparoscope and with laparoscopic ultrasound. The procedure then follows three distinct phases: (1) portal dissection, (3) caval dissection, and (3) parenchymal division.

Portal Dissection. Cholangiography is performed via the cystic duct, but the gallbladder is not removed until later because it is useful in retraction. Using hook diathermy and harmonic shears (5 mm Ultracision; Ethicon, Cincinnati, OH), the right hepatic duct and artery are dissected and divided between clips. The right portal vein is carefully identified and divided with a linear stapler, and a line of demarcation along the midplane of the liver is seen. Portal clamping is not routinely used, but a doubled sling can be placed around the portal triad for extra control in case of bleeding.

Vena Caval Dissection. The right hepatic vein is exposed from above using diathermy. It is difficult to divide from this angle, and the preferred extrahepatic approach is thus from below the liver. The liver is lifted anteriorly using two 5 mm graspers to create a tunnel, and the minor hepatic veins are divided with harmonic shears or clips. There is usually no need to mobilize the lateral peritoneal attachments. Working along the vena cava, the right hepatic vein will be seen against the diaphragm. The vein is divided from below with a linear stapler (Fig. 1).

Parenchymal Division. Following the line of demarcation along the midplane of the liver, harmonic shears and linear staplers are used to divide the liver. Up to nine vascular staplers have been used, insinuating the thin arm of the device through the liver substance, firing after resistance is reached. Bleeding can occur, most commonly from branches of the middle vein. This can be controlled by a repeat firing of the stapler, or suture ligation if the vessel is within the remaining liver. A low central venous pressure is helpful, as is the ability to suture quickly laparoscopically.

After liver transection, the lateral attachments of the right liver are divided and the specimen is removed using a plastic bag retrieval device through a

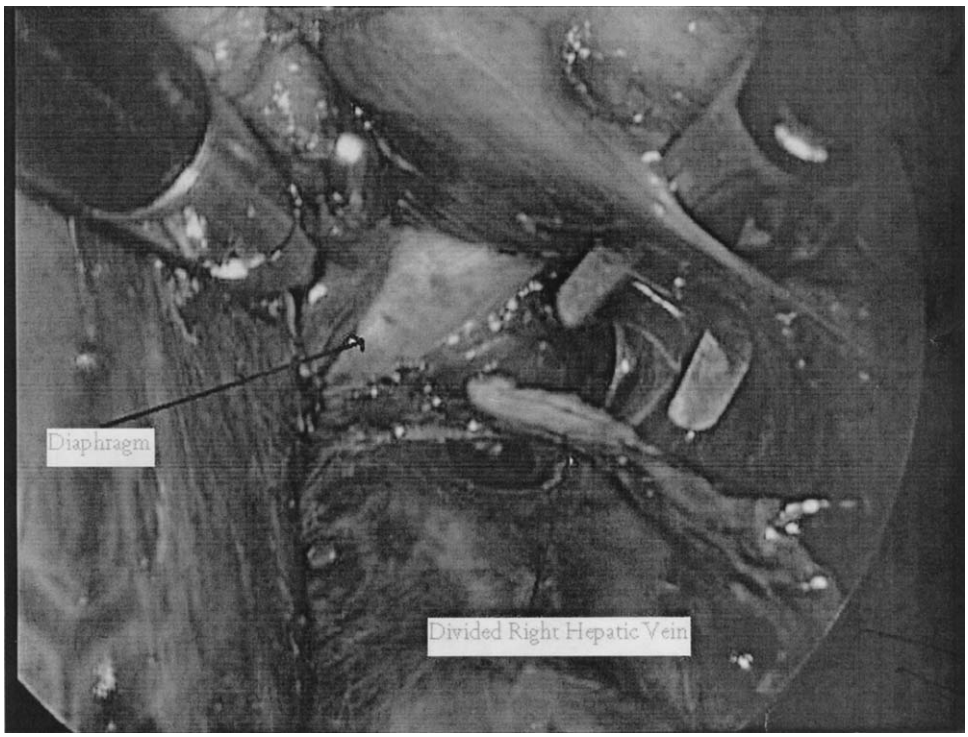

Fig. 1. Laparoscopic view of the right hepatic vein divided from beneath the liver.

wound of 5 to 6 cm, or the specimen is manipulated whole through an 8 to 10 cm wound with a plastic wound protector in place.

Hand ports were used in two cases, with placement in the right subcostal region. An assistant's hand was used to lift and retract the right lobe for parenchymal division and intrahepatic division of the right hepatic vein. This maneuver can be useful when complete caval dissection and right hepatic vein division cannot be accomplished by tunneling beneath the liver.

RESULTS

The operation was completed totally laparoscopically in five patients; in another five the operation was completed laparoscopically but assisted by a hand port or a 10 cm incision, which was needed to complete the hepatic transection; two patients were converted to an open hepatectomy. In one patient conversion was necessary because of unusual biliary anatomy; the other was the result of troublesome bleeding from minor hepatic veins. There was no catastrophic bleeding requiring rapid conversion. Four patients required blood transfusion of 1 to 4 units. Gas embolism was not seen or suspected in any of the patients. Operation times ranged from 5 to 7 hours.

None of the patients died, but major morbidity occurred in two patients. One case of bile leakage resolved spontaneously by day 8. One patient undergoing a laparoscopic-assisted procedure had wound dehiscence and right pleural effusion. The average length of hospital stay was 8 days for the whole group (range 2 to 21 days). For those undergoing a total laparoscopic procedure, the average stay was 4 days (range 2 to 7 days).

Nine patients had cancer. One had hepatocellular cancer and eight had solitary colorectal metastases. In one patient with suspected colorectal metastasis, no tumor was found on pathologic examination despite a positive PET scan. All lesions were well clear of surgical margins reflecting patient selection. The patient with hepatocellular carcinoma died at 12 months with multiple intrahepatic recurrences. One patient with colorectal cancer died of metastatic melanoma at 9 months. The remaining seven patients with colorectal cancer are alive and disease free with follow-up varying from 6 to 24 months. No port-site metastases have been seen.

DISCUSSION

We began performing laparoscopic wedge resections in the early 1990s and soon progressed to left lateral segmentectomy. This is usually a very straightforward procedure in which, after the left lateral segment is mobilized, vascular staplers are used to divide the liver along the line of the falciform ligament.

Laparoscopic right hepatectomy is a much more technically demanding and time-consuming procedure. We have shown that in selected patients it can be performed with acceptable morbidity and low mortality. The most daunting step is parenchymal division with the potential problems of major bleeding and gas embolism. The risk of bleeding from the liver substance is reduced by maintaining low central venous pressure. Inflow and outflow control of the right lobe vessels obviously also reduces bleeding. We also used vascular staplers liberally. These staplers are expensive (up to $1500 USD per case), but their effectiveness has led to increased usage in our open hepatectomy procedures, as has been reported by others.[8]

As others have shown, clinical gas embolism in laparoscopic hepatic surgery is surprisingly rare.[9,10] The high solubility of carbon dioxide may explain this. The use of staplers to close veins quickly may also prevent large volumes of CO_2 from entering a low venous pressure system.

Clinical review of wound or port-site recurrence has demonstrated no specific oncologic disadvantage to laparoscopic procedures, per se, as long as standard principles are followed.[11] Indeed, a recent randomized trial of laparoscopic vs. open surgery for bowel cancer has demonstrated better oncologic outcomes in the laparoscopic group.[12] With laparoscopic right hepatectomy there may be an advantage in that the minor hepatic veins and right hepatic vein are divided from below the liver without the usual compression of the right lobe that occurs during a standard open right hepatectomy. Liu et al.[13] have demonstrated fewer circulating tumor cells and a possible oncologic advantage when right lobe manipulation is minimized by an anterior approach at open surgery. Our technique uses even less hepatic manipulation prior to outflow division. We are currently conducting trials of routine laparoscopic caval dissection prior to open hepatectomy to minimize tumor compression.

CONCLUSION

Laparoscopic right hepatectomy is feasible and safe in highly selected patients with benign or malignant conditions. It can offer the usual benefits of laparoscopic surgery and may have an oncologic advantage. However, surgeons do need to have experience in

both advanced laparoscopic surgery and open liver surgery.

REFERENCES

1. Mala T, Edwin B, Gladhaug I, et al. A comparative study of the short-term outcome following open and laparoscopic liver resection of colorectal metastases. Surg Endosc 2002;16: 1059–1063.
2. Gigot JF, Glineur D, Azagra JS, et al. Laparoscopic liver resection for malignant liver tumors: Preliminary results of a multicenter European study. Ann Surg 2002;236:90–97.
3. Descottes B, Glineur D, Lachachi F, et al. Laparoscopic liver resection of benign liver tumours. Surg Endosc 2003;17: 23–30.
4. Farges O, Jagot P, Kirstetter P, et al. Prospective assessment of the safety and benefit of laparoscopic liver resections. J Hepatobiliary Pancreat Surg 2002;9:242–248.
5. Descottes B, Lachachi F, Sodji M, et al. Early experience with a laparoscopic approach for solid liver tumors: Initial 16 cases. Ann Surg 2000;232:641–645.
6. Cherqui D, Soubrane O, Husson E, et al. Laparoscopic living donor hepatectomy for liver transplantation in children. Lancet 2002;359:392–396.
7. Huscher CG, Lirici MM, Chiodini S, Recher A. Current position of advanced laparoscopic surgery of the liver. J R Coll Surg Edinb 1997;42:219–225.
8. DeMatteo RP, Fong Y, Jarnagin WR, Blumgart LH. Recent advances in hepatic resection. Semin Surg Oncol 2000;19: 200–207.
9. Biertho L, Waage A, Gagner M. Laparoscopic hepatectomy. Ann Chir 2002;127:164–170.
10. Cherqui D. Laparoscopic liver resection. Br J Surg 2003; 90:644–646.
11. Allardyce RA. Is the port site really at risk? Biology, mechanisms and prevention: a critical view. Aust N Z J Surg 2000;70:74–75.
12. Lacy AM, Garcia-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: A randomized trial. Lancet 2002;359:2224–2229.
13. Liu CL, Fan ST, Lo CM, et al. Anterior approach for major right hepatic resection for large hepatocellular carcinoma. Ann Surg 2000;232:25–31.

Intrahepatic Cholangiocarcinoma Masked as Fever of Unknown Origin

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Intrahepatic cholangiocarcinoma is a rare malignancy that often presents in an advanced stage. For many patients, early diagnosis is often delayed, secondary to vague symptoms and a lack of physical findings. Herein, we report an unusual case of fever of unknown origin secondary to intrahepatic cholangiocarcinoma. (J GASTROINTEST SURG 2004;8:217–219)

KEY WORDS: Fever, liver tumor, cholangiocarcinoma

Cholangiocarcinoma is a rare tumor that most commonly involves the biliary confluence. An estimated 20% to 30% of cholangiocarcinomas originate in the extrahepatic bile duct, whereas less than 10% begin at the intrahepatic level.[1] Although cholangiocarcinoma is the second most common primary hepatic tumor after hepatocellular carcinoma, the intrahepatic variant accounts for less than 10% of malignant tumors of the liver. Furthermore, the intrahepatic variant of this unusual cancer often remains asymptomatic until advanced stages. Herein we report a case of intrahepatic cholangiocarcinoma (IHC) that presented as a fever of unknown origin (FUO).

CASE REPORT

A 64-year-old white man presented for evaluation of a persistent fever that spanned 4 weeks. Medical history included an open aneurysmorrhaphy and graft placement for an infrarenal abdominal aortic aneurysm. The patient showed no signs of abdominal pain, pruritus, or jaundice. Furthermore, he denied having weight loss, change in bowel habits, or symptoms of peripheral ischemia. Physical examination revealed a diaphoretic, well-nourished male with an elevated temperature (100° F) and a well-healed laparotomy incision but was otherwise unremarkable. An extensive outpatient and in-patient diagnostic workup was initiated and included routine laboratory assays, blood and urine cultures, and serial chest roentgenography. The serum hepatic transaminase and bilirubin levels were normal; however, the alkaline phosphatase was slightly elevated. CT of the abdomen demonstrated a large hypodense lesion within Couinaud segments II and III. Based on the suspicion that the lesion was an intrahepatic abscess, CT-guided transcutaneous aspiration was performed and a surgical consultation was subsequently obtained. Pathologic findings were consistent with anaplastic carcinoma of unknown origin. A preoperative metastatic evaluation was performed and revealed a marginally elevated serum CA 19-9 level. The remainder of the workup was unremarkable and included CT of the thorax, bone scan, and upper/lower endoscopies. Because the patient was not jaundiced and did not demonstrate radiographic evidence of biliary obstruction, endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography were not performed. The patient underwent an exploratory laparotomy, left hepatectomy, and cholecystectomy without complications. The intraoperative findings included a large mass within Couinaud hepatic segments II and III, with intraoperative ultrasonography showing extension to segment IV. Tumor also extended into the falciform ligament, which was completely resected. Histopathologic examination revealed a 13 cm anaplastic IHC

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with areas of necrosis, hemorrhage, and calcification. Immunohistochemical staining showed that the tumor cells were positive for CK27 and negative for CK20, carcinoembryonic antigen, alpha fetoprotein, prostate-specific antigen, prostatic acid phosphatase, CD31, and TTF-1. The patient remained afebrile postoperatively and was discharged home on the fifth postoperative day. He was referred for adjuvant therapy because of a single microscopic focus of soft tissue involvement that was adjacent to the cauterized margin of the left triangular ligament. Unfortunately the fever returned after 3 months of adjuvant chemotherapy and external-beam radiation. A CT scan showed multiple small pulmonary nodules consistent with metastatic disease. Ironically, there was no evidence of tumor recurrence within the liver.

Table 1. The most common causes of FUO

Category	Common disorders
Infections	Tuberculosis, intra-abdominal abscess, subacute bacterial endocarditis, cytomegalovirus infection, toxoplasmosis, renal and perirenal abscesses, splenic abscess
Tumors	Lymphoma, renal cell carcinoma, hepatocellular carcinoma, leukemia, central nervous system tumors
Autoimmune disorders	Juvenile rheumatoid arthritis, temporal arteritis, polyarteritis nodosa, systemic lupus erythematosus, vasculitis
Miscellaneous	Drug fever, hepatitis, regional enteritis, hyperthyroidism, factitious fever

DISCUSSION

Fever of unknown origin can be a diagnostic dilemma. It has been categorized into the following four variants: classic, neutropenic, HIV-associated, and nosocomial. The definition of the classic variant requires that the patient's temperature exceed 38.3C for more than 3 weeks, while under investigation for 3 days, or for three outpatient visits. Also, the elevated temperature cannot be attributed to other categories with an indefinite source.[2] The diagnostic approach should include a thorough history and physical examination. Also, an extensive laboratory evaluation may be necessary to provide supplemental information that could support the clinical findings. These assays may include a complete blood count with microscopic examination, serum chemical analysis, urinalysis, cultures, serology, and various imaging studies. Despite an exhaustive evaluation, in 5% to 15% of patients the diagnosis will remain uncertain with relation to the cause attributed to the fever. Such patients usually have a benign and indolent course; however, adherence to a systematic reevaluation through close follow-up may help avoid missed etiologies.[3]

Multiple etiologies should be considered when FUO is present (Table 1). Infection, however, has historically remained the most common cause of FUO and accounts for approximately 20% to 40% of cases. In contrast, neoplastic lesions (5% to 20%), collagen vascular disorders (15% to 20%), and other rare illnesses have been implicated less frequently.[2–6] Hepatobiliary disorders may account for up to 30% of the causes related to a diagnosis of FUO.[7] Of these, infectious or inflammatory processes (hepatitis, cholangitis, or cholecystitis) and neoplastic disorders (primary or secondary) are the more common etiologies. In particular, solid tumors of the liver have the potential to cause fever secondary to mechanical and chemical processes. Several theories have subsequently been purported to be potential tumor-related causes of FUO, which may include the direct neoplastic process, presence of obstruction and subsequent infection, production of endogenous pyrogens, and the associated inflammatory process secondary to necrosis.[3]

The relationship between FUO and IHC is unknown. Perhaps this is related to the infrequent occurrence of the tumor, which may develop in approximately 1000 to 2000 patients in the United States per year.[8] Most patients are over 65 years of age and have known risk factors, such as primary sclerosing cholangitis, Caroli's disease, or hepatocholedocholithiasis. Other risk factors include infestation of the biliary system with parasitic organisms such as *Clonorchis sinensis* or *Opisthorchis viverrini*.[9] Some patients may remain asymptomatic in the early stages of tumor progression; however, most present with advanced disease. The most common symptoms are epigastric or right upper quadrant pain and weight loss. Unlike tumors of the extrahepatic bile duct, however, jaundice is uncommon and may occur in only 24% of cases.[9] When IHC is suspected based on clinical findings and appropriate imaging studies, serum tumor assays should be performed. These assays include serum carcinoembryonic antigen and CA 19-9 levels. Some investigators have also suggested the relevance of the K-ras mutation, which has been detected in 70% of patients with IHC.[9] In addition to solidifying the diagnosis, these tumor markers can be helpful in assessing the response to treatment or the development of recurrence. Finally, the diagnosis of IHC should be considered in all patients with a presumed metastatic liver lesion and unknown primary neoplasm. Ironically the patient

described in the present report did not have any associated risk factors; his only symptom was fever of unknown origin.

Most cases of IHC can be pathologically defined as adenocarcinomas. Some investigators have defined IHC as a tumor that originates distal to the secondary branches of the main hepatic duct.[10] Most Western classification systems, however, differentiate between intrahepatic and extrahepatic tumors, and the latter group is divided into proximal, middle, and distal subgroups. Although a specific staging system does not exist for IHC,[9] advanced lesions intuitively portend a less favorable outcome. Additional features, such as the longitudinal spread of tumor along the duct wall or invasion of the periductal tissues, have been implicated as potential measures of outcome.[9] Recently the Liver Cancer Study Group of Japan divided IHC into three types, which included the mass-forming type, the periductal-infiltrating type, and the intraductal growth type.[11] The study also suggested that the mass-forming type more frequently invades other organs and has a tendency to attain a larger mass size. Also, there were more frequent intrahepatic metastases around main lesions in the mass-forming type, suggesting that a wider margin is required during the resection. The periductal-infiltrating type was found to have more frequent metastases within the hilar lymph nodes and along Glisson's capsule, therefore implicating the need for a liver resection, extrahepatic biliary duct resection, and lymph node dissection. Last, because the intraductal growth type was rarely found to have nodal metastases, the prognosis was favorable after a complete resection. The patient in the present report had anaplastic IHC that would most suitably be classified as a mass-forming type.

Several recent studies have suggested that hepatic resection with clear margins confers the best long-term survival.[12–16] For example, Weimann et al.[17] have reported overall 1-year, 2-year, and 5-year survival rates of 47%, 28%, and 13%, respectively. Because the tumor is usually advanced at the time of diagnosis, however, a curative resection is not always possible. Such patients may benefit from biliary decompression and palliative care. Unfortunately, adjuvant, neoadjuvant, or palliative chemotherapy and/or radiation therapy have not been shown to definitively prolong survival.[18] Perhaps the future development of innovative diagnostic modalities, continually improved operative therapies, and improved adjuvant treatment options may eradicate this potentially fatal disease.

REFERENCES

1. Nakeeb A, Pitt H, Sohn T, et al. Cholangiocarcinoma: A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463–473.
2. Petersdorf RG, Beeson PB. Fever of unexplained origin: Report on 100 cases. Medicine 1961;40:1–30.
3. Gelfand JA, Wolff SM. Fever of unknown origin. In Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 4th ed. New York: Churchill Livingstone, 1995, pp 536–549.
4. De Kleijn EM, Vanderbroucke JP, Vander Meer JW. Fever of unknown origin (FUO). A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. Medicine 1997;76:392–400.
5. Knockaert DC, Vanneste LJ, Vanneste SB, Bobbaers HJ. Fever of unknown origin in the 1980's. An update of the diagnostic spectrum. Arch Intern Med 1992;152:51–55.
6. Handa R, Singh S, Singh N, Wali JP. Fever of unknown origin: A prospective study. Trop Doct 1996;26:169–170.
7. Salama HM, Abdel-Wahab MF, Farid Z. Hepatobiliary disorders presenting as fever of unknown origin in Cairo, Egypt: The role of diagnostic ultrasonography. J Trop Med Hyg 1988;91:147–149.
8. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer Statistics, 2003. CA Cancer J Clin 2003;53:5–26.
9. Talbot S, Neugut AL. Cancer of the gallbladder and biliary tree. In Kelsen DP, Daly JM, Kern SE, Levin B, Tepper JE, eds. Gastrointestinal Oncology, Principles and Practice, 1st ed. Philadelphia: Lippincott–Williams & Wilkins, 2002, pp 603–613.
10. Terada T, Nakanuma Y. Pathological observations of intrahepatic peribiliary glands in 1,000 consecutive autopsy livers: II. A possible source of cholangiocarcinoma. Hepatology 1990;12:92–97.
11. The Liver Cancer Study Group of Japan. Intrahepatic cholangiocarcinoma. In Classification of Primary Liver Cancer, 1st English edition. Tokyo: Kanehara, 1997, pp 6–7.
12. Pichlmayr R, Lamesch P, Weimann A, et al. Surgical treatment of cholangiocellular carcinoma. World J Surg 1995;19:83–88.
13. Berdah SV, Delpero JR, Garcia S, et al. A Western surgical experience of peripheral cholangiocarcinoma. Br J Surg 1996;83:1517–1521.
14. Pavilla FA, Marsh JW, Iwatsuki S, et al. Hepatic resection and transplantation for peripheral cholangiocarcinoma. J Am Coll Surg 1997;185:429–436.
15. Cherqui D, Tantawi B, Alon R, et al. Intrahepatic cholangiocarcinoma: Results of aggressive surgical management. Arch Surg 1995;130:1073–1078.
16. Aser MJ, Barry MK, Rowland C, et al. Surgical management of intrahepatic cholangiocarcinoma: A 31-year experience. J Hepatobiliary Pancreatic Surg 1998;5:41–47.
17. Weimann A, Varnholt H, Schlitt HJ, et al. Retrospective analysis of prognostic factors after liver resection and transplantation for cholangiocellular carcinoma. Br J Surg 2000;87:1182–1187.
18. Pitt H, Nakeeb A, Abrams R, et al. Perihilar cholangiocarcinoma: Postoperative radiotherapy does not improve survival. Ann Surg 1995;221:788–797.

A Duodenum-Preserving and Bile Duct–Preserving Total Pancreatic Head Resection With Associated Pancreatic Duct-to-Duct Anastomosis

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A duodenum-preserving pancreatic head resection technique was first reported in 1980, but the indications have been limited to benign pancreatic disease as it involves a subtotal pancreatic head resection. In 1988 we detailed a duodenum-preserving total pancreatic head resection (DPTPHR) technique. This procedure involved a total pancreatic head resection and as such expanded the indications for this approach to include tumorigenic masses. The original method involved closure of the proximal pancreatic duct and an anastomosis of the pancreatic duct of the distal pancreas to a newly created small hole in the duodenum (we termed this a "pancreatoduodenostomy"). Our current technique involves a duct-to-duct anastomosis of the proximal pancreatic duct and the distal pancreas to better preserve anatomic structure. DPTPHR was performed in 26 patients from 1988 to 2002, including 12 cases of DPTPHR with pancreatoduodenostomy and 14 cases of DPTPHR with pancreatic duct-to-duct anastomosis. No differences were observed between the two methods with respect to operative time or blood loss during surgery. Postoperatively, there was one case of cholecystitis and one case of pancreatitis in a patient who underwent a pancreatoduodenostomy; both of these patients were treated conservatively with curative intent. No complications were observed in the group undergoing duct-to-duct anastomosis. The advantage of duct-to-duct anastomosis is that the pancreatic head is totally resected, thus allowing removal of neoplastic disease such as an intraductal papillary mucinous tumor and also therapy for chronic pancreatitis. A key benefit of this procedure is that sphincter function of the duodenal papilla is preserved permitting drainage of pancreatic/bile juice into the duodenum, preserving a more physiologic state than is the case after a pancreatoduodenostomy. (J GASTROINTEST SURG 2004;8:220–224)

KEY WORDS: Duodenum-preserving total pancreatic head resection, DPTPHR, chronic pancreatitis, intraductal papillary mucinous tumor, pancreatic cancer

Duodenum-preserving pancreatic head resection was first reported by Beger et al.[1] in 1980. This operation involved a subtotal pancreatic head resection with attachment of the remaining bulk of the pancreas to the side of the duodenum to preserve the gastroduodenal artery–anterior superior pancreaticoduodenal artery arcade ensuring blood supply to the duodenum, which limited the indications to pancreatitis due to a benign process. In 1988 we devised an alternative resection method and have been using a duodenum-preserving total pancreatic head resection (DPTPHR) technique since 1990.[2] This has expanded the clinical indications to include not only benign pancreatic disease but also low-grade malignancies such as intraductal papillary mucinous tumor (IPMT).[3,4] Our earlier technique used a small hole in the duodenum to anastomose the distal pancreatic duct (DPTPHR with pancreatoduodenostomy). The technique reported herein involves a duct-to-duct anastomosis to the proximal pancreatic duct because we reasoned that sphincter function of the duodenal papilla would not be fully preserved using the DPTPHR with pancreatoduodenostomy technique.

METHODS

Patients

Twenty-six DPTPHR procedures were performed from 1988 to 2002. Patients were divided into two

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groups. The first group who underwent DPTPHR and pancreatoduodenostomy consisted of 12 patients (6 men and 6 women; average age, 59.1 years). The patients had chronic pancreatitis (n = 5), benign IPMT (n = 2), malignant IPMT (n = 2), and other pancreatobiliary diseases (n = 5). The second group who underwent DPTPHR and duct-to-duct anastomosis consisted of 14 patients (9 male, 5 female patients; average age, 55.3 years). These patients had chronic pancreatitis (n = 2), benign IPMT (n = 5) and malignant IPMT (n = 5).

Postoperative Examination

All patients were evaluated postoperatively using endoscopic retrograde cholangiopancreatography to evaluate the incidence of anastomosed pancreatic ductal stenosis and also to evaluate injected contrast material into the duodenum. Furthermore, all patients underwent a gastrointetestinal barium roentgenographic examination irrespective of reflux into the ductal system. Additionally, the incidence of postoperative pneumobilia was assessed for reflux of duodenal contents into the biliary tree.

Operative Technique

After the initial laparotomy, instead of performing the Kocher maneuver to preserve the integrity of the mesoduodenal vessels, the gastrocolic ligament is dissected, after which the right gastroepiploic artery and vein are ligated on the surface of the pancreas and then divided.

The superior mesenteric vein is exposed at the inferior border of the pancreas, and a portal vein tunneling procedure is performed. The pancreas is then transected above the portal vein, followed by hemostasis of the divided end of the distal pancreas. A polyvinyl tube is then inserted into the distal pancreatic duct and fixed with 5-0 nylon sutures.

Next the anterosuperior pancreaticoduodenal artery is double ligated and divided at the duodenal margin (Fig. 1, *left*). The posterosuperior pancreaticoduodenal artery is preserved and communicated with the posteroinferior pancreaticoduodenal artery through the superior mesenteric artery. Several supportive sutures are placed at the cut end of the pancreas, after which the head of the pancreas is dissected from the duodenum and the biliary tract as the sutures are pulled (see Fig. 1, *middle*). The pancreatic tissue between the biliary tract and the duodenum is also removed while the head of the pancreas is being pulled. Branches of the posteroinferior pancreaticoduodenal artery are ligated and divided where they enter the pancreatic parenchyma, while preserving the main arcade of posteroinferior pancreaticoduodenal artery and anterosuperior pancreaticoduodenal artery (see Fig. 1, *right*). When dissecting the pancreas from the duodenum, care should be taken to preserve the mesoduodenal blood vessels, avoiding injury to the integrity of the mesoduodenal blood vessel arcade.

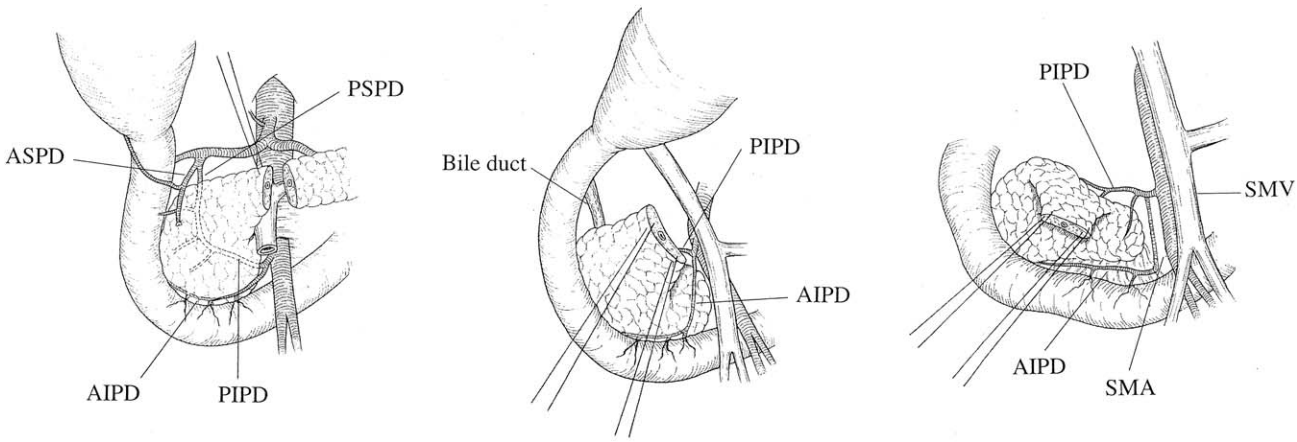

Fig. 1. Schematic representation of total removal of the pancreatic head. *Left*, Pancreatic resection is performed immediately above the portal vein. The anterosuperior pancreatoduodenal artery (*ASPD*) is excised, but the posterosuperior pancreatoduodenal artery (*PSPD*) should be preserved. While pulling the cut section of the pancreas, pull the pancreas apart from the back wall. Care must be taken not to damage the posterosuperior pancreatoduodenal artery in doing so. AIPD = anteroinferior pancreaticoduodenal artery; PIPD = posteroinferior pancreaticoduodenal artery. *Middle*, The bile duct is exposed while pulling the cut section of the pancreas and pulling the pancreas apart from the back wall. Again, care must be taken not to damage the PSPD. *Right*, While pulling the uncinate process, pull the pancreas apart from the superior mesenteric artery (*SMA*), the superior mesenteric vein (*SMV*), and the duodenum. Care must be taken not to damage the PIPD and the mesoduodenal vessels during this process.

As the pancreas is dissected from the surrounding surface of the bile duct and the confluence of the pancreatic duct and bile duct, the proximal pancreatic duct is cut with sufficient length to perform the end-to-end pancreatic anastomosis. On dissecting the pancreatic duct, the head of the pancreas is removed while preserving the biliary tract, gallbladder, duodenal papilla, and sphincter of Oddi (Fig. 2).

Reconstruction is accomplished using an end-to-end pancreatic duct-to-duct anastomosis (Fig. 3). After posterior wall fixation of the pancreas and duodenum, the proximal pancreatic duct is anastomosed to the distal duct with five or six interrupted 5-0 Vicryl sutures. This posterior fixation is very important when reapproximating the pancreatic duct with an end-to-end pancreatic duct-to-duct anastomosis, because the duodenal wall has the capacity to move and decrease tension at the anastomosis. When the tension would be too great to allow end-to-end anastomosis, we would change the method to pancreatoduodenoanastomosis (end to side), allowing the anastomosis to be performed without tension. The top of the pancreatic tube for the stent is placed in the distal pancreatic duct, and the opposite side of the tube is passed through the duodenal papilla and placed in the duodenum. Following this, anterior wall fixation of the pancreas and duodenum is performed (Fig. 4).

RESULTS

There were no significant differences between the mean operation time of 5.0 hours for the DPTPHR with pancreaticoduodenostomy group and 4.8 hours for the DPTPHR with pancreatic duct-to-duct anastomosis group, or mean blood loss (925 ml in the pancreatoduodenostomy group and 939 ml in the duct-to-duct anastomosis group). There were few postoperative complications with either procedure. Among patients who received a pancreatoduodenostomy, there was one case of cholecystitis and one case of pancreatitis, both of which were treated conservatively without serious complications. No complications were observed in the patients treated with duct-to-duct anastomosis. Postoperative endoscopic retrograde cholangiopancreatography revealed no abnormalities in the pancreatobiliary system, and there were no cases of ductal stenosis. Also, injected contrast material was smoothly discharged into the duodenum. No patient required reoperation, and there were no cases of barium regurgitation into the biliary tree and pancreatic duct during roentogenographic examination. Additionally, none of the patients developed pneumobilia.

DISCUSSION

The Whipple procedure, or pylorus-preserving pancreatoduodenostomy, has been widely used for

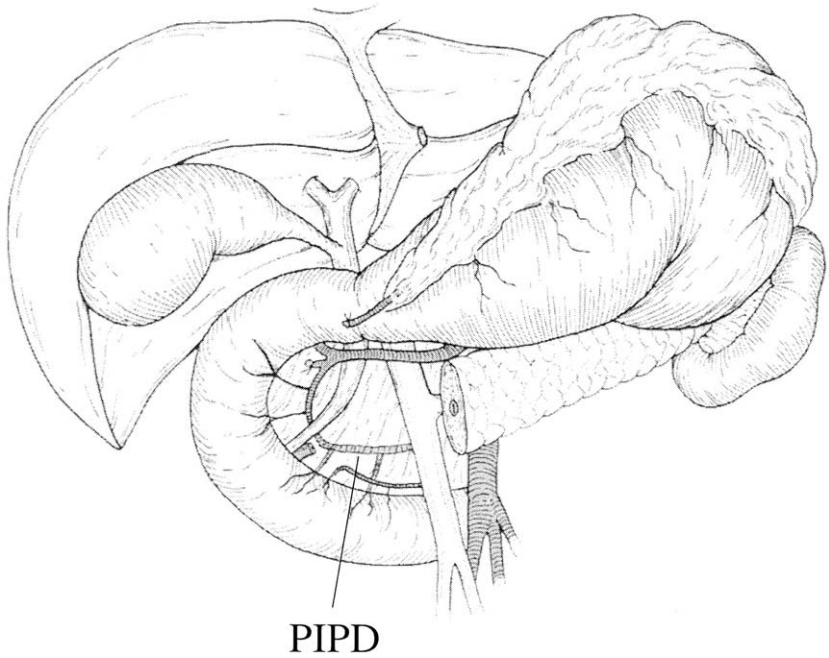

Fig. 2. Completion of total removal of the head of the pancreas while preserving digestive and biliary tracts. Total pancreatic head resection is achieved, while the sphincter function of Oddi together with the duodenum and biliary tract and the gallbladder are preserved. PIPD = posteroinferior pancreaticoduodenal artery.

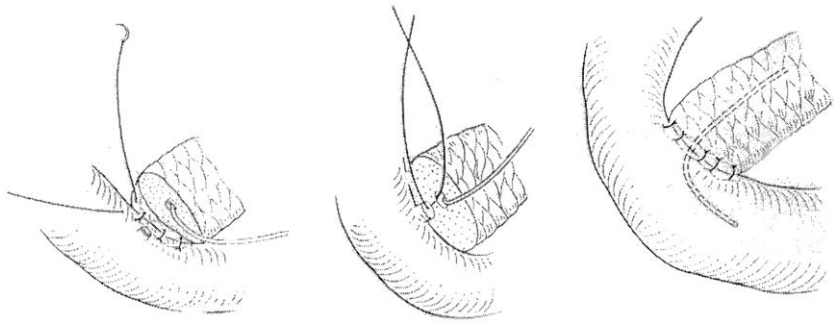

Fig. 3. Reconstruction. The pancreas and backside of the duodenum are sutured using a nodus anastomosis. The inserted stent tube remains in the distal pancreatic duct. A suture is inserted into the pancreatic duct for suture fixation and the proximal end of the tube is left inside the duodenum. The proximal pancreatic duct and the distal pancreatic duct are sutured with knotted 5-0 or 6-0 Vicryl.

resection of the head of the pancreas.[5–9] However, even with pylorus-preserving pancreatoduodenostomy, only 4 to 5 cm of the duodenum from the pyloric ring can be preserved. Beger et al.[10,11] reported duodenum-preserving pancreatic head resection for mass-producing chronic pancreatitis, which effectively eliminated pain. Despite duodenal preservation, Beger's operation involved a subtotal resection of the head of the pancreas.

If the head of the pancreas could be completely removed without leaving pancreatic tissue in the duodenum, as in Beger's operation, operative indications could be expanded to include low-grade malignant tumors such as IPMT, and also pancreatic cystic disease, pancreatic divisum, and chronic pancreatitis. A pancreaticoduodenostomy or pancreatic duct-to-duct anastomosis might be possible in these instances, resulting in preservation of gastrointestinal tract integrity. Further, if the ampulla of Vater, biliary tract, gallbladder, and the sphincter of Oddi could be preserved, then normal pancreatic, biliary, and digestive physiologic function could be maintained. Our technique leaves the gallbladder intact because we reasoned that preservation of the sphincter of Oddi would avoid regurgitation of the digestive tract contents into the biliary tree and also maintain the cooperative function of these structures. In this study no patient had reflux of duodenal contents into the biliary tree with either procedure. Although there was one case of mild cholecystitis and one case of mild pancreatitis postoperatively, the causes were unknown and both resolved with conservative treatment.

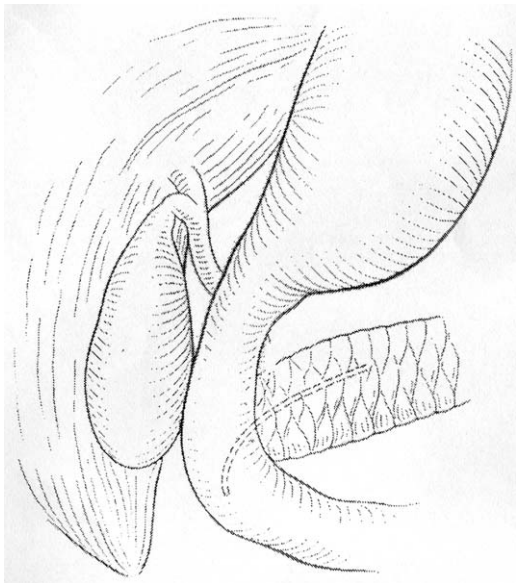

Fig. 4. Completion of duodenum-preserving total pancreatic head resection after pancreatic duct-to-duct anastomosis.

A duodenum-preserving and bile duct–preserving total pancreatic head resection is a novel technique for pancreatic surgery. The major objective of this operation is to maintain duodenal blood supply. For this purpose we found it necessary to preserve the posterosuperior pancreaticoduodenal artery and mesoduodenal vessels.[3,4] There are eight steps in this operation: (1) division of the gastroepiploic artery/vein in front of the pancreas; (2) division of the pancreas over the portal vein; (3) division of the anterosuperior pancreaticoduodenal artery along the duodenum while preserving the posterosuperior pancreaticoduodenal artery; (4) isolation of the head of the pancreas from the duodenum and bile duct; (5) division of the vessels along the excised pancreas while preserving the main arcade of the posterior pancreaticoduodenal artery; (6) division of the proximal pancreatic duct just before it merges into the confluence of the bile duct; (7) preservation of the duodenal papilla and sphincter of Oddi; and (8) end-to-end pancreatic duct anastomosis.

According to our previous studies,[12,13] when postoperative pancreatic exocrine function was compared with the various types of pancreatectomies, preservation of the entire duodenum maintained pancreatic exocrine function better than the Whippple procedure, or pylorus-preserving pancreatoduodenostomy. The advantage of our operation is the resultant preservation of duodenal papilla sphincter function allowing drainage of pancreatic/bile juice into the duodenum, which is theoretically considered a more physiologic state than Beger's operation, because bile juice flows into the duodenum but pancreatic juice discharges into the reconstructed jejunal loop in Beger's operation. A comparative study is necessary in the future among the three types of duodenum-preserving pancreatic head operations, involving a duodenum- and bile duct–preserving total pancreatic head resection with associated pancreatic duct-to-duct anastomosis, a duodenum- and bile duct–preserving total pancreatic head resection with associated pancreatoduodenostomy, and Beger's operation.

This report describes a new operative technique of duodenum- and bile duct–preserving total pancreatic head resection.

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REFERENCES

1. Beger HG, Witte C, Kraas E, Bittner R. Erfahrung mit einer das Duodenum erhaltenden Pankreaskopfresection bei chronischer Pankreatitis. Chirirug 1980;51:303–307.
2. Takada T, Yasuda H, Uchiyama K, Hasegawa H. A proposed new pancreatic classification system according to segments. J Hepatobiliary Pancreat Surg 1994;1:322–326.
3. Takada T, Yasuda H, Uchyama K, Hasegawa H. Duodenum-preserving pancreatoduodenostomy: A new technique for complete excision of the head of the pancreas with preservation of biliary and alimentary integrity. Hepatogastroenterology 1993;40:356–359.
4. Takada T, Yasuda H, Uchiyama K, Hasegawa H. Complete duodenum-preserving resection of the head of the pancreas with preservation of the biliary tract. J Hepatobiliary Pancreat 1995;2:32–37.
5. Traverso LW, Longmire WP Jr. Preservation of the pylorus in pancreaticoduodenostomy. Surg Gynecol Obstet 1978;146: 959–962.
6. Braasch JW, Rossi RL, Watkins E Jr, et al. Pylorus and gastric preservation pancreatic resection: experience with 87 patients. Ann Surg 1986;204:411–417.
7. Kamal M, Itani F, Coleman RE, et al. Pylorus-preserving pancreaticoduodenectomy: A clinical and physiologic appraisal. Ann Surg 1986;204:655–664.
8. Pearlman NW, Stiegman GV, Ahnen DJ, et al. Acid and gastric levels following pyloric-preserving pancreaticoduodenectomy. Arch Surg 1986;121:661–664.
9. Takada T, Yasuda H, Shikata J, Eatanabe S, Shiratori K, Takeuchi T. Postprandial plasma gastrin and secretin concentration after a pancreaticoduodenectomy: A comparison between a pylorus-preserving pancreaticoduodenectomy and the Whipple procedure. Ann Surg 1989;210:47–51.
10. Beger HG, Krautzbeger W, Bittner R, Buchler M, Limmer J. Duodenum-preserving resection of the head of the pancreas in patients with severe chronic pancreatitis. Surgery 1985;97: 467–473.
11. Beger HG, Buchler M, Bittner R. Duodenum-preserving resection of the head of the pancreas—an alternative to Whipple's procedure in chronic pancreatitis. Hepatogastroenterology 1990;37:283–289.
12. Toyota N. Postoperative pancreatic exocrine function in various kinds of pancreatectomies evaluated by fecal pancreatic enzyme and pancreatic function diagnostant test. J Teikyo Univ Med 1998;21:449–463 (in Japanese with English abstract).
13. Yasuda H, Takada T, Toyota N, Amano N, Yoshida M, Takada Y, Takada K, Hijikata H. Limited pancreatectomy: Significance of postoperative maintenance of pancreatic exocrine function. J Hepatobiliary Pancreat Surg 2000;7:466–472.