Postoperative Changes in Body Composition After Gastrectomy

Teruo Kiyama, M.D., Takashi Mizutani, M.D., Takeshi Okuda, M.D., Itsuro Fujita, M.D., Akira Tokunaga, M.D., Takashi Tajiri, M.D., Adrian Barbul, M.D., F.A.C.S.

Nutritional status is one of the most important clinical determinants of outcome after gastrectomy. The aim of this study was to compare changes in the body composition of patients undergoing laparoscopy-assisted gastrectomy (LAG), distal gastrectomy (DG), or total gastrectomy (TG). Total body protein and fat mass were measured by performing a multifrequency bioelectrical impedance analysis using an inBody II machine (Biospace, Tokyo, Japan) in 108 patients (72 men, 36 women) who had undergone LAG (n = 24), DG (n = 39), or TG (n = 45). Changes between the preoperative data and results obtained on postoperative day 14 and 6 months after surgery were then evaluated. The mean preoperative body weight of the subjects was 57.6 ± 10.7 kg, the mean body mass index was 22.5 ± 3.4 kg/m^2, and the mean fat % was 24% ± 7%. In the immediate postoperative period (14 days), the body weight loss in the LAG group was significantly lower than in the DG and TG groups (2.5 ± 0.9 kg vs. 3.5 ± 1.8 kg and 4.0 ± 1.9 kg, respectively; $P < 0.0001$). The body composition studies demonstrated a loss of total body protein rather than fat mass. Six months after surgery, body weight was not significantly different from preoperative values in the LAG and DG groups (−1.2 ± 3.8 kg and −1.8 ± 4.7 kg, respectively), but had decreased by 8.9 ± 4.9 kg in the TG group ($P = 0.0003$). A body composition analysis revealed a loss of fat mass in the DG and TG groups. The patients who underwent gastrectomy lost body protein mass during the early postoperative period. The type and extent of surgery has an effect on long-term body mass and composition. Bioelectric impedance analysis can be used to assess body composition and may be useful for nutritional assessment in patients who have undergone gastrectomy. (J GASTROINTEST SURG 2005;9:313–319)

KEY WORDS: Body composition, gastrectomy, bioelectrical impedance analysis

Weight loss is a common problem after gastrectomy; the main mechanisms implicated include impaired food intake and malabsorption.[1,2] Weight loss occurs principally during the first 3 months after surgery.[3] Patients who undergo a subtotal gastrectomy consume fewer calories during the first 3 months after surgery, after which their intake improves.[4] Nutritional status is one of the most important clinical determinants of outcome after gastrectomy.

The body can be divided into two or more compartments based on its anatomic, fluid, or chemical components.[5] The most commonly used body composition model is a two-component model, in which the body is divided into fat mass and lean body mass (Fig. 1). Multicomponent techniques allow the lean body mass to be broken down into as many as four components, such as extracellular water, total body water, body protein mass (muscle mass), and bone.

Presented at the Forty-Fifth Annual Meeting of The Society for Surgery of the Alimentary Tract, New Orleans, Louisiana, May 15–19, 2004 (poster presentation).

From the Department of Surgery I, Nippon Medical School (T.K., T.M., T.O., I.F., A.T., T.T.), Tokyo, Japan; and Department of Surgery, Sinai Hospital and The Johns Hopkins Medical Institutions (A.B.), Baltimore, Maryland.

A Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science supported this study.

Reprint requests: Teruo Kiyama, MD, Department of Surgery I, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. e-mail: kiyama@nms.ac.jp

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.11.008

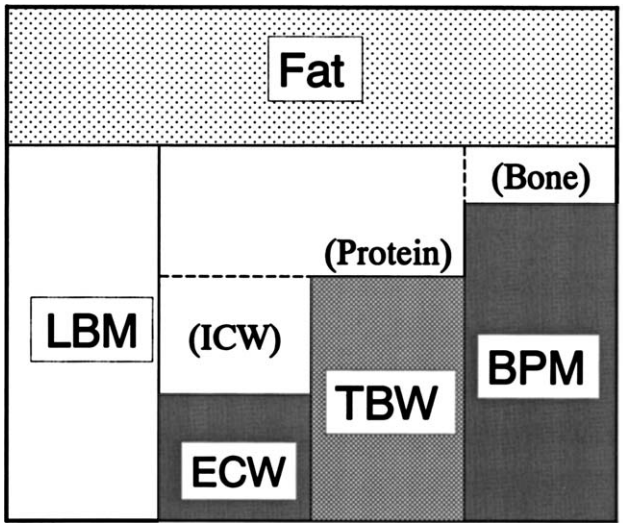

Fig. 1. Graphic representation of two-compartment and multicompartment models. According to this approach, fat is considered to be an extractable lipid and the remainder of the body weight is regarded as the lean body mass (LBM). Water is the single largest compartment, and total body water (TBW) is divided into intracellular water (ICW) and extracellular water (ECW). The lean body mass is also the sum of two fat-free components: body protein mass (BPM) and bone.

Bioelectrical impedance appears to provide a noninvasive, safe, rapid, and accurate method for evaluating body composition.[6] The method is based on the bioelectrical principle of impedance, the vector sum of resistance and reactance. Resistance is the opposition to electrical current in relation to the length and diameter of a cylinder. The human body resembles a set of serially connected cylinders (arms, trunk, and legs) with a known height and relatively constant diameter. As a result, height^2/resistance is proportional to hydrated portion of the body, such as total body water and lean body mass. By subtracting the lean body mass from the weight, the fat mass (the nonhydrated portion of the body) can be calculated.

Reactance reflects the component of impedance resulting from the presence of capacitive elements, such as the cell membrane. Multifrequency bioelectrical impedance analysis operates on the principle that the body's resistance is dependent on the frequency of the applied alternating current. Total body water is distributed between intracellular water and the extracellular water spaces, which are separated by the cell membranes. At a low frequency, the cell membranes act as capacitors, and the amount of extracellular water is predominantly measured. At a higher frequency, however, the membranes become permeable, and the total amount of body water can be measured. The ratio of extracellular water to total body water (edema index) is correlated with the ratio of the resistance at a high frequency to the resistance at a low frequency.[7] Segmental bioelectrical impedance of the arms and limbs enables the segmental body protein mass (muscle mass), as well as total body protein, to be precisely determined.[8]

Body composition is altered after surgery, and the metabolically active body mass is diminished (catabolic phase).[9] Once the patient recovers from the surgical insults, positive nitrogen balance and weight gain occur (anabolic phase). However, few body composition studies have been carried out following gastrectomy; furthermore, there is no data regarding the impact of various types of gastrectomy on body composition alterations.[10–12] The aim of this study was to compare postoperative changes in body composition in patients undergoing laparoscopic-assisted gastrectomy, distal gastrectomy, or total gastrectomy.

PATIENTS AND METHODS

The nutritional status of 108 patients with gastric cancer (72 men, 36 women) was evaluated at the Nippon Medical School Hospital between January 2002 and September 2003. Twenty-four patients underwent laparoscopy-assisted gastrectomy (LAG), 39 patients underwent distal gastrectomy (DG), and 45 patients underwent total gastrectomy (TG). LAG was indicated for the resection of T1 (mucosa or submucosa) N0 tumors and included partial gastrectomies (n = 2), segmental gastrectomies (n = 8), and distal gastrectomies (n = 14). DG with gastroduodenal or gastrojejunal anastomosis was performed for cancers located in the distal or middle third regions of the stomach. TG was carried out for lesions larger than 3 cm in diameter located in the proximal or middle third of the stomach; Roux-en-Y antecolic reconstruction was performed using a 40 to 50 cm jejunal limb. The degree of lymph node dissection varied from D0 to D2 in the surgery for stage IA and IB tumors; D2 nodal dissection was used routinely for stage II or higher stages.[13,14]

Patients were managed postoperatively according to an established clinical pathway. This included provision of drinking water (500 ml/day) on the fourth postoperative day. Food ingestion progressed every 2 days in four steps from liquid meals to solids starting on the fifth postoperative day to achieve a targeted energy intake of 1450 kcal. Hospital discharge was routinely planned for the 14th postoperative day, although earlier discharge was permitted if more than 1000 kcal/day intake had been achieved.

Body protein mass, fat mass, and the ratio of extracellular water to total body water (edema index) were

measured using a segmental multifrequency bioelectrical impedance analysis performed with an inBody II machine (Biospace, Tokyo, Japan), which was developed by Cha et al. to determine the physical fitness and body shape of healthy people.[8] Patients stood upright, stepping on the foot electrodes and loosely gripping the hand electrodes, with their arms held vertically. In this manner, the eight tactile electrodes were placed in contact with the thumb and palm of each hand and the front and rear soles of each foot. The microprocessor-controlled switches and impedance analyzer were started to measure the segmental resistances of the arms, trunk, and legs without accounting for fluid redistribution. Alternating currents with a magnitude of 100 μA and frequencies of 5 to 500 kHz were used. The height and weight of each patient was measured using electric scales. The body mass index (BMI) was calculated as body weight/height^2 (kg/m^2), and the degree of obesity was calculated as body weight/ideal body weight (%). All assessments were obtained preoperatively, on the 14th postoperative day (before hospital discharge), and at 6 to 12 months after surgery in the outpatient clinic.

All data are expressed as mean ± SD. Statistical analysis employed a paired Student's *t* test for each of the patients and one-factor ANOVA with a post hoc test for the operative procedures using StatView software (SAS Institute, Cary, NC). A *P* value of <0.05 was considered to be statistically significant.

RESULTS

The clinical characteristics of the patients in each of the three study groups were comparable, although the patients allocated to the LAG group were significantly older than those in the other groups (Table 1). Coexisting diseases were present in 30% of the patients. There was no in-hospital mortality and all patients were available for follow-up examination at 6 to 12 months. Postoperative complications occurred in seven cases (6.5%): two cases of pneumonia, two wound infections, two anastomotic strictures, and one heart failure. The length of hospital stay was longest in the TG group (19.9 ± 8.5 days); the LAG and DG groups hospital stays were 13.7 ± 1.9 and 16.7 ± 5.5 days, respectively. Distribution of cases by cancer stage is shown in Table 2. The LAG group consisted of patients with only stage IA or IB tumors.

The preoperative nutritional evaluations indicated that body size and degree of obesity were similar in all groups (Table 3). The mean preoperative body weight of all subjects was 57.6 ± 10.7 kg, the mean BMI was 22.5 ± 3.4 kg/m^2, and the mean fat % was 24% ± 7%. The mean degree of obesity was 109% ± 17 %.

Table 1. Clinical status

	LAG (n = 24)	DG (n = 39)	TG (n = 45)
Age (y)	72.0 ± 6.8*	64.3 ± 9.4	63.3 ± 12.3
Male (no.)	15	25	32
Length of hospital stay (days)	13.7 ± 1.9	16.7 ± 5.5	19.9 ± 8.5†
Coexisting disease			
DM	1	6	11
Ischemic heart disease	2	3	1
CHF	1	1	1
COPD	1	0	3
Comorbid disease			
Pneumonia		1	1
Wound infection			2
Anastomotic stricture	1		1
Heart failure			1

LAG = laparoscopy-assisted gastrectomy; DG = distal gastrectomy; TG = total gastrectomy; DM = diabetes mellitus; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease.
*$P = 0.005$ vs. DG; $P = 0.001$ vs. TG.
†$P = 0.0003$ vs. LAG; $P = 0.025$ vs. DG.

In the immediate postoperative period (14 days), body weight loss was significantly lower in the LAG group compared to the DG and TG groups (2.5 ± 0.9 kg vs. 3.5 ± 1.8 kg and 4.0 ± 1.9 kg, respectively; $P < 0.05$) (Fig. 2). Body composition analysis revealed a loss of body protein mass rather than fat mass in all groups. Body protein or fat loss did not differ among the groups, although the changes in fat loss ranged from 0.6 ± 1.0 kg in the LAG group to 1.5 ± 2.7 kg in the TG group. The mean BMI had decreased in all three groups on the 14th postoperative day (Table 4). The ratio of extracellular water to total body water (edema index) was similar in the LAG and DG groups, but was higher in the TG group on the 14th postoperative day (Table 5).

Table 2. Clinical stages of gastric cancers*

	LAG (n = 24)	DG (n = 39)	TG (n = 45)
IA	21	20	5
IB	3	8	6
II	0	3	9
IIIA	0	1	6
IIIB	0	3	11
IV	0	4	8

LAG = laparoscopy-assisted gastrectomy; DG = distal gastrectomy; TG = total gastrectomy.
*According to Japanese Classification of Gastric Carcinoma.[11]

Table 3. Preoperative nutritional assessment

	LAG (n = 24)	DG (n = 39)	TG (n = 45)
Body weight (kg)	54.4 ± 9.1	57.2 ± 11.3	59.6 ± 10.1
Degree of obesity (%)	106 ± 19	108 ± 16	112 ± 17
Body protein (kg)	38.6 ± 7.3	40.8 ± 8.0	42.6 ± 8.3
Fat (kg)	13.5 ± 5.2	13.9 ± 5.5	14.5 ± 5.8
BMI (kg/m^2)	21.8 ± 3.5	22.3 ± 3.2	23.2 ± 3.4

LAG = laparoscopy-assisted gastrectomy; DG = distal gastrectomy; TG = total gastrectomy; BMI = body mass index.

Table 4. Postoperative changes in body mass index

	LAG (n = 24)	DG (n = 39)	TG (n = 45)
14 d	−0.8 ± 0.7*	−1.0 ± 0.7*	−1.4 ± 1.0*
6 mo	−0.3 ± 1.4	−0.3 ± 1.8	−3.4 ± 2.4†

LAG = laparoscopy-assisted gastrectomy; DG = distal gastrectomy; TG = total gastrectomy.
*$P < 0.0001$.
†$P = 0.0072$.

At 6 months after surgery, mean body weight had returned to its preoperative values in the LAG and DG groups (−1.2 ± 3.8 kg and −1.8 ± 4.7 kg, respectively) (Fig. 3), but had decreased by 8.9 ± 4.9 kg in the TG group ($P = 0.0003$). A body composition analysis revealed that the mean fat mass had decreased in the DG group (−1.5 ± 2.9 kg), but both the mean body protein and the mean fat mass had decreased in the TG group (−3.6 ± 1.8 kg and −5.2 ± 4.2 kg, respectively). The mean BMI was similar to the preoperative value in the LAG and DG groups, but had decreased in the TG group (Table 4). The ratio of extracellular water to total body water (edema index) 6 months after surgery was similar to the preoperative value in the LAG group, but had increased in the DG and TG groups (Table 5).

From the 14th postoperative day to 6 to 12 months after surgery, a gain in the mean body protein mass was observed in the LAG and DG groups (1.1 ± 1.1 kg and 1.3 ± 1.5 kg, respectively) (Fig. 4). In the TG group, no difference in the mean body protein mass was observed between those two time periods, but the mean body weight and mean fat mass had decreased (−4.1 ± 3.4 kg and −3.5 ± 3.2 kg, respectively). The edema index increased in the TG group only after the patients were discharged.

DISCUSSION

This study investigated changes in the body composition of patients undergoing laparoscopy-assisted gastrectomy, distal gastrectomy, or total gastrectomy. Body weight, body protein, and fat mass decreased during the immediate postoperative period. Laparoscopy-assisted gastrectomies resulted in a smaller loss of body weight and a shorter hospital stay compared with open surgeries. Laparoscopic procedures represent a less invasive approach for the treatment of gastric cancer, similar to laparoscopic cholecystectomies.[15,16] Many organs and cells of the body use glucose, not fat, as their primary fuel.[17] Although fat is the largest deposit of energy in the body, fat cannot be effectively converted to carbohydrates in mammalian tissues. Fat is composed of fatty acid, which is used as a substrate for the synthesis of ketone bodies as fuel in the liver, and glycerol, which can be used for gluconeogenesis. Body protein constitutes the next

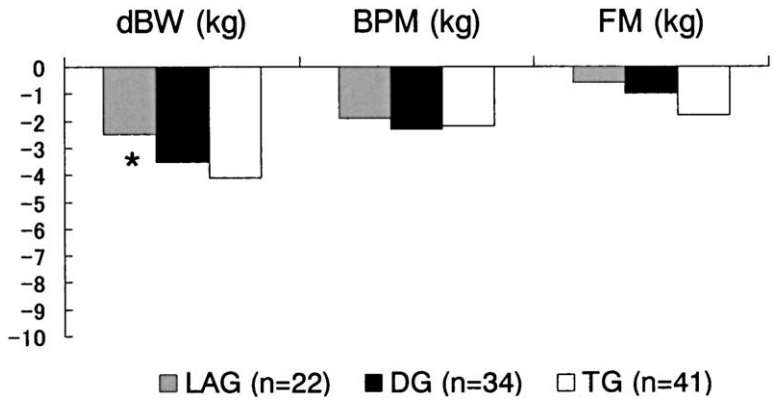

Fig. 2. Comparison of perioperative changes in the body composition of patients undergoing laparoscopy-assisted (LAG), distal (DG), and total gastrectomy (TG), from before surgery to 14th postoperative day. *$P = 0.039$ vs. DG and $P = 0.002$ vs. TG. dBW = change in body weight; BPM = body protein mass; FM = fat mass.

Table 5. Edema index

	LAG (n = 24)	DG (n = 39)	TG (n = 45)
Preoperative	0.341 ± 0.013	0.340 ± 0.016	0.336 ± 0.013 †
14 d postoperative	0.344 ± 0.011	0.342 ± 0.012 *	0.344 ± 0.014 **
6 mo postoperative	0.346 ± 0.015	0.343 ± 0.010	0.355 ± 0.014 ‡

LAG = laparoscopy-assisted gastrectomy; DG = distal gastrectomy; TG = total gastrectomy; edena index = extracellular fluid/total body water.
*P = 0.0006 vs. preoperative.
†P = 0.0001 vs. preoperative.
‡P = 0.0095 vs. 14 d postoperative.
**P = 0.0003 vs. preoperative.

largest mass of usable energy. Following surgery, proteolysis is accelerated to generate amino acids for the support of gluconeogenesis and other key synthetic processes. Therefore, endogenous protein must be broken down for conversion to glucose after surgery. This results in the simultaneous, rather than sequential, depletion of body protein and fat mass.[18]

In this study, the body weight loss that occurred during the immediate postoperative period consisted mainly of body protein loss rather than fat loss. The changes in body composition after surgery were characterized by a loss of body protein and fat mass and the expansion of the extracellular fluid compartment.[7] Although no differences in body protein or fat loss were seen among the three groups, the edema index of the TG group, but not that of the LAG or DG groups, increased during the early postoperative period. Within the confines of the multicomponent model, the body protein mass includes extracellular water as well as total body water. These findings suggest that the increase in interstitial water after a total gastrectomy may result in an underestimation of the decrease in the body protein mass during this altered state, compared with the results for patients who have undergone other surgical procedures. On the other hand, the serum albumin levels were similar among the groups before surgery and 6 months after surgery (mean value of 4.1 ± 0.5 and 4.3 ± 0.3 g/dl, respectively). Only in the immediate postoperative period were the levels of the TG group (3.6 ± 0.4 g/dl) lower than the levels of the LAG (4.0 ± 0.2 g/dl) and DG (3.9 ± 0.4 g/dl) groups.

The anabolic phase starts 3 to 6 days after an operation with a high level of insult, such as gastrectomy, and often coincides with the commencement of oral feeding.[7] In this study, the length of the hospital stay was longer in the TG group because adequate food intake was often delayed in this group. After the start of the anabolic phase, the patient enters a prolonged period of early anabolism, characterized by a positive nitrogen balance and weight gain. In the postoperative period, from the time of hospital discharge until 6 months after surgery, the patients in the LAG and DG groups regained their body protein mass, but no gain in body protein mass occurred in the TG group. The edema index of the TG group also increased, so the active body protein mass was likely diminished. Moreover, losses of body weight and fat mass were recorded in the TG group during

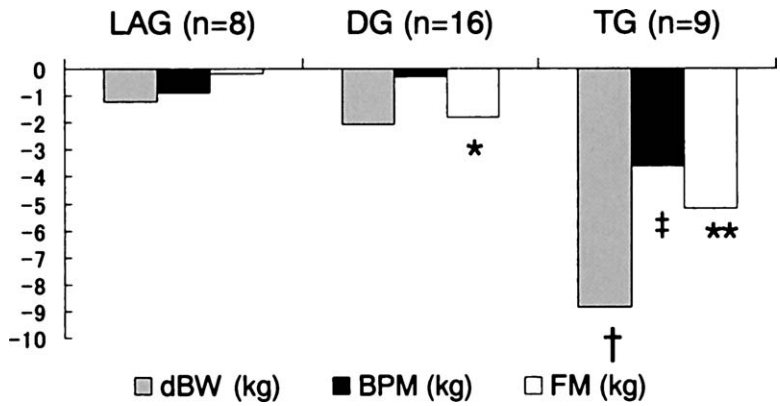

Fig. 3. Overall changes in the body composition of patients undergoing laparoscopy-assisted (LAG), distal (DG), and total gastrectomy (TG), from before surgery until 6 months after surgery. *P = 0.031, †P = 0.0003, ‡P = 0.0001, **P = 0.0038. dBW = change in body weight; BPM = body protein mass; FM = fat mass.

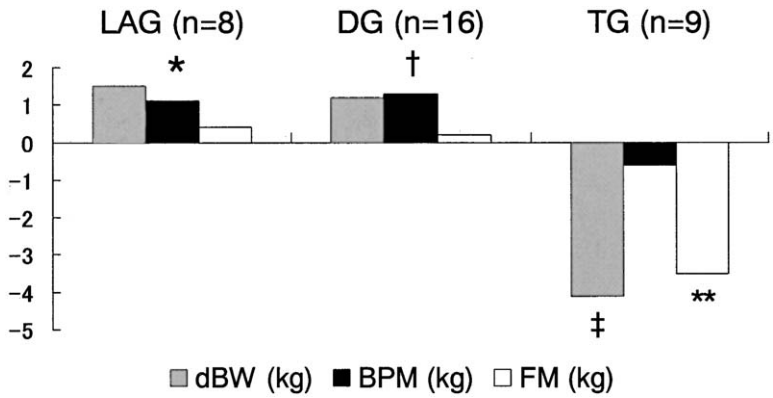

Fig. 4. Postoperative changes in body composition of patients undergoing laparoscopy-assisted (LAG), distal (DG), and total gastrectomy (TG), from the 14th postoperative day until 12 months after surgery. *$P = 0.020$, †$P = 0.0027$, ‡$P = 0.0036$, **$P = 0.0077$. dBW = change in body weight; BPM = body protein mass; FM = fat mass.

this period, although protein synthesis may have been increased as a result of sustained oral feeding.

The overall changes in body composition from before surgery to 6 months after surgery showed that the body weight loss that occurred during the immediate postoperative period was recovered in the LAG and DG groups, although a loss of fat mass was recorded in the DG group. This finding may reflect the fact that patients undergoing partial and segmental gastrectomy (LAG group) had larger remnant stomach than patients who underwent a distal gastrectomy (DG group). In the TG group, overall losses of 15% body weight, 8% body protein, and 36% fat were recorded during this period. These results are consistent with the findings of previous studies in which weight loss (10% of preoperative weight) occurred early after total gastrectomy and body fat decreased by 40% during the first 6 months after gastrectomy.[19] In a long-term follow-up study, the weight loss consisted mainly of the depletion of body fat stores, whereas no significant decrease in lean body mass was observed.[10] Similar changes in body composition, including an increase in interstitial fluid (edema), were observed in the TG group during the postoperative period in the present study. Fat loss may be correlated with insufficient food intake after surgery.

Presumably, patients in the LAG and DG groups were able to regain their body protein mass during the postoperative period and return to their previous quality of life earlier after surgery.[20] The patients in the DG and TG group may have impaired nutritional intake, which seems to be associated with fat loss. Clearly, the small size of the residual gastric pouch and the absence of the stomach limit the amount of food consumed at one sitting. However, gastrectomy patients are expected to increase the frequency and caloric density of their meals postoperatively. In contrast, individuals who have undergone a Roux-en-Y gastric bypass typically eat fewer meals and voluntarily restrict their consumption of calorie-dense foods.[21,22] These alterations arise in part from a generalized loss of hunger that extends beyond postprandial satiety. One hypothesis explaining this phenomenon is that the procedure affects gut-derived factors involved in appetite regulation. Patients who have undergone a Roux-en-Y gastric bypass have markedly lower ghrelin levels and do not exhibit any of the meal-related oscillations observed in control subjects.[23] Future studies are required to define the clinical significance of ghrelin and develop nutritional interventions to prevent the depletion of body fat.

CONCLUSION

Patients who underwent a gastrectomy lost body protein during the perioperative period, and the resulting loss of body weight was significantly smaller in the LAG group than in the DG or TG groups. Six months after surgery, the body weight of the patients in the LAG and DG groups had recovered to the preoperative level, but a further decrease was observed in the TG group. The main postoperative change in body composition was a loss of fat mass in the DG and TG groups. Multifrequency bioelectrical impedance analyses can be used to assess body composition and may be useful for performing nutritional assessments in patients who have undergone a gastrectomy.

REFERENCES

1. Junginger TH, Walgenbach S. Postgastrectomy reconstruction by esophagojejunostomy Roux-en Y. Nutrition 1988;4: 239–242.

2. Armbrecht U, Lundell L, Lindstedt G, Stockbrugger RW. Causes of malabsorption after total gastrectomy with Roux-en-Y reconstruction. Acta Chir Scand 1988;154:37–41.
3. Adams JF. The clinical and metabolic consequences of total gastrectomy. I. Morbidity, weight and nutrition. Scand J Gastroenterol 1967;2:137–149.
4. Liedman B, Andersson H, Berglund B, et al. Food intake after gastrectomy for gastric carcinoma: The role of a gastric reservoir. Br J Surg 1996;83:1138–1143.
5. Heymsfield SB, Lichtman S, Baumgartner RN, et al. Body composition of humans: Comparison of two improved four-compartment models that differ in expense, technical complexity, and radiation exposure. Am J Clin Nutr 1990;52: 52–58.
6. Lorenzo AD, Andreoli A. Segmental bioelectrical impedance analysis. Curr Opin Clin Nutr Metab Care 2003;6:551–555.
7. Cha K, Chertow GM, Gonzalez J, Lazarus JM, Wilmore DW. Multifrequency bioelectrical impedance estimates the distribution of body water. J Appl Physiol 1995;79:1316–1319.
8. Cha K, Shin S, Choi CSS, Wilmore DW. Evaluation of segmental bioelectrical impedance analysis (SBIA) for measuring muscle distribution. J ICHPERSD-ASIA 1997;11–14.
9. Souba WW, Austen WG. Nutrition and metabolism. In Greenfield LJ, ed. Surgery: Scientific Principles and Practice, 2nd ed. Philadelphia: Lippincott-Raven, 1997, pp 42–67.
10. Liedman B, Bosaeus I, Hugosson I, Lundell L. Long-term beneficial effects of a gastric reservoir on weight control after total gastrectomy: A study of potential mechanisms. Br J Surg 1998;85:542–547.
11. Liedman B, Henningsson A, Mellstrom D, Lundell L. Changes in bone metabolism and body composition after total gastrectomy: Results of a longitudinal study. Dig Dis Sci 2000;45:819–824.
12. Fuchs KH, Thiede A, Engemann R, Deltz E, Stremme O, Hamelmann H. Reconstruction of the food passage after total gastrectomy: Randomized trial. World J Surg 1995;19: 698–706.
13. Japanese Research Society for Gastric Cancer. Japanese Classification of Gastric Carcinoma, 1st English ed. Tokyo: Kanehara and Co Ltd, 1995.
14. Onodera H, Tokunaga A, Yoshiyuki T, et al. Surgical outcome of 483 patients with early gastric cancer: Prognosis, postoperative morbidity and mortality, and gastric remnant cancer. Hepatogastroenterology 2004;51:82–85.
15. Reyes CD, Weber KJ, Gagner M, Divino CM. Laparoscopic vs open gastrectomy: A retrospective review. Surg Endosc 2001;15:928–931.
16. Uchiyama K, Takifuji K, Tani M, Onishi H, Yamaue H. Effectiveness of the clinical pathway to decrease length of stay and cost for laparoscopic surgery. Surg Endosc 2002; 16:1594–1597.
17. Jacobs DO, Robinson MK. Body composition. In: Fischer JE, editor. Nutrition and Metabolism in the Surgical Patient, 2nd ed. Boston: Little, Brown and Co, 1996, pp 3–26.
18. Moore FD. Energy and the maintenance of the body cell mass. JPEN J Parenter Enteral Nutr 1980;4:228–260.
19. Liedman B, Andersson H, Bosaeus I, Hugosson I, Lundell L. Changes in body composition after gastrectomy: Results of a controlled, prospective clinical trial. World J Surg 1997;21: 416–421.
20. Liedman B, Hugosson I, Lundell L. Treatment of devastating postgastrectomy symptoms: The potential role of jejunal pouch reconstruction. Dig Surg 2001;18:218–221.
21. Halmi KA, Mason E, Falk JR, Stunkard A. Appetitive behavior after gastric bypass for obesity. Int J Obes 1981;5:457–464.
22. Kenler HA, Brolin RE, Cody RP. Changes in eating behavior after horizontal gastroplasty and Roux-en-Y gastric bypass. Am J Clin Nutr 1990;52:87–92.
23. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med 2002;346:1623–1630.

Systematic Follow-up After Curative Surgery for Colorectal Cancer in Norway: A Population-Based Audit of Effectiveness, Costs, and Compliance

Hartwig Körner, M.D., Kjetil Söreide, M.D., Pål J. Stokkeland, M.D., Jon Arne Söreide, M.D.

In this study, we analyzed the Norwegian guidelines for systematic follow-up after curative colorectal cancer surgery in a large single institution. Three hundred fourteen consecutive unselected patients undergoing curative surgery for colorectal cancer between 1996 and 1999 were studied with regard to asymptomatic curable recurrence, compliance with the program, and cost. Follow-up included carcinoembryonic antigen (CEA) interval measurements, colonoscopy, ultrasonography of the liver, and radiography of the chest. In 194 (62%) of the patients, follow-up was conducted according to the Norwegian guidelines. Twenty-one patients (11%) were operated on for curable recurrence, and 18 patients (9%) were disease free after curative surgery for recurrence at evaluation. Four metachronous tumors (2%) were found. CEA interval measurement had to be made most frequently (534 tests needed) to detect one asymptomatic curable recurrence. Follow-up program did not influence cancer-specific survival. Overall compliance with the surveillance program was 66%, being lowest for colonoscopy (55%) and highest for ultrasonography of the liver (85%). The total program cost was € 228,117 (US $ 280,994), translating into € 20,530 (US $ 25,289) for one surviving patient after surgery for recurrence. The total diagnosis yield with regard to disease-free survival after surgery for recurrence was 9%. Compliance was moderate. Whether the continuing implementation of such program and cost are justified should be debated. (J GASTROINTEST SURG 2005;9:320–328)

KEY WORDS: Colorectal cancer, surgery, curative, follow-up

Colorectal cancer (CRC) is the second most common malignant disease, affecting both sexes in a worldwide perspective.[1–3] Recurrence after curative resection is reported in 30–50% of the patients and causes considerable morbidity and mortality.[4–6] Systematic postoperative surveillance after curative surgery for CRC has been applied widely. Early detection of recurrence has been regarded as important to enable curative surgical treatment of localized hepatic or pulmonary metastases in selected patients.[7–10] Although the effectiveness of such programs has been questioned,[11,12] two recent reviews have provided some support to the evidence that systematic follow-up of these patients does have a beneficial effect on survival.[13,14]

In Norway, national guidelines were established in the 1990s by the Norwegian Gastro-Intestinal Cancer Group (NGICG) with a focus on both intraluminal recurrence and distant spread[15,16] (Table 1). The cost-effectiveness of these guidelines was shown in a model.[17] However, little is known about the real yield of this program and compliance with the recommendations, and the cost of its implementation had not been accurately determined. The need for

From the Institute of Surgical Sciences (H.K., J.A.S.), University of Bergen, Bergen, Norway; and the Department of Surgery (H.K., K.S., P.J.S., J.A.S.), Division of Gastrointestinal Surgery, Rogaland Central Hospital, Stavanger, Norway.
Supported by the Centre for Clinical Research, Armauer Hansens House, Haukeland University Hospital, Bergen, Norway.
Reprint requests: Hartwig Körner, M.D., Ph.D., Department of Surgery, Rogaland Central Hospital, P.O. Box 8100, N-4068 Stavanger, Norway. e-mail: koha@sir.no

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.09.023

Table 1. Norwegian follow-up guidelines after curative surgery of colorectal cancer as recommended by the Norwegian Gastro-Intestinal Cancer Group (NGICG) for patients younger than 76 years

	Postoperative month											
	3	6	9	12	18	24	30	36	42	48	54	60
Carcinoembryonic antigen	•	•	•	•	•	•	•	•	•	•	•	•
Ultrasonography of the liver		•		•	•	•	•	•	•	•	•	•
Chest radiograph		•		•	•	•	•	•	•	•	•	•
Colonoscopy				•								•

cost identification of follow-up programs has been expressed by some authors.[13] The objective of this study was to evaluate the effectiveness of the Norwegian guidelines for follow-up after curative surgery for CRC in a population-based patient cohort in terms of asymptomatic resectable recurrent disease, compliance with guidelines, and cost.

PATIENTS AND METHODS

All patients with a diagnosis of adenocarcinoma of the colon and rectum seen at our institution between July 1996 and June 1999 were included in the study. Our institution provides regional surgical and oncologic care for a population of 280,000. Surgical treatment was performed according to general recommendations, including total mesorectal excision (TME) in rectal cancer with preoperative radiation therapy in selected cases.[16,18] Patients younger than 76 years of age with stadium Dukes C colon cancer were offered postoperative adjuvant chemotherapy for 6 months (5-fluorouracil/leucovorin).

Follow-up

All curatively treated patients 75 years old or younger had follow-up according to the NGICG guidelines (Table 1),[16] whereas older patients were not followed routinely. Modifications of this schedule were made in some cases mainly according to the wishes of the patients, and in rare cases by the responsible surgeon.

Data Collection

Patients with CRC were identified from hospital data using *ICD-9* codes 153 and 154; in addition, data from the Department of Pathology. Histology for all patients were reviewed. The hospital records of the identified 441 patients were evaluated. Date of death was obtained from the electronic patient record system of our hospital, which is directly linked via a unique 11-digit personal identification number to the government Public Registry of inhabitants. Cause of death was verified by a review of patient records or, in a few cases, from various sources, including patients' general practitioners or convalescent houses. The ASA classification was used to express the state of health.[19] All postoperative examinations were reviewed. Carcinoembryonic antigen (CEA) values were registered preoperatively and postoperatively, as well as in the case of local recurrence and/or distant spread. Recurrence at the site of primary tumor and distant spread were registered, based on clinical findings, imaging studies, and/or histologic diagnosis. Treatment of relapse was recorded with regard to type of treatment (curative versus palliative). Cause of death was recorded and categorized in each case. The diagnostic modality establishing recurrent disease was recorded.

Definitions

Curative treatment was defined as macroscopically complete surgical resection (R0) in the absence of distant disease on preoperative ultrasonogram of the liver and radiograph of the chest and after surgical exploration of the abdominal cavity. *Local recurrence* was categorized as either intraluminal or extraluminal. Histologic confirmation was made when feasible. *Distant metastasis* was defined as evidence of a secondary tumor away from the primary location and was diagnosed clinically with imaging studies or tissue biopsy. The *effectiveness* of a test was defined as the ability to detect curable asymptomatic recurrent disease in all patients with systematic postoperative surveillance. *Compliance* with the follow-up program was defined as the proportion represented by dividing the total number of surveillance tests performed into the total number of tests scheduled according to the surveillance program.

Statistical Analysis

Data were analyzed with regard to local recurrence, distant metastases, and survival, related to patients with systematic follow-up. Category variables were compared by χ^2 test and Fisher's exact test when

appropriate. Risk was estimated by calculating odds ratio (OR) with 95% confidence interval (CI). Continuous variables were compared by Mann-Whitney *U* test, assuming a nonparametric distribution. Survival data were assessed by Kaplan-Meier statistics and log-rank test, whereas the occurrence of local recurrence and distant spread was assessed by 1 – survival Kaplan-Meier statistics and log-rank test. Cost identification studies were performed by calculating the numbers and 95% CI of examinations needed for the various diagnostic tests to identify one patient with asymptomatic resectable secondary disease. Costs were estimated based on hospital charges and expressed in Euro (€). Conversion rates of currencies were calculated in June 2003 (1 € = 7.88 Norwegian Crowns).

RESULTS

Four hundred forty-one patients were diagnosed with CRC during the study period, translating into an annual incidence of 52.5/100.000, or an average of 150 patients. Three hundred fourteen patients were treated with curative intention (71%; annual incidence of 37.4/100.000). Among these patients, systematic follow-up was indicated in 194 (62%; age ≤75 years of age) according to the NGICG guidelines (Fig. 1). Patient and tumor characteristics are given in Table 2. Median follow-up time was 66 months (range, 48–84 months). Median age as well as distribution of ASA classification was significantly different compared with the patient group with and without systematic follow-up, respectively. No differences with regard to gender or tumor characteristics were observed (Table 2).

Postoperative mortality (30 days) was 3.5% (11 patients). Crude survival was significantly better ($P < 0.0001$) in the follow-up group (73%) compared with the patients without follow-up (52%) (Fig. 2, *A*). Cancer-specific survival, however, was similar (79% versus 86%, $P = 0.7$) in both groups (Fig. 2, *B*).

Effectiveness of Postoperative Surveillance

Details from follow-up are shown in Table 3. From all observed recurrences, 23% were asymptomatic with curative potential, whereas 77% were either symptomatic and/or incurable. The effectiveness to detect asymptomatic resectable recurrence was 11% (21 patients) from 194 surveyed patients (Fig. 3), whereas the overall effectiveness (resectable recurrence regardless of whether asymptomatic) was 16% (31 patients). The numbers of patients with distant spread were significantly higher in the group with systematic follow-up. The median time until diagnosis of local recurrence or distant spread, however, was similar in both groups (21 months; interquartile range, 13–30 months; Figs. 2, *C* and *D*). In the Dukes A group, six recurrences (two liver metastases, two lung metastases, two local recurrences) were seen (n = 55; 11%). All had rectal cancer, whereas none of those with Dukes A colonic cancer had recurrence. In the Dukes B and C groups, recurrences were equally distributed. Local recurrences were found in 7% of the rectal cancer patients and 10% of the colon cancer patients ($P = 0.4$). Of the patients with asymptomatic resectable disease, nine hepatic resections, five pulmonary resections, five bowel resections, and two other procedures were performed. Clinical examination revealed an additional nine patients with symptomatic

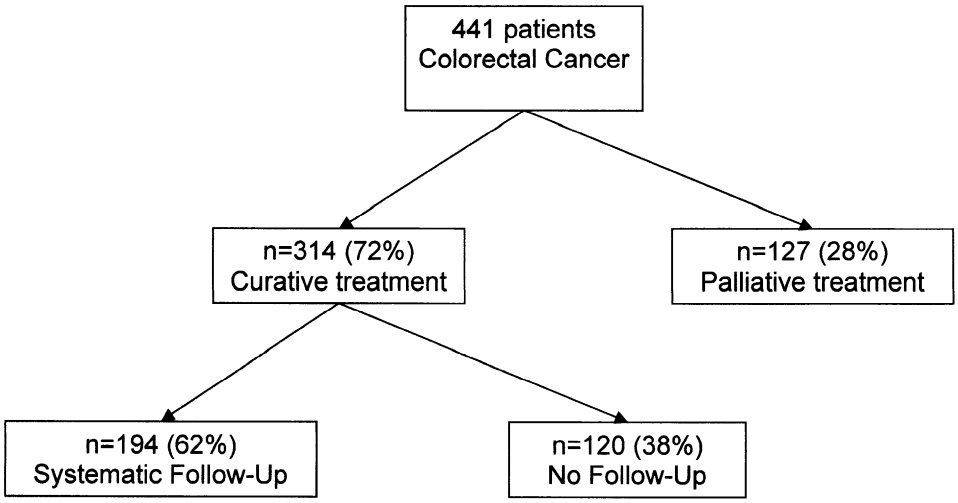

Fig. 1. Distribution of 441 patients with diagnosis of colorectal cancer with regard to curative treatment and follow-up.

Table 2. Characteristics of 314 patients undergoing curative surgery for colorectal cancer

Characteristic	All patients	Follow-up	No follow-up	*P*
Males	145 (46)	95 (65)	50 (35)	0.25*
Females	169 (54)	99 (59)	70 (41)	
Age (yr; median, interquartile range)	72 (63–81)	66 (60–72)	81 (77–85)	<0.0001*
ASA				
1	143 (46)	107 (74)	36 (26)	
2	124 (39)	70 (56)	54 (44)	<0.0001*
3	47 (15)	17 (37)	30 (63)	
Observation time (mo; median, interquartile range)	66 (57–75)	65 (56–74)	67 (59–74)	0.24*
Colon	205 (62)	125 (61)	78 (39)	0.52*
Rectum	109 (38)	66 (61)	42 (39)	
Dukes A	55 (18)	35 (64)	20 (36)	
Dukes B	160 (50)	100 (62)	60 (38)	0.60†
Dukes C	99 (32)	59 (59)	40 (41)	

One hundred ninety-four patients had systematic follow-up versus 120 patients without follow-up. Values given as n (%).
*χ^2 Test for category variables; mann-whitney *U* test for continuous variables.
†χ^2 Test of trend.

recurrence, and they underwent bowel resections with curative intention. At last follow-up, 18 of 21 asymptomatic patients (86%) were still alive without evidence of disease. Accordingly, the yield of this strict surveillance program was 9% of the 194 patients. The effectiveness of the various modalities of routine examination is shown in Table 4 and was greatest for colonoscopy after 1 and 5 years, respectively, and lowest for CEA. The effectiveness of computed tomography examinations done on specific indications was 3.1%. The number of tests needed to detect one asymptomatic patient with curable disease is given in Table 4. Numbers varied widely between the various test modalities.

Compliance With Follow-up

The overall compliance with the follow-up program was 66% (3661 of 5519 scheduled tests). Twenty-one patients (11%) older than 75 years (between 76 and 83 years of age) had been followed systematically. For various tests, compliance varied from 55% (1-year colonoscopy) to 85% (ultrasonography of the liver) (Table 4). Compliance with 5-year colonoscopy was calculated with regard to the 104 patients with an observation time of at least 60 months. When extrapolating the values from Table 4, a 100% follow-up might have yielded an additional 11 patients with potentially curable recurrent disease.

Cost

The costs were calculated based on hospital charges, which are confined to the reimbursements from the government (National Insurance Administration) and patient fees. Total cost of the surveillance program was 95,842 € (US $ 118,058) (145,215 € [US $ 178,875] for 100% compliance). Cost per patient was 494 € (US $ 608) (749 € [US $ 923] for 100% compliance). In addition to charges for clinic visits and imaging tests (computed tomography of liver and chest), the total cost was 228,117 € (US $ 280,994) (345,632 € [US $ 425,749] for 100% compliance; per patient 1176 € [US $ 1449]; 1782 € [US $ 2195] at 100% compliance). The total cost for follow-up of a single patient to survive after curative treatment of recurrence was 20,530 € [US $ 25,289] (31,106 € [US $ 38,316] for 100% compliance). CEA generated the lowest cost compared with its diagnostic yield. Liver ultrasonogram and chest radiograph incurred the highest cost.

DISCUSSION

The findings of our study concur well with the national statistics from the Norwegian Cancer Registry.[20] Our population-based observations should apply to the general population.

Our postoperative surveillance program had an effectiveness of 11% with regard to curable asymptomatic recurrence and increased to 16% in symptomatic patients. Nine percent of the patients with follow-up eventually received curative treatment for recurrent disease, and most remained free of disease (85%). In this select group, the benefit of surveillance is apparent. However, it is important to note that our observed figures apply to patients 75 years old or

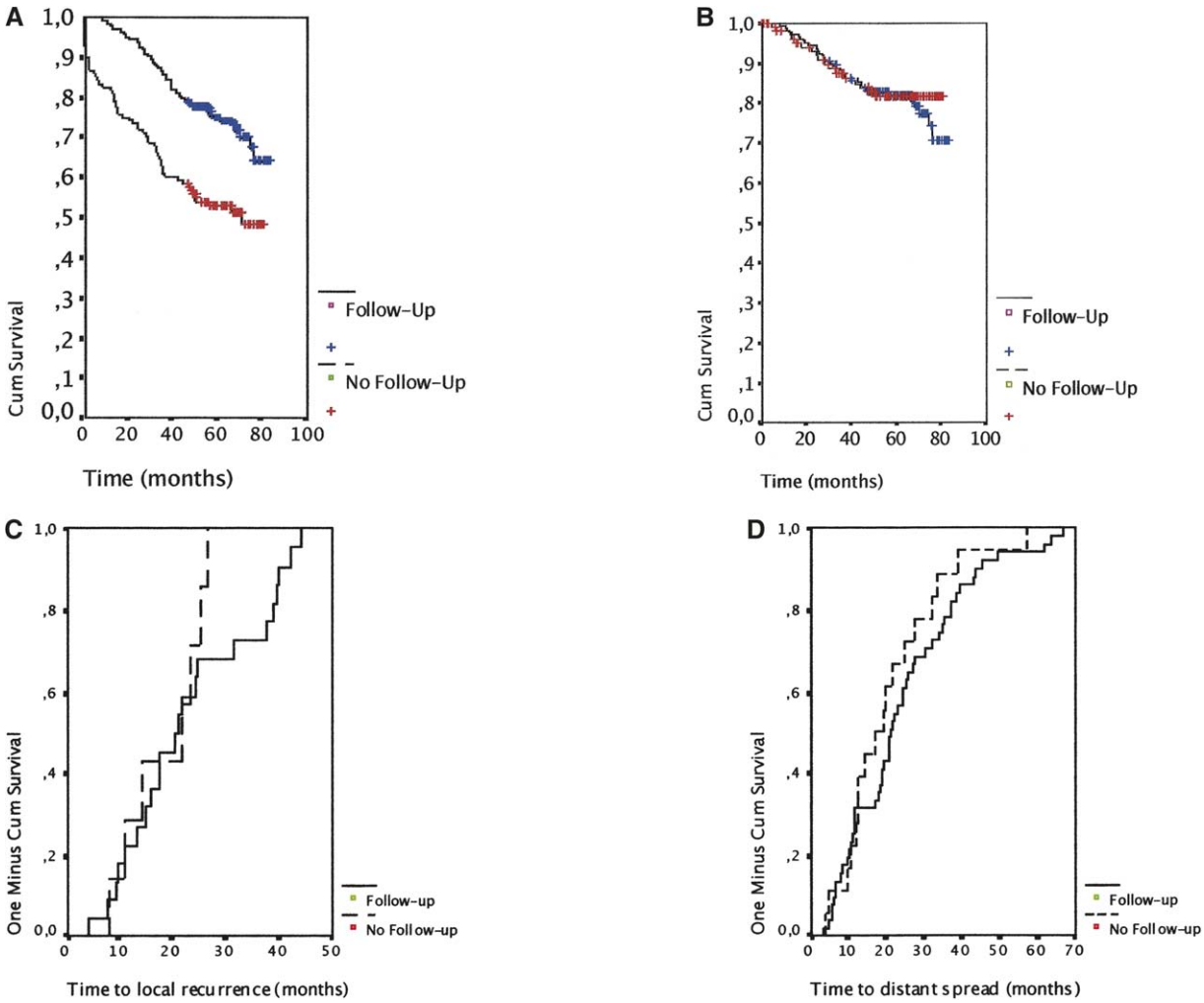

Fig. 2. Survival and recurrence after curative surgery for colorectal cancer. Kaplan-Meier survival curves are given. Differences between groups are assessed by log-rank test. Solid lines represent patients with follow-up. (**A**) Overall survival. (**B**) Cancer-specific survival. (**C**) Time to abdominal recurrence (1 – survival function). (**D**) Time to distant spread (1 – survival function).

younger in whom surgery for recurrent disease may be warranted. Patients of greater age and most likely a higher frequency of comorbidity have not been followed according to a fixed schedule (Table 1). The effectiveness of follow-up after curative surgery for CRC is reported to vary considerably, with a range between 2% and 20%.[21–24] This depends largely on which study population is analyzed. Although some studies report on patients participating in trials for adjuvant chemotherapy,[21,22] other focus on particular sites of recurrence.[23] Furthermore, at the present time, there is no general consensus as to which examinations and tests should be included.[13] Some studies focus on the detection of intraluminal recurrence,[25,26] and others also include the detection of distant spread by CEA monitoring or imaging studies.[27,28] However, the problem of postoperative cancer surveillance is that a vast majority of patients—in the present study, 89%—have to undergo a large number of tests without any benefit, or even with some harm, to identify a few patients with curable recurrence. Most patients will not have a recurrence (60%) or are diagnosed because of symptoms (19%). It has been shown that close follow-up can lead to psychological stress.[29] In a Danish randomized controlled trial, health-related quality of life was only marginally improved in patients with regular follow-up.[30] Patients with asymptomatic but incurable disease (9%) represent probably the most controversial group and raise serious ethical considerations.[31] Even with more effective palliative chemotherapy during the past decade, cure is seldom seen.[32,33] Although systematic postoperative surveillance is extensively studied with regard to cure and survival, the possible

Table 3. Local recurrences, metachronous cancers, and distal metastases in 314 patients operated curatively for colorectal cancer

Characteristic	All patients	Follow-up	No follow-up	Odds ratio (95% confidence interval)	Follow-up, asymptomatic patients	No follow-up, asymptomatic patients	Odds ratio (95% confidence interval)
Local recurrence	29 (9)	22 (76)	7 (24)	2.95 (0.93–5.42)	6 (27)	—	—
Metachronous colorectal cancer	4 (1)	4 (100)	—	—	4 (100)	—	—
Distant metastases*	70 (23	52 (74)	18 (26)	2 (1.14–3.76)	31 (60)	2 (11)	5.3 (1.16–54.7)
Hepatic	28 (40)	22 (79)	6 (21)	2.4 (0.95–6.12)	14 (64)	1 (5)	3.8 (0.42–24.7)
Pulmonary	17 (24)	13 (76)	4 (24)	2 (0.66–6.54)	11 (85)	1 (25)	3.4 (0.33–35)
Central nervous system	2 (3)	1 (50)	1 (50)	0.6 (0.04–9.95)	—	—	
Skeleton	3 (4)	2 (67)	1 (33)	1.24 (0.11–13.8)	—	—	
Multiple sites	11 (16)	7 (63)	4 (37)	1.1 (0.31–3.8)	4 (57)	—	
Miscellaneous sites	9 (13)	7 (78)	2 (22)	2.2 (0.45–10.8)	2 (28)	—	

One hundred ninety-four patients had systematic follow-up versus 120 patients without follow-up.
Values given as n (%).
*Twelve patients had both local recurrence and distant metastases.

benefit of surveillance with regard to a better outcome of palliative care and quality of life is, to our knowledge, not well described.

In the present study, 270 tests were needed to find one patient with recurrent disease, in whom curative surgery was achievable. Kievit[34] reported a number of 360 diagnostic efforts that was needed to achieve the same. However, a great uncertainty is related to the effectiveness of figures and costs of follow-up as expressed by the large CIs (Table 4). We are not aware of any previous studies reporting 95% CIs as shown in our report. Our observations reflect the small gain of a strict follow-up program as expressed by low numbers of recurrences even in a large patient series undergoing thousands of examinations. The major problem of all follow-up programs for CRC is that there is, at the present time, no sufficient diagnostic tool with acceptable sensitivity and specificity to detect recurrent disease at an early stage when curative treatment is possible. Therefore, a multimodality follow-up covering the sites of highest incidence of recurrence and where effective treatment options are available is necessary. The Norwegian follow-up program with focus on hepatic, pulmonary, and intraluminal recurrences as well as metachronous tumors showed an effectiveness of 9%.

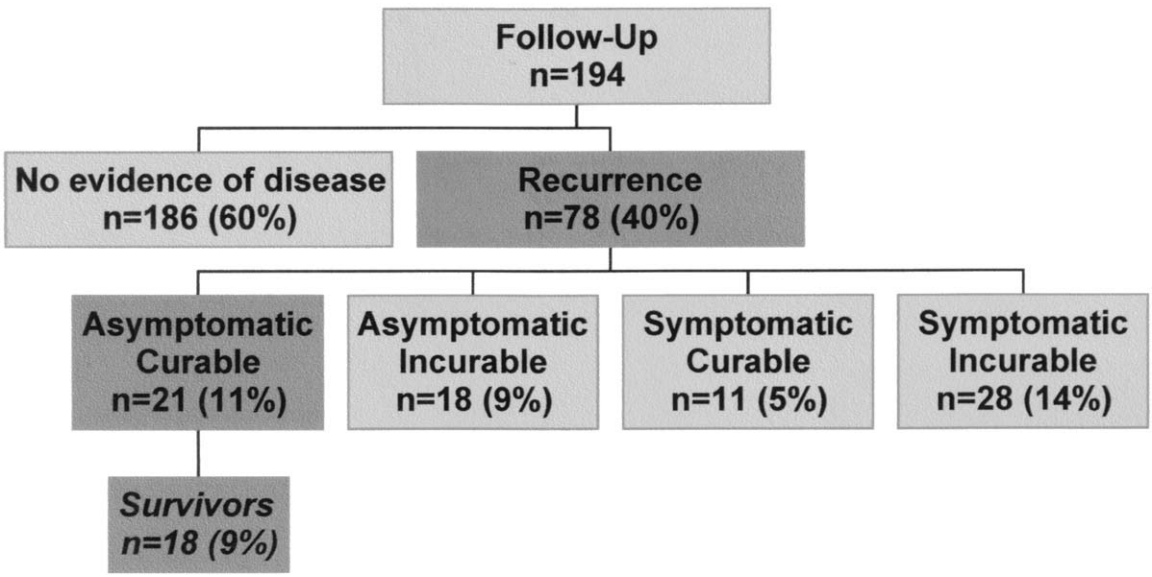

Fig. 3. Outcome of 194 patients with systematic follow-up after curative treatment for colorectal cancer with regard to recurrence, presence of symptoms, and treatment of recurrence.

Table 4. Diagnostic tests performed during follow-up of 194 patients with curative resection of colorectal cancer

Diagnostic test (Cost for a single test, US$)	No. of tests performed (% compliance with guidelines)	No. of patients detected (%)	Effectiveness (No. of patients with curable disease, %; 95% confidence interval)	No. of tests needed to detect one patient with curable disease (95% confidence interval)	Costs in US$ (95% confidence interval)
S-CEA ($4.70)	1601 (63)	17 (1.1)	3 (0.2; 0.05–0.53)	534 (190–1958)	2.032 (725–7.456)
Colonoscopy 1 yr after surgery ($214)	107 (55)	3 (3.7)	3 (2.8; 0.8–7.5)	36 (13–130)	5.658 (2.256–22.555)
Colonoscopy 5 yr after surgery ($214)	51 (58)	2 (3.9)	2 (3.9; 0.7–12.8)	27 (8–143)	4.685 (1.388–195.481)
Ultrasound of the liver ($45.30)	990 (85)	11 (1.1)	3 (0.3; 0.08–0.85)	330 (118–1210)	12.147 (4.342–44.528)
CT scan of the liver ($215)	159*	25 (15.7)	6 (3.8; 1.7–7.9)	27 (13–60)	5.601 (2.275–10.500)
Chest radiograph ($38.90)	912 (78)	9 (1)	4 (0.4; 0.15–1)	228 (92–836)	7.177 (2.896–26.317)
CT scan of the chest ($210.00)	32*	2 (6.3)	1 (3.1; 0.2–16)	32 (6–624)	5.569 (1.044–108.594)
Clinical examination ($63)	1809*	33 (1.8%)	9 (0.5; 0.2–0.9)	201 (106–405)	12.820 (6.084–23.085)

For each test modality, compliance and the number of patients with asymptomatic curable disease (effectiveness) by that particular test are calculated, as well as the number of tests to be done to detect one asymptomatic curable patient.
*Not part of the guidelines; computed tomography scans of liver and lungs were done when ultrasound and/or chest radiographic examination were unsatisfactory.

Our guidelines are based on CEA measurements. As the value of serial CEA measurement is still unclear, this aspect deserves further evaluation.[28,35,36]

The evidence of the benefit of systematic surveillance was earlier characterized as inconclusive,[37] two recent meta-analyses support the attitude that postoperative surveillance is probably associated with a survival benefit.[13,14] However, the conclusions that can be drawn from these meta-analyses seem to be limited because of serious methodologic flaws of the primary studies, like insufficient power to detect any statistically significant differences and the fact that the various follow-up programs were hard to compare.[2,36] It has been suggested that an appropriate randomized controlled trial to address these issues would require inclusion of at least 25,000 patients.[38] However, when effective treatment of hepatic and pulmonary recurrences is available,[7–10] it is questionable whether a randomized controlled trial with regard to a follow-up or not is feasible and ethically justifiable. Thus, the question should be not only whether surveillance should be performed but also which follow-up program should be applied and which patient group should be surveyed. Furthermore, surveillance programs should take into account whether the individual patient will be a candidate for salvage surgery for recurrence.[39,40] Thus, it is a challenge to determine which patient groups will benefit from follow-up and what kind of program is appropriate.

The cost-effectiveness of the Norwegian guidelines was earlier found to be acceptable when applied to a model based on outcome figures from the literature.[17] This study suggested a recurrence rate of 40% with a median recurrence time of 10 months and a 10% rate of curative surgery. Figures from our study are in accordance with the earlier reported results. However, time to relapse was in our study twice as long as suggested in this analysis. The assumptions made by Norum and Olsen[17] are based on patients treated between 1971 and 1991, before the concept of TME was widely implemented, and local recurrences rates of 20–30% were reported, which often occurred within the first 18 months after surgery.[41,42] Since 1994, the TME technique is used routinely in the treatment of rectal cancer in Norway.[16,43]

The follow-up program used at our department adhered almost completely to the Norwegian guidelines. Both CEA measurement and ultrasound imaging of the liver were offered independently of preoperative CEA values. This program was prolonged from 4 to 5 years. The overall compliance was 66%. Our compliance figures are in concert with others.[22,44] We believe our findings reflect the overall compliance of such programs in routine clinical practice, even though the compliance in a randomized controlled trial is supposed to be higher.[22]

The costs of follow-up as calculated in our study were lower than estimated in the study of Norum and Olsen.[17] This is mostly explained by a lower charge for CEA analysis.[17] In addition, cost is calculated and expressed at different times and in different currencies, which make a meaningful comparison difficult. Cost analyses should also take the discount

index into account and are ideally measured in generally comparable terms like cost-utility analyses, which requires a comparative study design.[45] Cost is also hard to compare with publications from other countries because of different reimbursement policy. A recent report from France reported cost figures from two different follow-up schedules.[46] The costs were fairly comparable to our figures in Table 4. However, the numbers of examinations according to the French schedules were lower than those from the Norwegian recommendations. The uncertainty of cost figures is reflected by the wide CIs (Table 4) as they depend not only on reimbursement practice but also on the frequency of examinations performed. Thus, care should be taken when comparing cost figures alone. Finally, to decide whether these expenses are cost-effective depends on what a given society is willing to pay for the potential benefits of treating recurrent CRC and how to make priorities with regard to other concurring patient groups. This decision is, beside the medicoethical issue of offering the best possible care to every single patient at any time, a matter of public discussion based on valid scientific recommendations.

The effectiveness of Norwegian guidelines in this unselected patient cohort was limited to 9%. Compliance was only moderate. Whether the identified costs are acceptable is a matter of public discussion based on valid scientific recommendations.

The authors wish to thank Olav Dahl, M.D., and Randi Eikeland at the Clinical Cancer Research Office, Haukeland University Hospital, Bergen, for valuable help with the database. We also thank Roger Bjugn, M.D., who provided revised histopathology data, and Maher A. Abbas, M.D., for valuable suggestions to the manuscript.

REFERENCES

1. Du WB, Chia KS, Sankaranarayanan R, Sankila R, Seow A, Lee HP. Population-based survival analysis of colorectal cancer patients in Singapore, 1968–1992. Int J Cancer 2002;99:460–465.
2. McArdle C. ABC of colorectal cancer: Effectiveness of follow up. BMJ 2000;321:1332–1335.
3. McCormack PM, Ginsberg RJ. Current management of colorectal metastases to lung. Chest Surg Clin N Am 1998;8: 119–126.
4. Biggs CG, Ballantyne GH. Sensitivity versus cost effectiveness in postoperative follow-up for colorectal cancer. Curr Opin Gen Surg 1994;94–102.
5. Kraemer M, Wiratkapun S, Seow-Choen F, Ho YH, Eu KW, Nyam D. Stratifying risk factors for follow-up: A comparison of recurrent and nonrecurrent colorectal cancer. Dis Colon Rectum 2001;44:815–821.
6. Langevin JM, Wong WD. What is appropriate follow-up for the patient with colorectal cancer? Can J Surg 1985;28: 424–428.
7. Beard SM, Holmes M, Price C, Majeed AW. Hepatic resection for colorectal liver metastases: A cost-effectiveness analysis. Ann Surg 2000;232:763–776.
8. Harms J, Obst T, Thorban S, et al. The role of surgery in the treatment of liver metastases for colorectal cancer patients. Hepatogastroenterology 1999;46:2321–2328.
9. Ohlsson B, Stenram U, Tranberg KG. Resection of colorectal liver metastases: 25-Year experience. World J Surg 1998;22: 268–276.
10. Ike H, Shimada H, Ohki S, Togo S, Yamaguchi S, Ichikawa Y. Results of aggressive resection of lung metastases from colorectal carcinoma detected by intensive follow-up. Dis Colon Rectum 2002;45:468–473.
11. Virgo KS, Vernava AM, Longo WE, McKirgan LW, Johnson FE. Cost of patient follow-up after potentially curative colorectal cancer treatment. JAMA 1995;273:1837–1841.
12. Kjeldsen BJ, Kronborg O, Fenger C, Jorgensen OD. A prospective randomized study of follow-up after radical surgery for colorectal cancer. Br J Surg 1997;84:666–669.
13. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: Systematic review and meta-analysis of randomised trials. BMJ 2002;324:813.
14. Jeffery GM, Hickey BE, Hider P. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev 2002(1):CD002200.
15. Norum J, Gerner T, Bergan A, Lange O. Follow up after potential curative surgery of colorectal cancer. Guidelines from the Norwegian Gastrointestinal Cancer Group. Tidsskr Nor Laegeforen 1997;117:2965–2968.
16. Norwegian Gastrointestinal Cancer Group. Colorectal cancer. Guidelines for Physicians. Oslo, Norway: Norwegian Cancer Society, 1999.
17. Norum J, Olsen JA. A cost-effectiveness approach to the Norwegian follow-up programme in colorectal cancer. Ann Oncol 1997;8:1081–1087.
18. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery: The clue to pelvic recurrence? Br J Surg 1982;69:613–616.
19. Leung JM, Dzankic S. Relative importance of preoperative health status versus intraoperative factors in predicting postoperative adverse outcomes in geriatric surgical patients. J Am Geriatr Soc 2001;49:1080–1085.
20. The Norwegian Cancer Registry. Available at http://www.kreftregisteret.no/. Accessed January 2003.
21. Bleeker WA, Mulder NH, Hermans J, Otter R, Plukker JT. Value and cost of follow-up after adjuvant treatment of patients with Dukes' C colonic cancer. Br J Surg 2001;88: 101–106.
22. Graham RA, Wang S, Catalano PJ, Haller DG. Postsurgical surveillance of colon cancer: Preliminary cost analysis of physician examination, carcinoembryonic antigen testing, chest x-ray, and colonoscopy. Ann Surg 1998;228:59–63.
23. Ketteniss M, Schutz G, Ulrich B. Costs and efficiency of a tumor follow-up program for the detection of colorectal liver metastases. Int J Colorectal Dis 2001;16:28–31.
24. Staib L, Link KH, Beger HG. Follow-up in colorectal cancer: Cost-effectiveness analysis of established and novel concepts. Langenbecks Arch Surg 2000;385:412–420.
25. Patchett SE, Mulcahy HE, O'Donoghue DP. Colonoscopic surveillance after curative resection for colorectal cancer. Br J Surg 1993;80:1330–1332.
26. Barlow AP, Thompson MH. Colonoscopic follow-up after resection for colorectal cancer: A selective policy. Br J Surg 1993;80:781–784.
27. de Goede E, Filez L, Janssens J, Van Cutsem E. Follow-up of colon cancer: Detection of liver metastases: Benefit and periodicity. Acta Gastroenterol Belg 1998;61:8–10.

28. Mulcahy MF, Benson AB 3rd. The role of carcinoembryonic antigen monitoring in management of colorectal cancer. Curr Oncol Rep 1999;1:168–172.
29. Graupe F, Schwenk W, Bracht B, Kroner-Herwig B, Stock W. Psychological stress on patients in tumor after-care after R0 resection of colorectal carcinomas. Chirurg 1996;67: 604–609.
30. Kjeldsen BJ, Thorsen H, Whalley D, Kronborg O. Influence of follow-up on health-related quality of life after radical surgery for colorectal cancer. Scand J Gastroenterol 1999;34: 509–515.
31. Moertel CG, Schutt AJ, Go VL. Carcinoembryonic antigen test for recurrent colorectal carcinoma. Inadequacy for early detection. JAMA 1978;239:1065–1066.
32. Glimelius B. Palliative treatment of patients with colorectal cancer. Scand J Surg 2003;92:74–83.
33. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: Systematic review and meta-analysis. Colorectal Cancer Collaborative Group. BMJ 2000;321:531–535.
34. Kievit J. Follow-up of patients with colorectal cancer: Numbers needed to test and treat. Eur J Cancer 2002;38:986–999.
35. Wichmann MW, Lau-Werner U, Muller C, Hornung HM, Stieber P, Schildberg FW. Carcinoembryonic antigen for the detection of recurrent disease following curative resection of colorectal cancer. Anticancer Res 2000;20:4953–4955.
36. Northover J. Follow-up after curative surgery for colorectal cancer. Scand J Surg 2003;92:84–89.
37. Richard CS, McLeod RS. Follow-up of patients after resection for colorectal cancer: A position paper of the Canadian Society of Surgical Oncology and the Canadian Society of Colon and Rectal Surgeons. Can J Surg 1997;40:90–100.
38. Kievit J. Colorectal cancer follow-up: A reassessment of empirical evidence on effectiveness. Eur J Surg Oncol 2000;26: 322–328.
39. Detry R. Follow-up after curative surgery for colorectal cancer. Acta Gastroenterol Belg 2001;64:268–271.
40. Wichmann MW, Muller C, Hornung HM, Lau-Werner U, Schildberg FW. Results of long-term follow-up after curative resection of Dukes A colorectal cancer. World J Surg 2002; 26:732–736.
41. Pihl E, Hughes ES, McDermott FT, Milne BJ, Price AB. Disease-free survival and recurrence after resection of colorectal carcinoma. J Surg Oncol 1981;16:333–341.
42. Wenzl E, Wunderlich M, Herbst F, et al. Results of a rigorous follow-up system in colorectal cancer. Int J Colorectal Dis 1988;3:176–180.
43. Wibe A, Möller B, Norstein J, et al. A national strategic change in treatment policy for rectal cancer: Implementation of total mesorectal excision as routine treatment in Norway. A national audit. Dis Colon Rectum 2002;45:857–866.
44. Cheah LP, Hemingway DM. Improving colorectal cancer follow-up: The dedicated single-visit colorectal cancer follow-up clinic. Ann R Coll Surg Engl 2002;84:260–262.
45. van den Hout WB, van den Brink M, Stiggelbout AM, van de Velde CJ, Kievit J. Cost-effectiveness analysis of colorectal cancer treatments. Eur J Cancer 2002;38:953–963.
46. Borie F, Daures JP, Millat B, Tretarre B. Cost and effectiveness of follow-up examinations in patients with colorectal cancer resected for cure in a French population-based study. J Gastrointest Surg 2004;8:552–558.

The Mechanism of Microsatellite Instability Is Different in Synchronous and Metachronous Colorectal Cancer

Fernando S. Velayos, M.D., Suk-Hwan Lee, M.D., Hongming Qiu, M.D., Ph.D., Sharon Dykes, M.D., Raymond Yiu, M.D., Jonathan P. Terdiman, M.D., Julio Garcia-Aguilar, M.D., Ph.D.

MLH1 promoter hypermethylation has been described as the primary mechanism for high-frequency microsatellite instability (MSI-H) in sporadic colorectal cancers (CRCs). The underlying molecular mechanism for microsatellite instability (MSI) in synchronous and metachronous CRCs is not well described. A total of 33 metachronous CRC patients and 77 synchronous CRC patients were identified from 2884 consecutive patients undergoing cancer surgery in an academic center. Evaluable tumors were tested for MSI, immunohistochemistry for MLH1 and MSH2 protein expression, and hypermethylation of the MLH1 promoter. MSI-H tumors were found in 12 (36%) metachronous CRC patients and 29 (38%) synchronous CRC patients. MSI-H metachronous CRC patients were younger at index cancer diagnosis (64 vs. 76 years, $P = 0.01$) and more often were diagnosed before 50 years of age (4 of 12 vs. 0 of 29, $P = 0.005$). Loss of MLH1 expression associated with promoter hypermethylation was common in all patients, although more common in MSI-H synchronous patients (50% metachronous vs. 83% synchronous, $P = 0.03$). Overall, MLH1 promoter hypermethylation was seen in 7 of 17 (41%) metachronous and 44 of 54 (81%) synchronous MSI-H CRCs tested ($P = 0.004$). Although MSI occurred with equal frequency among patients with synchronous and metachronous CRCs, the underlying mechanism for MSI was different. Observed differences in MLH1 promoter hypermethylation and patient characteristics suggest most MSI-H synchronous CRCs in our population were sporadic in origin. In contrast, more MSI-H metachronous CRCs were associated with patient and tumor characteristics suggestive of underlying hereditary nonpolyposis CRC. (J GASTROINTEST SURG 2005;9:329–335)

KEY WORDS: Colorectal cancer, synchronous colorectal cancer, metachronous colorectal cancer, multiple tumors, hereditary nonpolyposis colorectal cancer, microsatellite instability, MLH1, MSH2, promoter methylation, epigenetic modification

Individuals with an inherited predisposition to cancer development are at an increased risk of developing multiple colorectal cancers (CRCs). Hereditary nonpolyposis colorectal cancer (HNPCC) is the most common hereditary colon cancer syndrome.[1] It is due to an autosomal dominant germline mutation in one of the DNA mismatch repair genes and accounts for approximately 3–5% of CRCs.[2–4] In over 90% of cases, the mutation is in the mismatch repair genes *MLH1* or *MSH2*.[5] Characteristic features include early-onset CRCs, predominance of cancers located proximal to the splenic flexure, and extracolonic malignancies.[6] Multiple colonic tumors are another common feature and occur in 20–40% of affected individuals. Multiple colonic tumors, however, can also occur in the absence of HNPCC. Up to 5% of patients with sporadic CRC have multiple CRCs (synchronous or metachronous).[6] Accordingly, the Bethesda Guidelines recommend testing of tumors from synchronous and metachronous CRC patients

Presented as a poster at Digestive Disease Week 2001, Atlanta, Georgia, May 20–23, 2001.
From the Division of Gastroenterology and Colorectal Cancer Prevention Center, Department of Medicine (F.S.V., J.P.T.), University of California San Francisco, San Francisco, California; Division of Colon and Rectal Surgery, Department of Surgery (S.-H.L., H.Q., S.D., R.Y.), University of Minnesota Cancer Center, Minneapolis, Minnesota; and Section of Colon and Rectal Surgery, Department of Surgery (J.G.-A.), University of California San Francisco, San Francisco, California.
Reprint requests: Julio García-Aguilar, M.D., Ph.D., Department of Surgery, Section of Colon and Rectal Surgery, 505 Parnassus Avenue, M-887, Box 0144, University of California San Francisco, San Francisco, CA. e-mail: garcia-aguilarj@surgery.ucsf.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.05.007

for the presence of microsatellite instability (MSI). Individuals whose tumors demonstrate MSI are at risk for having HNPCC and are referred for more specific and expensive germline testing to confirm or reject the diagnosis.[3,4]

Not all MSI cancers are due to HNPCC. Epigenetic inactivation of the *MLH1* gene by hypermethylation of its promoter has been recognized as the principal mechanism of gene inactivation in high-frequency microsatellite instability (MSI-H) sporadic CRC. This mechanism explains in part the discrepancy between the 10–20% rate of MSI seen in unselected patients with CRC and the 2% rate of HNPCC among these same patients.[7,8] The role that MLH1 promoter hypermethylation may play in the MSI-H phenotype in synchronous and metachronous cancer is unknown.

Little distinction has been made between these two types of multiple cancers with respect to the risk of underlying hereditary cancer. The aim of this study was to analyze a large series of unselected metachronous CRCs and assess the frequency of MSI, describe the molecular mechanism responsible for the MSI phenotype, and assess the contribution of MLH1 promoter hypermethylation to the MSI-H phenotype. We compared these results with a previously described group of synchronous CRC.[9]

PATIENTS AND METHODS

Study Population and Data Collection

Patients were identified from a series of 2884 consecutive patients with CRC treated at the University of Minnesota from January 1987 to December 1998. *Metachronous CRCs* were defined as occurring more than 12 months apart. *Synchronous CRCs* were defined as simultaneously diagnosed multiple invasive adenocarcinomas located in different anatomic segments of the large bowel. Patients with carcinoma in situ, inflammatory bowel disease, local recurrences, and familial adenomatous polyposis were excluded. Tumors were classified as proximal and distal, based on their location in relation to the splenic flexure. A total of 46 patients (1.6%) with metachronous CRC and 85 patients (2.9%) with synchronous CRC were identified.

Paraffin blocks from the surgical specimens were available in 33 of 46 patients with metachronous CRC. In 10 patients, paraffin blocks from the index and second tumors were available (21 tumors). In the remaining 23 patients, only paraffin blocks for the second tumors were available (24 tumors). In the synchronous group, paraffin blocks were available in 77 of 85 patients (170 tumors). Patients with available tumors constitute the study population.

Family history of CRC was obtained from patient self-report noted in the University of Minnesota Colorectal Cancer Database and by reviewing all patient medical records. We attempted to confirm family history data with a mailed questionnaire and telephone interview with the patient or next of kin. The questionnaire specifically inquired about the total number of first-degree relatives and the number of relatives with HNPCC-related disease. Completed family history information was available for 25 of 33 patients (76%) with metachronous CRC and 59 of 77 (77%) patients with synchronous CRC. Among patients with at least one MSI-H tumor, completed family history was available in 11 of 12 patients (92%) with metachronous CRC and 22 of 29 patients (76%) with synchronous CRC.

Tumor Analysis

Methods of DNA extraction, MSI analysis, immunohistochemistry, and MLH1 promoter methylation have been described previously.[13] Briefly, representative samples of hematoxylin and eosin–stained normal mucosa and cancer tissue were microdissected into separate Eppendorf tubes (Eppendorf, Inc, Hamburg, Germany) using a sterile scalpel. Individual DNA samples from tumors were amplified by polymerase chain reaction (PCR) using a set of five fluorescent-labeled microsatellite markers (*BAT25*, *BAT26*, *D2S123*, *D5S346*, and *D17S250*) recommended by the National Cancer Institute Workshop on Microsatellite Instability in Colorectal Cancer and analyzed using an automated sequencer.[14] PCR products were separated in 6% denaturing polyacrylamide gels and visualized with silver staining. Matched tumor and normal DNA were compared. The presence of new microsatellite alleles at two or more loci was scored as MSI-H. Tumors were otherwise considered microsatellite stable (MSS).[10]

Formalin-fixed, paraffin-embedded 5μm-thick sections containing both malignant tissue and normal mucosa were stained for presence (positive) or absence (negative) of MLH1 and MSH2 expression using monoclonal antibodies against MLH1 (clone G168-15; PharMingen, San Diego, CA) or MSH2 (clone EF11; Oncogene Sciences, Cambridge, MA), respectively.

MLH1 promoter methylation status was determined by a methylation-specific PCR assay described by Herman et al.[11] Approximately 100 ng of genomic DNA was extracted from each tumor. DNA was denatured and modified samples were purified using the Wizard DNA purification kit (Promega, Madison, WI). Separate PCRs were subsequently performed with MLH1 promoter methylated or unmethylated-

specific primers. Primer sequences were 5′-TTTTGATGTAGATGTTTTATTAGGGTTGT-3′ (sense) and 5′-ACCACCTCATCATAACTACCCACA-3′ (antisense) for unmethylated reactions and 5′-ACGTAGACGTTTTATTAGGGTCGC-3′ (sense) and 5′-CCTCATCGTAACTACCCGCG-3′ (antisense) for methylated reactions. The SW480 cell line DNA, which contains only unmethylated MLH1, was used as negative control, while the cell line HT29 that contains both methylated and unmethylated MLH1 alleles was used as positive control. For each set of reactions, control PCR lacking genomic DNA was performed. Ten milliliters of each PCR product was loaded onto 2% agarose gels and visualized under UV transillumination.

Statistical Analysis

Comparisons were performed by the Fisher exact or the Student *t* tests. A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient Population

Table 1 summarizes selected patient and tumor characteristics in 33 metachronous CRC patients and 77 synchronous CRC patients. At least one MSI-H tumor was present in 12 of 33 (36%) metachronous and 29 of 77 (38%) synchronous CRC patients. Patients with metachronous CRC overall were younger at first CRC diagnosis compared with those with synchronous cancer. This trend was seen for both MSI-H and MSS cancers. Of the seven patients with a diagnosis of CRC before the age of 50, five had metachronous CRC (four MSI and one MSS), and two had synchronous CRC (both MSS). More women than men had MSI-H CRCs. There was no difference in family history of CRC among the two groups. One patient with metachronous CRC and no patients with synchronous CRC met the Amsterdam criteria for HNPCC.

Frequency and Mechanism of Microsatellite Instability

A total of 45 metachronous CRCs and 170 synchronous CRCs were available for testing (Table 1). High-frequency MSI was present in 17 of 45 (38%) metachronous cancers and 54 of 170 (32%) synchronous cancers. Metachronous and synchronous tumors with MSI-H tended to be located proximal to the splenic flexure. The proportion of patients with tumors developing along the same molecular pathway (being all MSI-H or MSS) was similar in both groups: 9 of 10 (90%) in patients with paired metachronous CRC and 63 of 77 (83%) in patients with paired synchronous CRC.

The results of individual microsatellite testing markers performed on MSI-H synchronous and metachronous CRCs are summarized in Table 2. A significant proportion of both tumor types demonstrated high instability for BAT26 and BAT25. Synchronous CRCs tended to show higher instability in dinucleotide repeats than metachronous CRCs.

The most frequent mechanism for MSI among both metachronous and synchronous CRCs was loss of MLH1 expression (Table 3). This occurred more

Table 1. Characteristics of patients with metachronous and synchronous colorectal cancers (CRCs)

	Mean age at diagnosis (yr) (range)*†	Age at diagnosis (n)‡‖		Gender (n)¶		CRC family history#	No. of tumors analyzed	Proximal tumor location
		≤50 yr	>50 yr	Male	Female			
Metachronous patients (n = 33)	65 (34–87)	5 (15%)	28 (85%)	16 (48%)	17 (52%)	9/25 (36%)	45	28 (62%)
MSHI-H (n = 2)	64 (34–87)	4 (33%)	8 (67%)	4 (33%)	8 (67%)	5/11 (45%)	17 (38%)	12 (71%)
MSS (n = 21)	66 (48–77)	1 (5%)	20 (95%)	12 (57%)	9 (43%)	4/14 (29%)	28 (62%)	16 (57%)
Synchronous patients (n = 77)	73 (45–94)	2 (3%)	75 (97%)	43 (56%)	34 (44%)	19/59 (32%)	170	72 (42%)
MSI-H (n = 29)	76 (52–96)	0 (0%)	29 (100%)	8 (28%)	21 (72%)	10/22 (45%)	54 (32%)	44 (81%)
MSS (n = 48)	71 (45–94)	2 (5%)	46 (96%)	35 (73%)	13 (27%)	9/37 (24%)	116 (68%)	28 (24%)

*For metachronous cancers, age at diagnosis is reported for the index (first) cancer. Mean age at diagnosis for the subsequent tumor was 73 yr (47–90 yr) for high microsatellite instability (MSI-H) and 74 yr (50–92 yr) for microsatellite stable (MSS) cancers.
†$P < 0.05$, metachronous vs. synchronous.
‡$P = 0.06$, metachronous vs. synchronous.
‖$P < 0.05$, metachronous MSI-H vs. metachronous MSS.
¶$P < 0.05$, synchronous MSI-H vs. synchronous MSS.
#Completed family history available for 25 metachronous CRC patients (11 MSI-H, 14 MSS) and 59 synchronous CRC patients (22 MSI-H, 37 MSS).

Table 2. Microsatellite mononucleotide and dinucleotide repeat results among patients with metachronous and synchronous colorectal cancers

	Mononucleotide PCR markers				Dinucleotide PCR markers					
	BAT26		BAT25		D2S123*		D5S346†		D17S250	
	Unstable	Stable	Unstable	Stable	Unstable	Stable	Unstable	Stable	Unstable	Stable
MSI-H tumors										
Metachronous (n = 17)	16 (94%)	1 (6%)	16 (94%)	1 (6%)	5 (29%)	12 (71%)	4 (24%)	11 (65%)	7 (41%)	10 (59%)
Synchronous (n = 54)	54 (100%)	0 (0%)	44 (81%)	10 (19%)	35 (65%)	19 (35%)	26 (48%)	27 (50%)	34 (63%)	20 (37%)

PCR = polymerase chain reaction; MSI-H = high microsatellite instability.
*$P = 0.01$.
†Loss of heterozygosity was present in two metachronous colorectal cancers (12%) and one synchronous (2%) colorectal cancer.

frequently in synchronous CRC ($P = 0.03$). In both tumor types, this loss was most commonly due to hypermethylation of the MLH1 promoter and was exclusively the mechanism for MLH1-negative synchronous cancers ($P = 0.03$). Overall, MLH1 promoter hypermethylation occurred in 7 of 17 (41%) metachronous and 44 of 54 synchronous (81%) MSI-H tumors ($P = 0.004$). More than twice as many MSI-H metachronous tumors exhibited loss of MSH2 expression compared with MSI-H synchronous tumors, although this was not statistically significant ($P = 0.14$). There were three metachronous CRCs and three synchronous CRCs that were MSI-H but did not exhibit loss of either MLH1 or MSH2 protein expression. One was diagnosed in an 81-year-old patient who had a subsequent matched tumor (age 85) that was MLH1 negative and hypermethylated. Another was the second tumor from a 72-year-old patient who was first diagnosed with CRC at the age of 55. The third was the second tumor from a 69-year-old man whose first tumor was diagnosed at age 66. Among synchronous CRCs, one was a right-sided cancer from a 75-year-old man with two additional simultaneous right-sided CRCs that had loss of MSH2 expression. Another was a right-sided cancer from a 52-year-old man with a simultaneous MSS left-sided colon cancer. Finally, the third was from a 76-year-old man with a left-sided cancer and an additional left-sided cancer that was MSS.

When analyzed by patient, at least half of all individuals had one or more MLH1-negative hypermethylated CRCs (Table 4). MLH1 promoter hypermethylation was significantly more common in MSI-H tumors in synchronous CRC patients compared with metachronous CRC patients ($P = 0.03$). Patients with MLH1-negative, promoter hypermethylated metachronous CRC tended to be older at their first cancer diagnosis than those with absent MLH1 expression but no evidence of promoter methylation or those with MSH2-negative tumors. Fewer patients with MLH1-negative, promoter hypermethylated cancers had a family history of CRC compared with the other groups.

DISCUSSION

Several studies have reported the proportion of MSI among patients with multiple (synchronous and/or metachronous) CRCs. Few have described or compared the molecular mechanism responsible for the underlying MSI phenotype in these cases. We identified patients with surgically resected synchronous and

Table 3. Immunohistochemistry and promoter methylation status among MSI-H metachronous and synchronous colorectal cancers

	MLH1 negative			
MSI-H tumors	Total*	PM/total*	MLH2 negative	Other MSI†
Metachronous (n = 17)	9 (53%)	7/9 (78%)	5 (29%)	3 (18%)
Synchronous (n = 54)	44 (81%)	44/44 (100%)	7 (13%)	3 (6%)

MSI-H = high microsatellite instability; PM = promoter methylation; MSI = microsatellite instability.
*$P < 0.05$.
†Other MSI = MSI-H tumor with MLH1 and MSH2 protein expression.

Table 4. Patient characteristics by mechanism of microsatellite instability

	No. of patients			Mean age (yr)			Family history		
	MLH1 negative		MSH2 negative	MLH1 negative		MSH2 negative	MLH1 negative		MSH2 negative
	PM†	No PM		PM	No PM		PM	No PM	
Metachronous*	6 (50)	2 (17)	2 (17)	72.7 (40–87)	59.5 (34–85)	46.0 (42–50)	2/6 (33%)	1/2 (50%)	2/2 (100%)
Synchronous*	24 (83)	0	3 (11)	78.1 (62–96)	—	67.0 (52–75)	4/24 (17%)	—	1/3 (33%)

PM = promoter methylation.
*Two patients with synchronous colorectal cancer and two patients with metachronous colorectal cancer had a high microsatellite instability cancer with staining for MLH1 and MSH2.
†$P < 0.05$.

metachronous CRCs from a large referral population with the aims of determining the rate of MSI (MSI-H) and the underlying mechanism responsible for the MSI-H phenotype.

We found that MSI-H tumors were common in both patient groups. At least one MSI-H tumor was present in 36% of metachronous CRC patients and 38% of synchronous CRC patients. These figures are similar to the average reported in the literature and higher than the average MSI rate of 10–20% reported for unselected single CRCs.[12–17] Given the association between multiple CRC and HNPCC as well as the higher MSI rate compared with unselected CRC, we expected that the majority of patients with synchronous or metachronous MSI-H CRC would have phenotypic features and tumor characteristics suggestive of underlying HNPCC. Unexpectedly, the phenotypic features and underlying molecular mechanism associated with MSI differed in each group.

We used molecular techniques to provide insight into whether the MSI-H cancers in our study were consistent with a sporadic etiology or with HNPCC. We found that loss of MLH1 protein expression with promoter hypermethylation was a common mechanism for MSI in both tumor types but was more prevalent among synchronous cancers. Overall, MLH1 hypermethylation accounted for the majority of synchronous lesions but less than half of metachronous cancers (81% vs. 41%). When analyzed by patient, loss of MLH1 expression with promoter hypermethylation occurred in 81% of synchronous CRC patients and 53% of metachronous CRC patients. In contrast, metachronous MSI-H tumors were more likely to be secondary to inactivation of MLH1 by some process other than promoter methylation or by inactivation of MSH2. Patients with metachronous and synchronous CRCs associated with MLH1 promoter hypermethylation were more likely to be older at cancer diagnosis and less frequently have a family history of CRC in a first-degree relative compared with patients with unmethylated MLH1-negative and MSH2-negative tumors. These characteristics are suggestive of a sporadic etiology for the majority of the hypermethylated cancers in our population.[5,18]

Hypermethylation of the MLH1 promoter is a well-recognized mechanism for gene inactivation in sporadic MSI-H CRC. In contrast, loss of MSH2 protein expression is rarely due to promoter hypermethylation and almost exclusively indicates an underlying germline defect.[7,8,19] In a prospective study, Cunningham et al[8] found 51 of 257 (20%) unselected patients undergoing surgery for CRC had an MSI-H cancer. Loss of MLH1 staining occurred in 48 of 51 (95%) MSI-H cancers, two of them had a germline mutation of the *MLH1* gene; the rest were associated with promoter hypermethylation of the *MLH1* gene. Only three tumors had loss of MSH2 staining, and all of them had a germline mutation of the *MSH2* gene. We did not perform germline testing in our patient population, but according to the experience of Cunningham et al.[8] our results suggest that patients with MSI-H synchronous tumors were more likely to be sporadic in etiology, whereas those with metachronous cancer were more likely to harbor an HNPCC germline mutation.

Our study suggests that availability of tumors for MSI testing may be different for synchronous and metachronous CRCs. Synchronous cancers were likely to be readily available for MSI testing because they were removed at the same surgery, whereas the index tumor in patients who developed a metachronous CRC was often unavailable because surgery occurred in a different center and/or in the remote past. We found a 90% concordance (all MSS or all MSI-H) among our matched metachronous CRC pairs, suggesting that in patients with metachronous CRC, testing of the index tumor is unlikely to have significantly altered our results.

Patients with synchronous CRCs were older compared with patients with metachronous CRCs. In the

synchronous group, patients with MSI-H tumors were older than patients with MSS tumors. This age difference was not observed in patients with metachronous CRC. If early age at presentation is considered a sign of hereditary predisposition, we cannot exclude the possibility that some of our patients with metachronous CRC in whom a single MSS tumor was available for analysis may indeed have HNPCC. This possibility would only increase the association between metachronous CRC and underlying hereditary predisposition.

The lack of germline testing is a limitation of this study. Both immunohistochemistry and promoter hypermethylation assays are complementary to MSI; however, germline testing would provide the most accurate estimate of HNPCC is this patient population. Germline testing would also help determine whether MSI in six patients (three synchronous, three metachronous) with MLH1 and MSH2 expression is due to inactivation of one of the other MMR genes that can be mutated in patients with HNPCC.[20,21]

In summary, we screened a large referral database of unselected CRC patients. We found that multiple CRC accounted for less than 5% of all cancers, MSI occurred with equal frequency among patients with synchronous and metachronous CRCs, and the underlying mechanism for MSI was different for each tumor type. Observed differences in MLH1 promoter hypermethylation and patient characteristics suggest most MSI-H synchronous CRCs in our population were sporadic in origin. In contrast, more MSI-H metachronous CRCs were associated with patient and tumor characteristics suggestive of underlying HNPCC. Although synchronous and metachronous CRCs have been assumed to carry a similar hereditary risk, our data suggest that development of a metachronous CRC may be a greater risk factor for underlying HNPCC.

The authors gratefully acknowledge the contributions of Debra Caldwell and Claudia Genung for data collection and management and Robin L. Bliss for statistical analysis.

REFERENCES

1. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003;348:919–932.
2. Mecklin JP. Frequency of hereditary colorectal carcinoma. Gastroenterology 1987;93:1021–1025.
3. Rodriguez-Bigas MA, Boland CR, Hamilton SR, Henson DE, Jass JR, Khan PM, Lynch H, Perucho M, Smyrk T, Sobin L, Srivastava S. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: Meeting highlights and Bethesda guidelines. J Natl Cancer Inst 1997;89:1758–1762.
4. Aaltonen LA, Salovaara R, Kristo P, Canzian F, Hemminki A, Peltomaki P, Chadwick RB, Kaariainen H, Eskelinen M, Jarvinen H, Mecklin JP, de la Chapelle A. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med 1998;338: 1481–1487.
5. Giardiello FM, Brensinger JD, Petersen GM. AGA technical review on hereditary colorectal cancer and genetic testing. Gastroenterology 2001;121:198–213.
6. Lynch HT, Smyrk TC, Watson P, Lanspa SJ, Lynch JF, Lynch PM, Cavalieri RJ, Boland CR. Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: An updated review. Gastroenterology 1993;104:1535–1549.
7. Cunningham JM, Kim CY, Christensen ER, Tester DJ, Parc Y, Burgart LJ, Halling KC, McDonnell SK, Schaid DJ, Walsh Vockley C, Kubly V, Nelson H, Michels VV, Thibodeau SN. The frequency of hereditary defective mismatch repair in a prospective series of unselected colorectal carcinomas. Am J Hum Genet 2001;69:780–790.
8. Cunningham JM, Christensen ER, Tester DJ, Kim CY, Roche PC, Burgart LJ, Thibodeau SN. Hypermethylation of the hMLH1 promoter in colon cancer with microsatellite instability. Cancer Res 1998;58:3455–3460.
9. Dykes SL, Qui H, Rothenberger DA, Garcia-Aguilar J. Evidence of a preferred molecular pathway in patients with synchronous colorectal cancer. Cancer 2003;98:48–54.
10. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Meltzer SJ, Rodriguez-Bigas MA, Fodde R, Ranzani GN, Srivastava S. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: Development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 1998;58:5248–5257.
11. Herman JG, Graff JR, Myohanen S, Nelkin BD, Baylin S.B. Methylation-specific PCR: A novel PCR assay for methylation status of CpG islands. Proc Natl Acad Sci U S A 1996;93:9821–9826.
12. Pedroni M, Tamassia MG, Percesepe A, Roncucci L, Benatti P, Lanza G Jr., Gafa R, Di Gregorio C, Fante R, Losi L, Gallinari L, Scorcioni F, Vaccina F, Rossi G, Cesinaro AM, Ponz de Leon M. Microsatellite instability in multiple colorectal tumors. Int J Cancer 1999;81:1–5.
13. Cawkwell L, Gray S, Murgatroyd H, Sutherland F, Haine L, Longfellow M, O'Loughlin S, Cross D, Kronborg O, Fenger C, Mapstone N, Dixon M, Quirke P. Choice of management strategy for colorectal cancer based on a diagnostic immunohistochemical test for defective mismatch repair. Gut 1999; 45:409–415.
14. Masubuchi S, Konishi F, Togashi K, Okamoto T, Senba S, Shitoh K, Kashiwagi H, Kanazawa K, Tsukamoto T. The significance of microsatellite instability in predicting the development of metachronous multiple colorectal carcinomas in patients with nonfamilial colorectal carcinoma. Cancer 1999;85:1917–1924.
15. Sengupta SB, Yiu CY, Boulos PB, De Silva M, Sams VR, Delhanty JD. Genetic instability in patients with metachronous colorectal cancers. Br J Surg 1997;84:996–1000.
16. Salovaara R, Loukola A, Kristo P, Kaariainen H, Ahtola H, Eskelinen M, Harkonen N, Julkunen R, Kangas E, Ojala S, Tulikoura J, Valkamo E, Jarvinen H, Mecklin JP, Aaltonen LA, de la Chapelle A. Population-based molecular detection of hereditary nonpolyposis colorectal cancer. J Clin Oncol 2000;18:2193–2200.
17. Samowitz WS, Curtin K, Lin HH, Robertson MA, Schaffer D, Nichols M, Gruenthal K, Leppert MF, Slattery ML. The

colon cancer burden of genetically defined hereditary nonpolyposis colon cancer. Gastroenterology 2001;121:830–838.
18. Miyakura Y, Sugano K, Konishi F, Ichikawa A, Maekawa M, Shitoh K, Igarashi S, Kotake K, Koyama Y, Nagai H. Extensive methylation of hMLH1 promoter region predominates in proximal colon cancer with microsatellite instability. Gastroenterology 2001;121:1300–1309.
19. Abe Y, Masuda H. Genetic alterations of sporadic colorectal cancer with microsatellite instability, especially characteristics of primary multiple colorectal cancers. J Surg Oncol 2000; 74:249–256.
20. Nicolaides NC, Papadopoulos N, Liu B, Wei YF, Carter KC, Ruben SM, Rosen CA, Haseltine WA, Fleischmann RD, Fraser CM, et al. Mutations of two PMS homologues in hereditary nonpolyposis colon cancer. Nature 1994;371:75–80.
21. Miyaki M, Konishi M, Tanaka K, Kikuchi-Yanoshita R, Muraoka M, Yasuno M, Igari T, Koike M, Chiba M, Mori T. Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. Nat Genet 1997;17:271–272.

Thymidylate Synthase Gene Polymorphism as a Prognostic Factor for Colon Cancer

Kwang Wook Suh, M.D., Joo Hyung Kim, M.D., Young Bae Kim, M.D., Jeongmi Kim, Ph.D., Soohyun Jeong, M.S.

The human thymidylate synthase (*TS*) gene promoter is polymorphic, having either double or triple tandem repeats of a 28–base-pair (bp) sequence. Here, we determined the significance of this polymorphism in predicting the clinical outcomes for patients with colon cancer. We reviewed 121 consecutive patients with stage II or III colon cancer who underwent a curative resection. After DNA extraction from paraffin-embedded tissues, the promoter region of the *TS* gene was amplified by polymerase chain reaction. In addition to the conventional prognostic factors, patient survivals were compared with regard to the pattern of TS polymorphism. Sixty-eight subjects were homozygotes for the triple-repeat variant (250 bp, group A), and 53 subjects (group B) were either homozygotes for the double-repeat variant (220 bp) or heterozygotes (220 and 250 bp). We found a significant difference between groups A and B in survival (53% versus 80%, $P = 0.0481$). The difference was particularly significant in the patients with stage III disease (41% versus 77%, $P = 0.0414$). Tumor stage and the TS polymorphism were identified as significant prognostic factors by multivariate analysis. We found the TS polymorphism to be a significant and independent prognostic factor for colon cancer. (J GASTROINTEST SURG 2005;9:336–342)

KEY WORDS: TS polymorphism, prognosis, colon cancer

Thymidylate synthase (TS) catalyzes the conversion of deoxyuridylate (dUMP) to deoxythymidylate (dTMP).[1] This conversion is essential for the provision of thymidine, a nucleotide needed for DNA synthesis and repair.[2] TS is also a target for major chemotherapeutic drugs, including 5-fluorouracil (5-FU). The substrate for TS, 5,10-methylene-tetrahydrofolate, is a central metabolite in folate metabolism and is diverted into different pathways, including thymidine synthesis, purine synthesis, and toward the provision of methyl groups for DNA methylation.[3]

Because TS plays a critical role in DNA synthesis, its clinical significance has been studied extensively in different tumor types.[4–6] In colon cancer, TS protein expression in the tumor tissues has been investigated as both a prognostic marker and a predictor of response to fluoropyrimidine-based therapies targeting TS.[4] However, the results from the literature regarding TS remain confusing. Among other factors responsible for the confusing results, the use of different techniques to quantify TS is an important factor. These include biochemical assays,[7] immunohistochemical stains,[8] and reverse transcriptase–polymerase chain reaction (PCR) technique to measure mRNA. [9] However, confirmatory studies are generally lacking.

The human *TS* gene is polymorphic with either double- or triple-tandem repeats of a 28-bp sequence downstream of the cap site in the 5′-terminal regulatory region.[10] In in vitro studies, the activity of a reporter gene linked to the 5′-terminal fragment of the *TS* gene with triple-tandem repeats was 2.6 times higher than that with double-tandem repeats.[11] Thus, this polymorphic region appears to be functional and may modulate *TS* gene expression.

In the present study, we hypothesized that by means of degree of polymorphism, *TS* genotypes may have a more solid correlation with treatment outcomes of colon cancer. Based on this hypothesis, we examined the prognostic relevancy of TS by measuring the degree of TS polymorphism in the colon cancer tissues.

From the Departments of Surgery (K.W.S., J.H.K.) and Pathology (Y.B.K.), Ajou University School of Medicine, Suwon, Korea; and PETAGEN Inc. (J.K., S.J.), Seoul, Korea.
Reprint requests: Kwang Wook Suh, M.D., Department of Surgery, Ajou University School of Medicine, Suwon 442-749, Korea. e-mail: suhkw@ajou.ac.kr

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.09.030

PATIENTS AND METHODS

Study Population

Among the patients with colon carcinoma who underwent curative surgery in Ajou University Hospital from June 1998 to July 2001, 121 consecutive patients with stage II or III were examined in this study. Operative treatment was performed by one surgeon (K.W.S). All patients were diagnosed as either stage II (T2 and 3N0 M0) or III (any TN1 and 2M0). Mean follow-up time was 38.6 months (range, 24–60 months). There was no follow-up loss, and all the paraffin blocks were in good condition. All the patients completed scheduled postoperative adjuvant chemotherapy; 54 patients with stage II disease completed 12-month oral 5-FU therapy (doxifluridine, 900 mg/day), and 84 patients with stage III disease underwent modified Mayo regimen (six cycles of continuous infusion of 5-FU 1000 mg/M^2) plus bolus injection of 30 mg of leucovorin for 5 consecutive days).[12] No other adjuvant treatments, such as radiotherapy or immunotherapy, were given. All patients signed an informed consent for evaluation of the TS polymorphism. Genotyping for the TS polymorphism was performed on paraffin-embedded tissues in all patients. Clinical outcome was analyzed by review of medical records and/or direct telephone calls. The recurrence was diagnosed by both clinical evidence and radiologic examination.

Patient Follow-up

Patients were followed after completion of their chemotherapy every 3 months for 2 years after initial operation and then on a 6-month basis. After 4 years, patients were seen annually. During their follow-up visits, patients underwent physical examination. Blood work was obtained to evaluate their complete blood cell count as well as to perform liver function tests and the carcinoembryonic antigen test. A chest radiograph was obtained every 6 months. A proctoscopic examination and barium enema or a flexible colonoscopy were performed at the 6- and 12-month visits and then at least every 24 months.

Analysis of *TS* Gene Polymorphism

All specimens were taken from paraffin-embedded tissues. Each paraffin block was sectioned into about 25 pieces before DNA extraction. A pathologist carefully examined the slides and identified the slide that contained the greatest amount of carcinoma cells. The carcinoma portion was taken out from the mounted section and was deparaffinized. DNA was extracted using the QiaAmp kit (QIAGEN, Valencia, CA), and the quality was adequate. The double-tandem repeat variant of the *TS* gene was designated as the *S* allele (S), whereas the triple repeat was designated as the *L* allele (L). The promoter region of the TS gene was amplified by PCR using the following primers: primer 1 (sense): 5′-GTGGCTCCTGCGTT TCCCCC-3′, and primer 2 (antisense): 5′-GCTC CGAGCCGGCCACAGGCATGGCGCGG-3′, as previously described.[10] Briefly, 25 ml reaction mixture containing 1.25 mmol/L $MgCl_2$ was transferred to a thermal cycler (PTC-100; MJ Research Laboratories, Watertown, MA) and amplified for 35 cycles. Each cycle consisted of 1 minute at 96°C, 30 seconds at 60°C, and 1 minute at 72°C with a final extension phase at 72°C for 5 minutes. The PCR product was analyzed by electrophoresis on a 4% agarose gel. Homozygotes for the triple-repeat variant (L/L) had 250-bp product, homozygotes for the double-repeat variant (S/S) had 220-bp product, and heterozygotes (S/L) had 220- and 250-bp products (Fig. 1).

Statistical Analysis

The χ^2 and Student *t* tests were used for comparison of patient characteristics between groups.[13] Survival curves were generated using the Kaplan-Meier method.[14] Survival was calculated from the date of surgical treatment to the date of death (any cause) or date last seen. The log-rank statistic was used to compare survival distributions.[15] Cox's proportional hazard model was used for multivariate analysis.[13] In the multivariate analysis, we chose five possible prognostic variables including TS polymorphism.

RESULTS

TS Genotypes

We found that among 121 patients with colorectal cancer analyzed for TS polymorphism, 68 (56.2%) were homozygous for the triple repeat (L/L, group A), 53 (43.8%) were either heterozygous (L/S, n = 3) or homozygous (S/S, n = 50), group B, for the double-repeat variant within the human TS promoter region. There was no demographic difference between the two groups (Table 1).

Relationship Between *TS* Genotypes and Clinical Outcome

The relationship between *TS* genotype and the clinical outcome was assessed by analysis of patient survival. Before analyzing the relationship, overall survivals of 121 patients according to pathologic stages were examined. A significant difference between stage II and stage III patients was observed with regard to the 5-year actuarial survival (87% versus 63%,

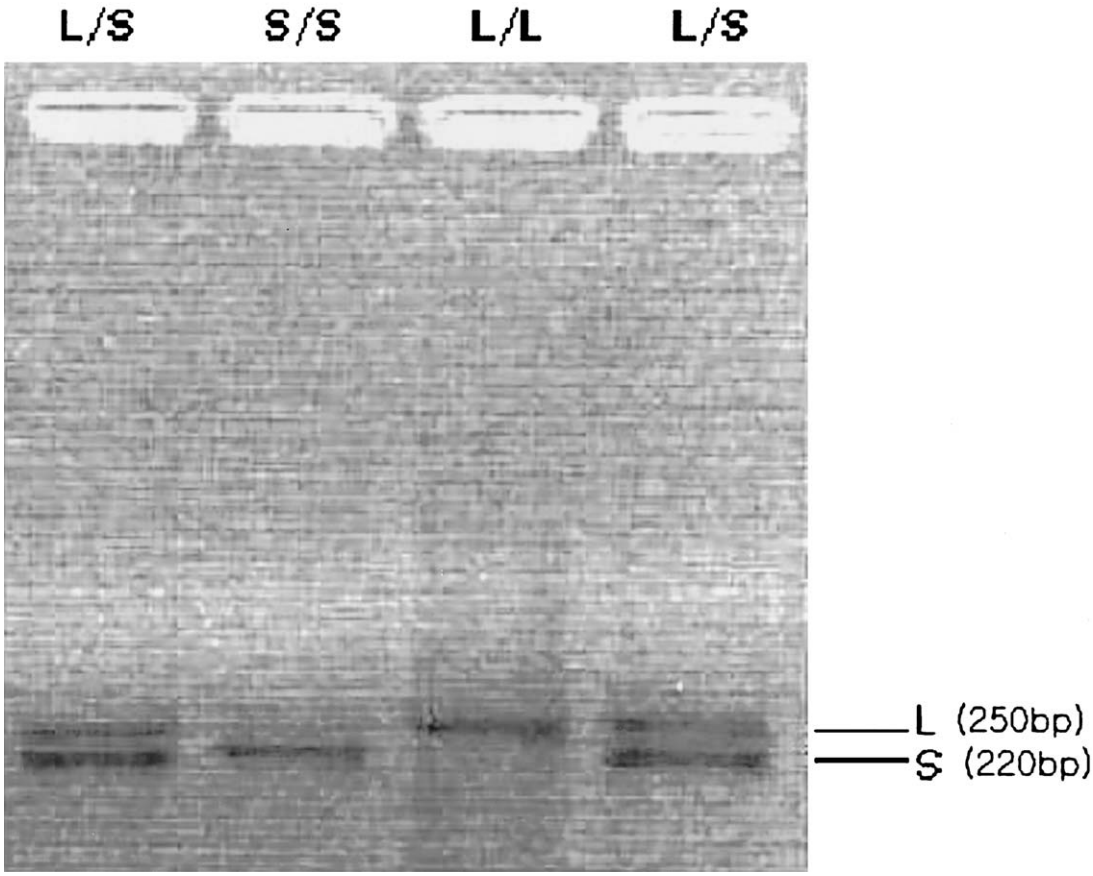

Fig. 1. Gel electrophoresis of polymorphism within TS promoter gene. There were three discrete patterns of polymorphism: homozygous for triple-repeat variants (250 bp, L/L), homozygous for the double-repeat variant (220 bp, S/S), and heterozygous of double- and triple-repeat variants (L/S).

$P = 0.0320$; Fig. 2). When we analyzed the survival according to the TS polymorphism, there was also a significant difference between group A and B (53% versus 80%, $P = 0.0481$; Fig. 3). In patients with the stage II disease, difference in survival rates between group A and B did not reach a statistical significance (43% versus 86%, $P = 0.1678$; Fig. 4). However, the difference was significant in the patients with stage III disease (41% versus 77%, $P = 0.0414$; Fig. 5).

Age, gender, pathologic stage, tumor differentiation, and TS polymorphism were analyzed by multivariate analysis. Tumor stage and the TS polymorphism were identified as significant prognostic factors (Table 2).

DISCUSSION

Despite the recent development of diagnosis and early treatment of colon cancer, the need for better tools to predict outcome and response to treatment is well recognized. In colorectal cancer, numbers of subcellular markers have been investigated as prognostic factors in addition to the conventional pathologic staging.[16] TS has been regarded as one of the most promising prognostic factors and has been investigated extensively for the last decade.

The first clinical investigation suggesting the importance of TS as a prognostic factor for the advanced colorectal cancer was performed by Johnston et al.[5] Using a monoclonal antibody (TS 106), they found the inverse relationship between TS expression and clinical outcomes; that is, the patients with a higher level of TS expression had a worse prognosis. However, the literature regarding TS has shown controversial results. Most studies using monoclonal antibodies have reported high TS level as a unfavorable prognostic marker. On the other hand, the studies by Tomiak et al.,[17] the largest study group using TS 106, and by van Triest et al.,[18] using polyclonal antibody, observed no difference between high-TS and low-TS groups. Moreover, Sanguedolce et al.[19] found a worse prognosis in the low-TS group through

Table 1. Comparison between groups

	All eligible patients (N = 121)	Group A (n = 63)	Group B (N = 53)	*P* value*
Mean age (yr)	63.0	62.8	64.9	0.422
Gender				
Male	70	40	30	0.355
Female	51	28	23	
Stage				
II	49	24	25	0.866
III	72	44	28	
No. of positive lymph nodes				
0	49	24	25	0.428
1–3	38	29	9	
>3	34	15	19	

Group A = patients with homozygous for triple repeat; group B = patients with either heterozygous for double and triple repeat or homozygous for double repeat.
*Student's *t* test.

the biochemical assay of TS. We were motivated by these controversial results to design a study to produce a more solid result. To achieve the fair comparison, we selected the patients who underwent curative resection by the single surgeon and received the same regimen of chemotherapy. We thought DNA analysis of a certain gene provides more solid, objective, and reproducible results than protein assay, and the technique of DNA study is even simpler.

It has been reported that TS protein expression in gastrointestinal cancer is associated with this TS polymorphism in the 5′-untranslated region.[10] It is also suggested that this TS polymorphism may be a significant predictor of *TS* gene and protein expression.[9,20] Recently, the measurement of intratumoral TS mRNA expression has been established as a predictor of response and survival to 5-FU chemotherapy.[20] It has been shown that low expression levels of TS mRNA were associated with a higher probability of response to 5-FU–based treatment and longer survival. Examination of mRNA is an important step to probe any subcellular mechanism. However, it may complicate the methodology and subsequent results. Pullarkat et al.[20] reported that higher intratumoral TS mRNA expression was observed with an increasing number of the 28-bp tandem repeats. We obviated the mRNA assay and designed a study to compare the status of 28-bp tandem repeats directly with clinical outcomes.

Regulation of intratumoral TS expression is not very well understood. Recent studies have demonstrated that mutant *p53* is associated with higher TS protein and gene expression.[21,22] It is extremely important whether intratumoral polymorphism is associated with germline polymorphism or not. If so, we

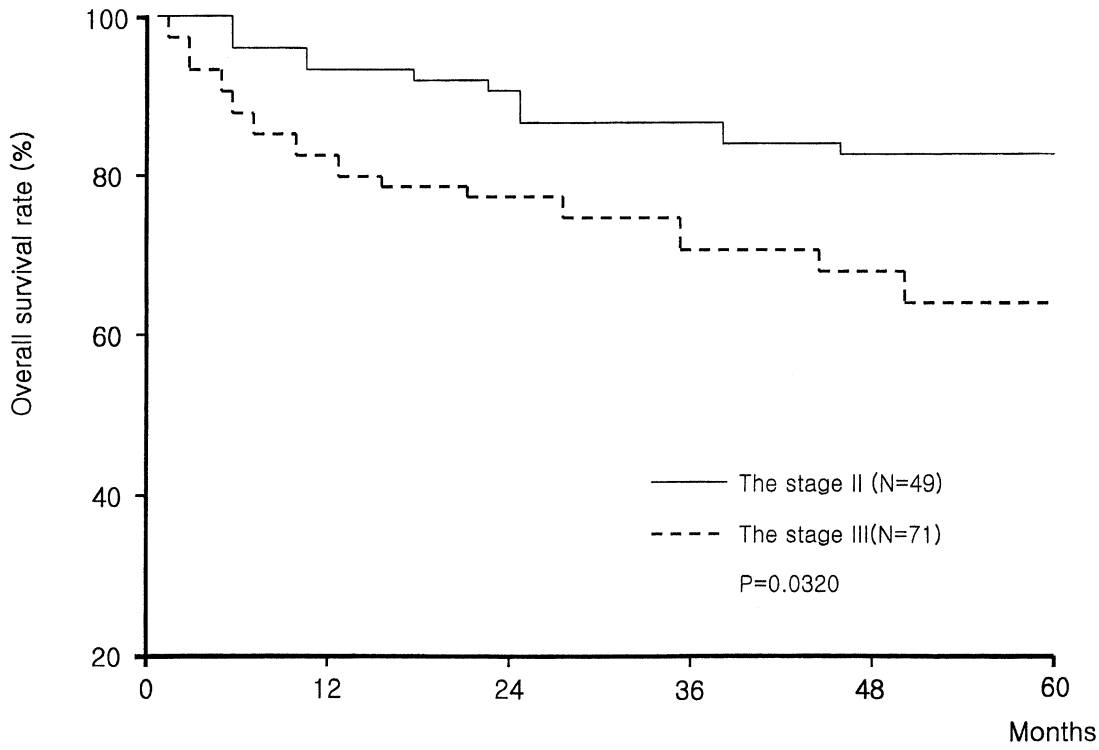

Fig. 2. Overall survival rates according to the pathologic stage.

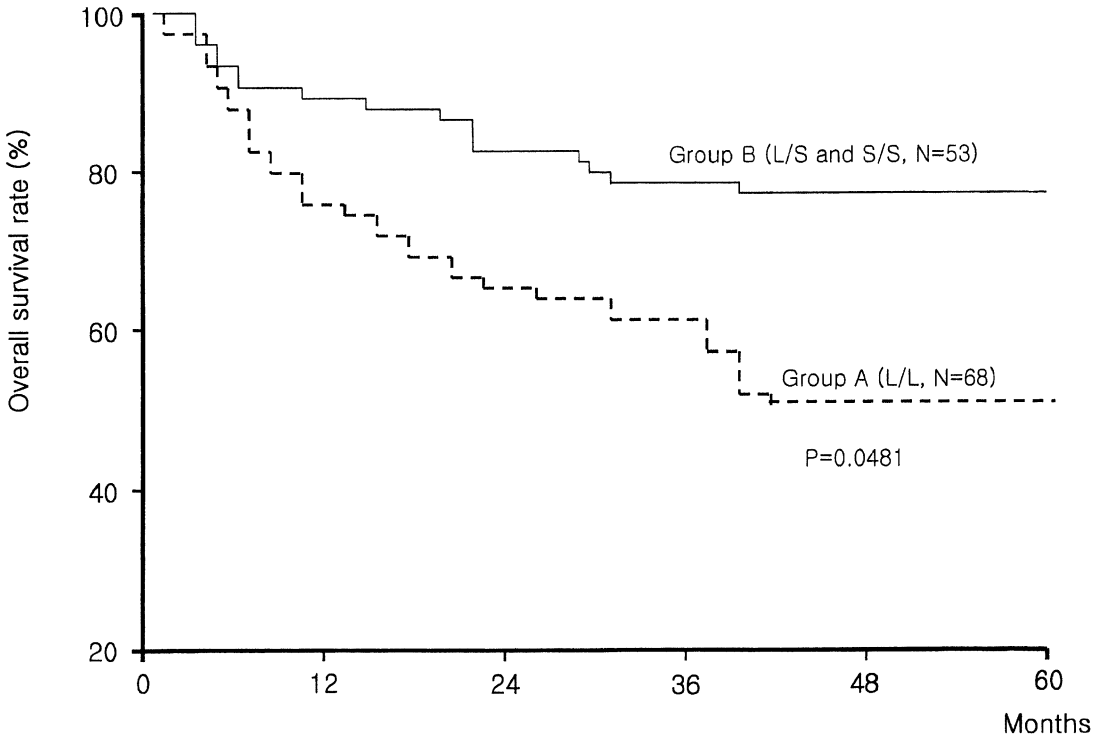

Fig. 3. Overall survival rates according to the TS polymorphism.

do not have to retrieve specimens from paraffin-embedded tissues, just from a small amount of peripheral blood. Obtaining blood samples may simplify the whole procedure of TS analysis and the prognosis will be expected even before surgery. Pullarkat et al.[20] also examined the TS polymorphism from adjacent

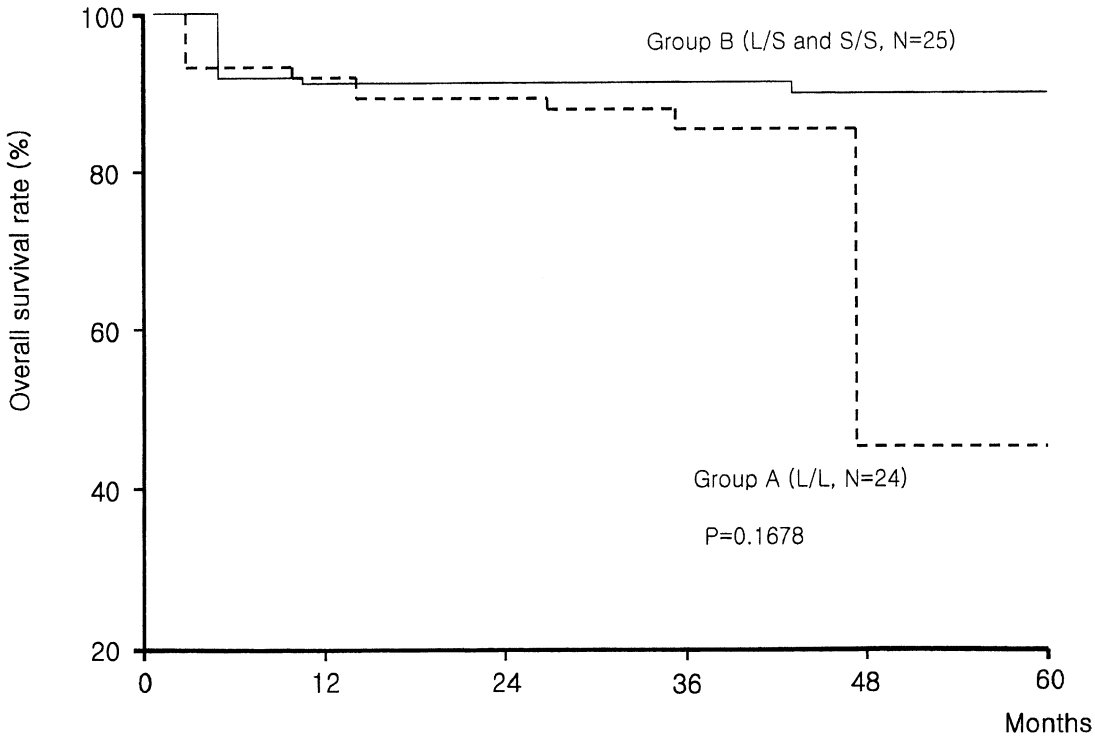

Fig. 4. Survival rates of stage II patients according to the TS polymorphism (n = 49).

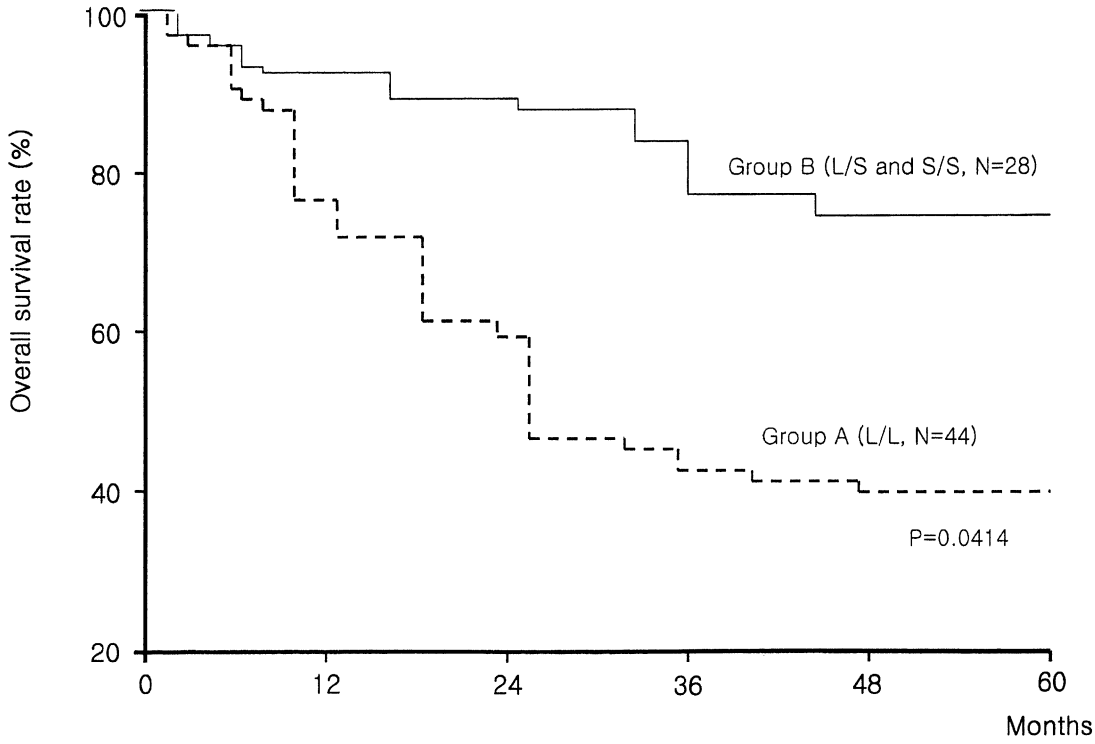

Fig. 5. Survival rates of stage III patients according to the TS polymorphism (n = 71).

normal tissues. Comparing the TS mRNA expression in metastasized tumor tissue and in adjacent normal liver tissue, they found significant higher TS levels in the tumor. They concluded that the increased expression of TS mRNA in tumor tissue may be due to a transcriptional or post-transcriptional process during carcinogenesis. However, in the adjacent normal tissues, TS polymorphism was found to be related to higher TS mRNA, so the possibility of germline polymorphism remains.

Recently, the molecular mechanism by which the tandem-repeat polymorphism enhances transcription has been studied. Mandola et al.[23] identified new proteins, USF-1 and -2, that bind within the tandem-repeat polymorphism of TS 5′-regulatory region. They also found a novel single-nucleotide polymorphism (G→C) within the tandem repeats that determines the binding and transactivating ability of USF complex. In a population-based experiment, this novel single-nucleotide polymorphism was commonly found in non-Hispanic whites, Hispanic whites, African Americans, and Singapore Chinese. We think the study regarding this single-nucleotide polymorphism should be conducted for the East Asian population, such as the Koreans and Japanese.

Recent studies have shown TS polymorphism to vary among world populations.[24] Reportedly, triple-tandem repeat (L/L) is significantly higher in Asian populations compared with other ethnic groups. In the present study, we found 56.2% to be L/L type, which is a much higher proportion than those from Western populations. Due to the small number of study population, our results are not confirmative as to ethnic variations of TS polymorphism. If the L/L type of TS polymorphism is genetically predominant in Asian populations, the overall prognosis would be worse than in Western populations. Larger prospective clinical studies are necessary to validate our data from this retrospective pilot study.

In conclusion, we found the TS polymorphism a significant prognostic factor for patients with stage II and III colon cancer. Patients with homozygous for the triple repeat had a worse prognosis than those with heterozygous or homozygous for the double-repeat variant. We think triple-tandem repeat of a

Table 2. Multivariate analysis of prognostic factors

Prognostic factors	RR	95% CI	*P* value
TS polymorphism (L/L, L/S, and S/S)	2.73	0.68–4.43	<0.001
Gender (male, female)	0.42	0.21–0.80	0.015
Stage (II, III)	3.88	1.45–5.52	<0.001
Tumor differentiation (well, moderately, or poor)	0.65	0.42–0.99	0.048
Age (<60, ⩾60 yr)	0.62	0.42–0.92	0.017

RR = relative risk; CI = confidence interval.

28-bp sequence may produce a higher level of TS protein in the tumor tissue. Larger prospective clinical studies are necessary to validate our data from this retrospective pilot study.

REFERENCES

1. Heidelberger C, Chaudhuri NK, Danneberg P, et al. Fluorinated pyrimidines: A new class of tumor inhibitory compounds. Nature 1957;179:663–666.
2. Danneberg P. Thymidylate synthase-alpha target enzyme in cancer chemotherapy. Biochem Biophys Acta 1977;473: 73–92.
3. Pinedo HM, Peters GF. Fluorouracil: Biochemistry and pharmacology. J Clin Oncol 1988;6:1653–1664.
4. Edler D, Hallstrom M, Johnston PG, Magnusson I, Ragnhammar P, Blomgren H. Thymidylate synthase expression: An independent prognostic factor for local recurrence, distant metastasis, disease-free and overall survival in rectal cancer. Clin Cancer Res 2000;6:488–492.
5. Johnston PG, Lenz HJ, Leichman CG, et al. Thymidylate synthase gene and protein expression correlate and are associated with response to 5-fluorouracil in human colorectal and gastric tumors. Cancer Res 1995;55:1407–1412.
6. Ogura O, Kanzaki A, Bando H, Ogura T, Toi M, Takebayashi Y. Expression of thymidylate synthase and thymidine phosphorylase in human breast carcinoma: Implication for method to detect expression of these molecules in clinic. Cancer Lett 2003;190:97–104.
7. Etienne MC, Chazal M, Laurent-Puig P, et al. Prognostic value of tumoral thymidylate synthase and p53 in metastatic colorectal cancer patients receiving fluorouracil-based chemotherapy: Phenotypic and genotypic analyses. J Clin Oncol 2002;20:2832–2843.
8. Yamachika T, Nakanishi H, Inada K, et al. A new prognostic factor for colorectal carcinoma, thymidylate synthase, and its therapeutic significance. Cancer 1998;82:70–77.
9. Leichman CG, Lenz HJ, Leichman L, et al. Quantitation of intratumoral thymidylate synthase expression predicts for disseminated colorectal cancer response and resistance to protracted-infusion fluorouracil and weekly leucovorin. J Clin Oncol 1997;15:3223–3229.
10. Horie N, Aiba H, Oguro K, Hojo H, Takeishi K. Functional analysis and DNA polymorphism of the tandemly repeated sequences in the 5′-terminal regulatory region of the human gene for thymidylate synthase. Cell Struct Funct 1995;20: 191–197.
11. Horie N, Chimoto M, Nozawa R, Takeishi K. Characterization of regulatory sequences and nuclear factors that function in cooperation with the promoter of the human thymidylate synthase gene. Biochim Biophys Acta 1993;1216:409–416.
12. Buroker TR, O'Connell MJ, Wieand HS, et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. J Clin Oncol 1994;12:14–20.
13. Zar JH. Biostatistical Analysis. Prentice-Hall: Englewood Cliffs, 1984.
14. Kaplan EL, Meier P. Nonparametric estimation for incomplete observations. J Am Stat Assoc 1958;53:457–481.
15. Pike MC. Contribution to the discussion on the paper by R Peto and J Peto, 'Asymmetrically efficient rank invariant procedures.' J R Stat Soc 1972;135:201–203.
16. Watanabe T, Wu TT, Catalano PJ, et al. Molecular predictors of survival after adjuvant chemotherapy for colon cancer. N Engl J Med 2001;344:1196–1206.
17. Tomiak A, Vincent M, Earle CC, et al. Thymidylate synthase expression in stage II and III colon cancer: A retrospective review. Am J Clin Oncol 2001;24:597–602.
18. van Triest B, Pinedo HM, Blaauwgeers JL, et al. Prognostic role of thymidylate synthase, thymidine phosphorylase/ platelet-derived endothelial cell growth factor, and proliferation markers in colorectal cancer. Clin Cancer Res 2000;6: 1063–1072.
19. Sanguedolce R, Vultaggio G, Sanguedolce F, et al. The role of thymidylate synthase levels in the prognosis and the treatment of patients with colorectal cancer. Anticancer Res 1998;18:1515–1520.
20. Pullarkat ST, Stoehlmacher J, Ghaderi V, et al. Thymidylate synthase gene polymorphism determines response and toxicity of 5-FU chemotherapy. Pharmacogenomics J 2001;1: 65–70.
21. Lenz HJ, Hayashi K, Salonga D, et al. p53 point mutations and thymidylate synthase messenger RNA levels in disseminated colorectal cancer: An analysis of response and survival. Clin Cancer Res 1998;4:1243–1250.
22. Lenz HJ, Danenberg KD, Leichman CG, et al. p53 and thymidylate synthase expression in untreated stage II colon cancer: Associations with recurrence, survival, and site. Clin Cancer Res 1998;4:1227–1234.
23. Mandola MV, Stoehlmacher J, Muller-Weeks S, et al. A novel single nucleotide polymorphism within the 5′ tandem repeat polymorphism of the thymidylate synthase gene abolishes USF-1 binding and alters transcriptional activity. Cancer Res 2003;63:2898–2904.
24. Marsh S, McLeod HL. Thymidylate synthase pharmacogenetics in colorectal cancer. Clin Colorectal Cancer 2001;1: 175–178.

Embolization as First-Line Therapy for Diverticulosis-Related Massive Lower Gastrointestinal Bleeding: Evidence From a Meta-analysis

Amit Khanna, M.D., M.P.H., Steven J. Ognibene, M.D., Leonidas G. Koniaris, M.D.

The study goal was to determine which etiologies of lower gastrointestinal bleeding (LGIB) may best be treated with superselective embolization. A meta-analysis was undertaken of 25 identified publications reporting the use of embolization and an unpublished series of 12 consecutive patients with LGIB from the authors' institution. Six published series and the authors' series met selection criteria for further analysis. Multiple regression analysis demonstrated no significant difference in pooled outcomes when varying the included study, age, or embolization method on the outcome of rebleeding. The pooled odds ratio for arteriovenous dysplastic lesions and other diseases was 3.53 compared with rebleeding after localization and embolization for diverticular disease (95% confidence interval odds ratio, 1.33, 9.41; $P < 0.01$]. Embolization for diverticular bleeding was successful in 85% of patients. In contrast, rebleeding after embolization for nondiverticular bleeding occurred in greater than 40% of patients and over a more protracted period. Embolization for LGIB is most effective for the treatment of diverticular bleeding. Caution should be used when applying embolization therapy for nondiverticular causes due to the considerably higher associated failure rate. An inpatient observation period of 2 days is suggested following embolization for diverticular bleeding. (J GASTROINTEST SURG 2005;9:343–352)

KEY WORDS: Diverticulosis, colon, arteriovenous abnormality, lower gastrointestinal bleeding

Massive lower gastrointestinal bleeding (LGIB) as defined as the requirement of greater than 6 units of packed red blood cells within a 24-hour period presents a diagnostic and therapeutic challenge. LGIB has an estimated annual incidence rate of 20.4 per 100,000, with an overall mortality rate of about 10%.[1] In the majority of patients, the causes of LGIB are either erosion of a vessel into a colonic diverticulum or an arteriovenous dysplastic lesion (AVD). Less common etiologies of LGIB include inflammatory bowel disease, neoplasia, colitis, postprocedural complications, rectal trauma, and solitary rectal ulcer.[2] Localization of the bleeding source is difficult, largely due to the intermittent nature of the hemorrhage. Multiple procedures over many days may be required to diagnose the site of bleeding, and failure rates are as high as 20% are encountered even in specialized centers with high-volume admissions of LGIB.[3]

Once localization of bleeding is accomplished, segmental colectomy or subtotal colectomy has been the standard therapy for both benign and malignant causes of massive or chronic LGIB, even though such procedures are associated with a 4- to 6-week convalescence period and substantial rates of severe morbidity and mortality.[4,5] Increasingly, however, superselective angiographic embolization is being used to treat LGIB from benign sources.[6–29] To date, the body of literature of superselective embolization for LGIB has been composed of small retrospective institutional case series. Here, we report an analysis of individual case level data of both unpublished series from our institution and the published experience, with the purpose of providing a more rigorous evaluation of its overall efficacy and to further define indications for superselective embolization in the treatment of LGIB. We present a systematic review of the published literature using the techniques of meta-analysis to determine the pooled odds of rebleeding within 30 days in diverticular versus nondiverticular sources of massive LGIB.

From the Department of Surgery (A.K., S.J.O.), University of Rochester School of Medicine, Rochester, New York; and The Dewitt Daughtry Family Department of Surgery (L.G.K.), University of Miami School of Medicine, Miami, Florida.
Reprint requests: Leonidas G. Koniaris, M.D., F.A.C.S., The Alan Livingstone Chair in Surgical Oncology, 3550 Sylvester Comprehensive Cancer Center (310T), 1475 NW 12th Avenue, Miami, FL 33136. e-mail: LKoniaris@med.miami.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.09.039

MATERIAL AND METHODS

Institutional Series

All patients at the Strong Memorial Hospital (Rochester, NY) undergoing attempted embolization for lower gastrointestinal (GI) hemorrhage from November 1999 through December 2001 were retrospectively reviewed. Institutional review board approval and human subject training was completed.

Literature Review

The Ovid (Ovid Technologies, New York, NY) and MEDLINE search engines were used to examine both PubMed and The Cochrane Library. The following phrases were used for the search: *embolization*, *angiography directed*, *catheter directed embolization*, *selective embolization*, *super-selective angiography*, *LGIB*, and *interventional management of LGIB*. The bibliographies of the identified papers were examined to identify any additional trials. Finally, academic surgeons in Rochester, NY, were queried for other trials that may have been omitted.

Inclusion and Exclusion Criteria

All case series of patients presenting with massive LGIB (>6 units packed red blood cells in 24 hours or transfusion-dependent hypotension with a systolic blood pressure <90 mm Hg) treated with both angiography and attempted embolization were evaluated for subsequent analysis. Case series for further evaluation were limited to those reports where 10 or more patients were included and greater than 6 units of blood was required to replace that lost on bleeding or transfusion-dependent hypotension was noted. Each study was then independently evaluated by two reviewers for data quality and to determine whether individual case data could be extracted from the manuscript. Individual case data extracted included: age (age >60 versus <60 years), disease process (AVD and other versus diverticulosis), rebleeding within 30 days of treatment, type of embolic agents used (microcoil use versus no microcoil use), repeat operation, postembolization ischemia, and duration of follow-up. Individual patients were excluded from further analysis if either a malignancy was identified as the etiology of bleeding before attempted embolization or vasopressin without vessel embolization was attempted. If multiple sites of bleeding were embolized and rebleeding occurred, it was assumed to be from the LGIB source. Twelve articles were identified for further analysis and reviewed for data quality and extractability. Of these 12 studies, 6 studies were excluded due to an inability to extract individual patient outcomes, leaving a total of 6 series (plus our unpublished series) that fulfilled selection criteria (Fig. 1).

Data Extraction

Two reviewers blinded to journal, authors, and publication dates performed independent extraction

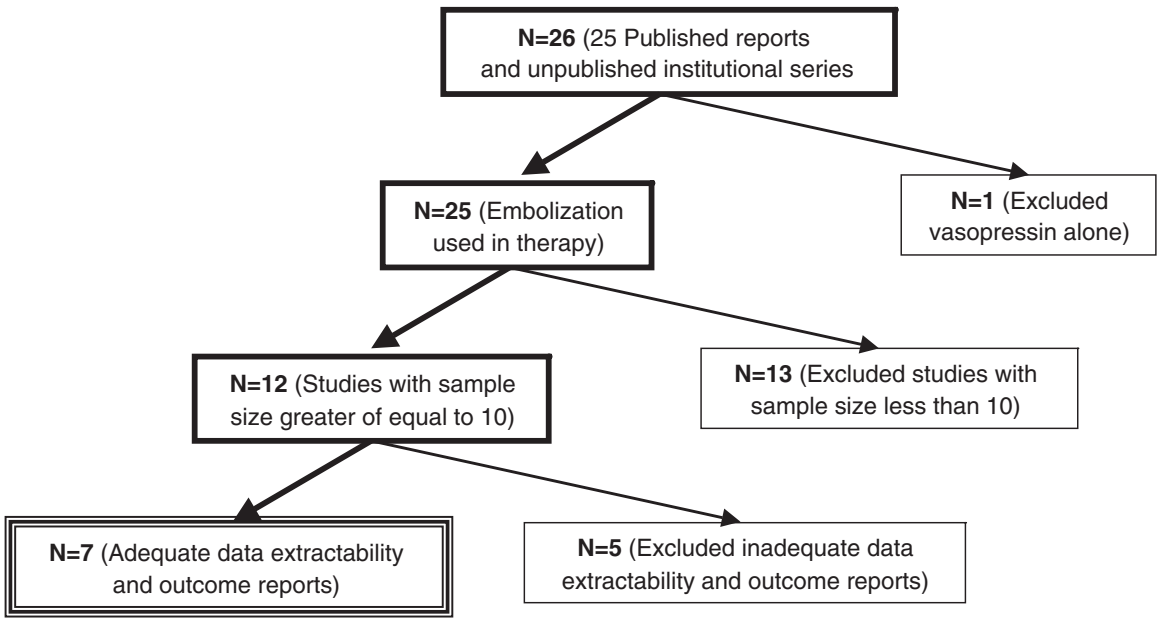

Fig. 1. Study flow and selection criteria. Twenty-five studies were identified in the published literature after systematic search. An additional unpublished series was also identified. One study was excluded on the basis of use of vasopressin alone, 13 studies were excluded due to lack of sample size, and an additional 7 studies were excluded based on inadequate individual data reporting. A total of seven studies fulfilled selection criteria for analysis (six published and one unpublished series).

and assessment of study quality. Discrepancies were resolved by consensus after discussion.

Statistical Analyses

Based on a priori criteria, the primary comparison was rebleeding rate at 30 days after successful embolization in patients with diverticulosis-related bleeding versus AVD-related and other causes of LGIB, which included ulcers of the lower GI tract and postprocedure bleeding. Studies were assessed for homogeneity, both qualitatively and quantitatively. Given that the studies were nonrandomized trials, interstudy and intrastudy heterogeneity was anticipated. Therefore, both fixed- and random-effects models were used to evaluate the dichotomous outcomes (rebleeding within 30 days versus no rebleeding within 30 days) of the pooled studies. Multiple logistic regression analysis was first applied to explore heterogeneity present in the pooled analysis by evaluating potential covariates that were predictive of rebleeding within 30 days of embolization (SAS; SAS Institute Inc., Cary, NC), using combined data from the selected studies. The procedure PROC LOGISTIC (SAS Institute Inc.) was used. The examined covariates included individual study (to determine interstudy correlation), age (>60 versus <60 years), type of embolic agents employed (microcoil use or not), and disease process (AVD and other causes versus diverticulosis). Odds ratios were calculated as the summary measures of effect for each study and the pooled analysis.

Meta-analysis using a random-effects model was first conducted on the data set to estimate the effect of disease process on the outcome of rebleeding within 30 days of embolization given the anticipated heterogeneity present in the pooled analysis. A fixed-effects model was also used to evaluate the robustness of the pooled analysis. For each included study, the odds ratio estimate and its standard error were calculated. A pooled odds ratio estimate was then calculated by combining individual odds ratios using the inverse variance-weighted method (Rev Man 4.2 or Metaview statistical package).[30] Sensitivity analyses were performed in jackknife fashion by serially omitting each study and analyzing its effect on the summary statistic. A funnel plot was also constructed to determine the influence of possible publication bias.

RESULTS

Unpublished Series

All patients at the Strong Memorial Hospital (Rochester, NY) undergoing attempted embolization for lower GI hemorrhage from November 1999 through December 2001 were retrospectively reviewed. Twelve patients (6 men and 6 women; age range, 38-81 years; average age, 67 years) were studied. Causes of bleeding were diverticular bleeding (n = 6), rectal ulcer (n = 2), cecal ulcer (n = 1), jejunal ulcer (n = 1), and postpolypectomy bleeding (n = 1). The average follow-up period was 5.4 months.

In this patient series, angiographic localization and superselective embolization of bleeding resulted in immediate control and cessation of hemorrhage in 11 of 12 patients (92%). In one patient, embolization was unsuccessful and emergent sigmoid resection was required for continued diverticular bleeding. In four patients with various underlying pathologies, there was short-term success only; these patients re-bled and three (75%) eventually required surgery. The fourth patient underwent a second embolization with good result. Long-term success was defined as the absence of surgical intervention for at least 30 days. No recurrent bleeders after 30 days were identified in this cohort. In this series, 7 of 12 patients achieved greater than 1-year median follow-up without evidence of rebleeding. Of note, no clinically significant instances of postembolization ischemia occurred. In addition, no postprocedural instances of acute renal failure were observed. Table 1 summarizes this institutional experience.

Published Series

A systematic review of the literature was undertaken to identify the published experience using embolization in the treatment of LGIB as described in Material and Methods. Overall, 25 studies published from 1977 to 2002 were identified.[4–29] These are summarized in Table 2. The mean patient number in these series was 12, with a range of 2–35. The median rebleeding rate for LGIB at 30 days postembolization was 14%, with a range from 0% to 75%. The most commonly observed complications after rebleeding were intestinal ischemia, in a reported range from 0% to 33%, and reoperation, with a reported range from 0% to 50%. The time to rebleeding after successful embolization varied widely across studies, with a range of 1–300 days postembolization. In reviewing case series after 1980, the average number of days to rebleeding was 4.0 ± 6.1, with 75% of rebleeding occurring within 3.5 days of successful localization and embolization.

Tests for heterogeneity of the pooled analysis were significant ($P < 0.01$) and therefore the following covariates were examined using multiple regression: age, use of microcoils, and disease type on the remaining six studies. No significant difference was

Table 1. Unpublished institutional series showing outcomes of superselective embolization for lower gastrointestinal bleeding

Patient age/gender	Past medical history	Disease	Site	Microcoils used	Rebleeding within 30 days	Type of resection	Follow-up
54/M	Patient anticoagulated	Cecal ulcer	Right colon	Yes	No		6 mo
76/F	Patient anticoagulated	Rectal ulcer	Rectal	Yes	No		9 mo
65/M	No	Diverticulosis	Right colon	No	Yes (9 days later)	Segmental R	Surgery 9 days later
72/M	Patient anticoagulated	Cecum, postpolypectomy bleeding	Right colon	Yes	Yes (3 days)	Segmental R	Surgery 3 days later
61/M	Renal disease	Jejunum	Jejunal	Yes	Yes		3 mo, reembolized
66/F	No	Rectum	Rectal	Yes	No		4 mo
53/F	No	Rectal ulcer	Rectal	No	Yes (10 days later)	Unknown	Surgery 2 wk later
81/F	No	Diverticulosis	Left colon	No	Yes (within 1 day)	Segmental sigmoid	Surgery
81/F	Patient anticoagulated	Diverticulosis	Left colon	Yes	No		8 mo
77/M	No	Diverticulosis	Right colon	Yes	No		6 mo
77/F	No	Diverticulosis	Left colon	Yes	No		NA
38/M	No	Diverticulosis	Right colon	Yes	No		2 mo

identified when varying either age or embolization technique on the outcome of rebleeding. Disease type was significant ($P < 0.01$), predicting rebleeding rates at 30 days postembolization (Table 3).

The primary outcome variable rebleeding at 30 days postembolization for AVD and other diseases was evaluated using a random-effects model. This yielded a pooled odds ratio for rebleeding at 30 days after successful localization and embolization for AVDs and other diseases of 3.53 (95% confidence interval, 1.33–9.41; $P < 0.01$) compared with bleeding due to diverticular disease. When using the fixed-effects model, the pooled odds ratio was calculated on six available studies and yielded a pooled odds ratio of 3.52 (95% confidence interval, 1.35–9.16; $P < 0.01$], suggesting an absolute risk reduction of 62% for diverticulosis-associated bleeding (Fig. 2).

Sensitivity Analyses

Further analyses of the trials by serially omitting each trial did not substantially alter the summary statistic. Each study was analyzed against the study by Uflacker et al.[23] to determine if any one study influenced the data significantly. No individual study when compared to the reference study by Uflacker et al.[23] achieved significance. In addition, employing study used as a covariate in the regression model also failed to achieve significance (Table 3).

In addition, pooled analysis of the seven studies using a fixed-effects model did not differ significantly in outcome compared with the random-effects model (Fig. 3). A funnel plot was next constructed with the pooled data to examine for possible publication bias (Fig. 4). The plot failed to reveal major asymmetry, but publication bias cannot be ruled out completely from this test alone.

Time to Rebleeding

Given the dramatic difference between diverticular and nondiverticular sources of bleeding based on the meta-analysis, we next compared the time to rebleeding. Using Kaplan-Meier statistics, time-to-rebleeding plots were generated using the available data from the six included studies and our own case series. As shown (Fig. 5), an overall failure rate of approximately 15% was noted for diverticular bleeding compared with an overall failure rate approaching 45% for the non–diverticular-cause group. Of note, failures in the diverticular group also appeared to occur earlier, with infrequent failures being noted after 2 days. In contrast, a high failure rate persisted in the nondiverticular group even at 5 days after successful embolization.

DISCUSSION

LGIB accounts for a substantial number of hospital admissions to both medical and surgical services. In

Table 2. Review results for angiographic selective embolization for lower gastrointestinal bleeding (LGIB) series (1977–2003)

Authors	Year	Sample size (n)	Success rate (%)*	Rebleed rate (%)	Days to rebleed	Ischemia rate (%)	Reoperation rate (%)
Khanna et al. (present study)	2003	12	66	33	5.8 ± 4.4 (1, 3, 9, 10)	0	25
DeBarros et al.[6]	2002	27	81	22	NA	7	22
Patel et al.[7]	2001	10	80	20	<7	0	10
Bandi et al.[8]	2001	35	60	34	NA	24	26
Defreyne et al.[9]	2001	10	91	27	NA	0	27
Funaki et al.[10]	2001	27	89	19	1.7 ± 0.9 (1, 1, 1, 2, 3)	15	11
Evangelista and Hallisey[11]	2000	17	76	13	8.6 ± 14.2 (1, 25)	5	18
Luchtefeld et al.[12]	2000	17	82	6	NA	6	12
Dobson and Nicholson[13]	1999	4	75	0	0	0	25
Ledermann et al.[14]	1999	5	100	0	NA	0	0
Ledermann et al[15]	1998	7	86	14	1	0	14
Nicholson et al.[16]	1999	14	86	14	1.0 (1, 1)	21	14
Peck et al.[17]	1998	21	48	33	2.1 ± 2.1 (0, 1, 1, 1, 2, 4, 6)	0	24
Skulski et al.[18]	1998	20	90	10	3, NA	5	5
Gordon et al[19]	1997	14	93	14	5.5 ± 6.4 (1, 10)	0	7
Encarnacion et al[20]	1992	6	NA	NA	NA	NA	NA
Guy et al.[21]	1992	9	78	33	9.0 ± 13.0 (1, 2, 24)	33	22
Okazaki et al.[22]	1992	6	100	0	0	0	0
Leitman et al.[5]*	1989	14	36	NA	NA	7	38
Uflacker et al.[23]	1987	13	80	20	0.5 ± 0.7 (0,1)	15	23
Gomes et al.[24]*	1986	3	100	0	0	0	0
Palmaz et al.[25]	1984	6	100	0	0	0	0
Chuang et al.[26,†]	1979	5	75	75	NA	0	25
Matolo et al.[27]	1979	4	100	0	0	0	0
Bookstein et al.[28]*	1978	7	100	43	170 ± 114 (90, 120, 300)	0	43
Goldberger and Bookstein[29]	1977	2	100	50	300	0	50

Successful embolization defined as no evidence of rebleeding at 30 days.
*Used vasopressin in therapy of LGIB in combination with embolization.
†Malignancy identified as cause of LGIB.

a large proportion of patients, with conservative management LGIB will cease spontaneously, especially in patients with diverticular bleeding.[1,31,32] Medical or surgical interventions are needed to control bleeding in only a small subset of massive LGIB patients. Many of the patients in this subset are hemodynamically unstable or are transfusion dependent. For those in this minority, overall mortality even at outstanding tertiary medical centers may exceed 15–20%.[6] Moreover, among those patients who undergo semiurgent surgical intervention, mortality rates of 20–50% have been noted.[3]

Given the high morbidity and mortality that may be associated with urgent surgery for LGIB, less invasive options for patients with ongoing LGIB have been developed and include therapeutic colonoscopy with coagulation and embolization. Colonoscopy in the setting of active massive LGIB has been limited, because the hemorrhage frequently may obscure the bleeding point. Nonetheless, it can benefit those patients in whom bleeding has stopped spontaneously and can be prepped appropriately.[33] It remains particularly useful in the setting of malignant disease, rectal pathology, new inpatient GI bleeding, and certain

Table 3. Multiple regression analysis of pooled data

Covariate	*df*	χ^2 Test	*P* value	Odds ratio estimate	Confidence interval
Age	1	1.5285	0.2163	3.763	0.460–30.755
Disease	1	6.6523	0.0099	6.842	1.587–29.503
Microcoils	1	1.1074	0.2926	2.505	0.453–13.847
Study	3	0.652	0.8844		

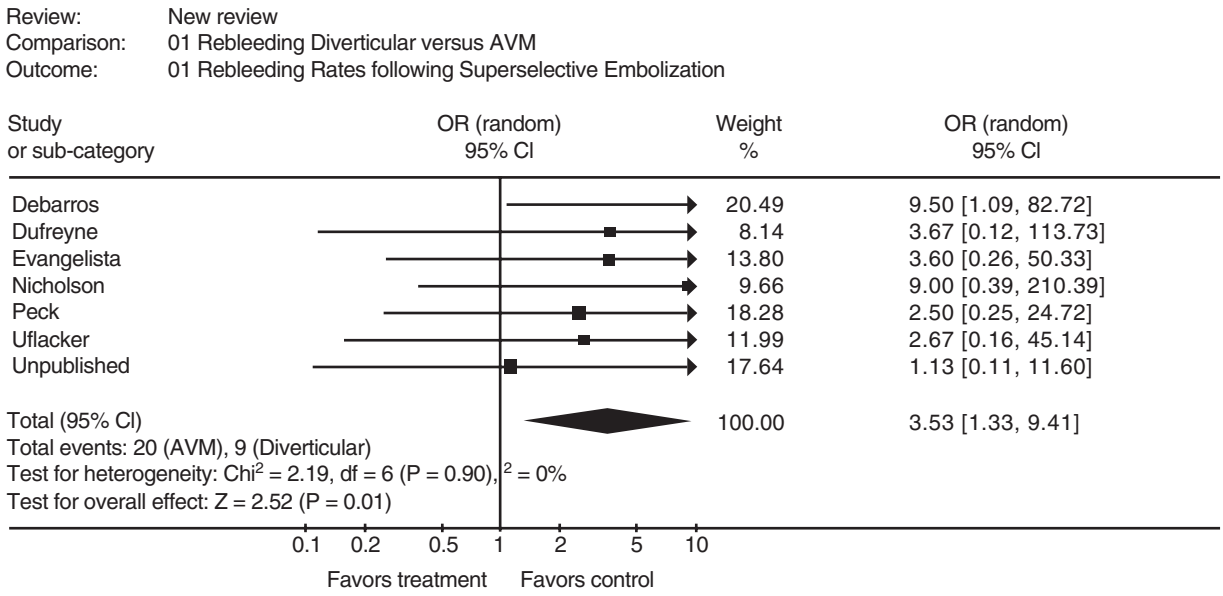

Fig. 2. Forest plot and pooled results of random-effects model. Pooled analysis of the seven studies using a random-effects model to adjust for heterogeneity between studies demonstrates a significant difference in rebleeding rate by etiology of lower gastrointestinal bleeding.

cases of slower but persistent LGIB such as may occur from ischemia or infectious colitis.[2,31,32]

Angiographic diagnosis and treatment of LGIB have evolved since the early 1970s, when the technique was first described in the treatment of GI bleeding. Early attempts at angiographic control used selective infusion of vasopressin. The use of selective vasoconstrictive agent infusion was associated with high recurrence rates and complications of ischemia, particularly of the GI tract, however.[34,35] Subsequently, improved microcatheters that allowed selective cannulation of secondary vessels and embolization agents such as PVA (polyvinyl alcohol) and metal coils were used with much greater success to treat a wide variety of clinical scenarios. Such interventions in LGIB were complicated by failure to

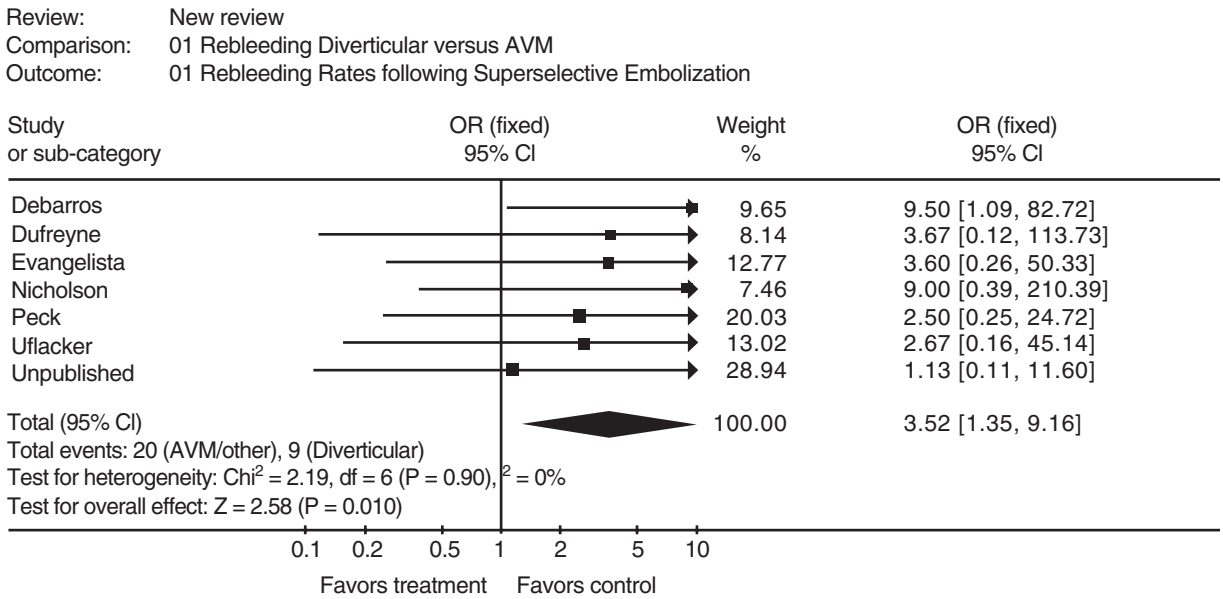

Fig. 3. Forest plot and pooled results of fixed-effects model. Pooled analysis of the six studies using a fixed-effects model did not differ significantly in outcome compared with the random-effects model. OR = odds ratio. $P < 0.05$ significance level.

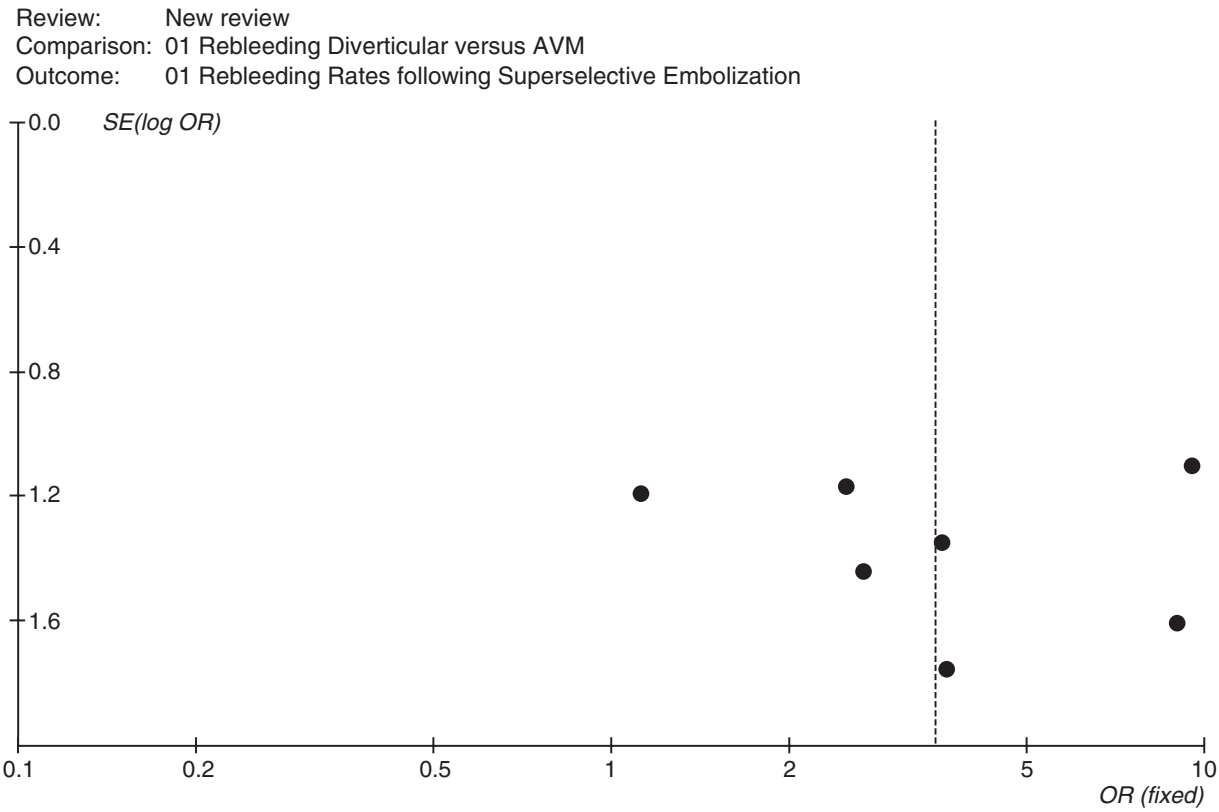

Fig. 4. Funnel plot of pooled data.

control bleeding or associated intestinal ischemia.[36] Failure of bleeding control in many early reports was ascribed to embolization proximal to the marginal artery, thus allowing bleeding to propagate via collateral intramural arteries. The incidence of ischemia related to selective embolization has ranged in the past decade from 0% to 22%, with fewer than 10% of patients requiring surgical resection for ischemia (see Tables 1 and 2). In the most recent series, the incidence of ischemia has markedly decreased due to the use of larger-particle PVA or metal coils and increased experience.[7] Notably, few reports of significant ischemia requiring exploration and resection have been reported in any of the included series since 1997, suggesting a current rate of significant ischemia of less than 5%.

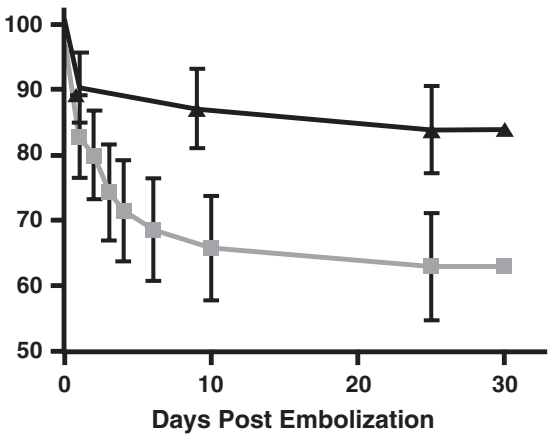

Fig. 5. Kaplan-Meier analysis of lower gastrointestinal rebleeding. Time to rebleeding within 30 days of successful embolization by etiology of bleeding (mean ± SE, diverticular versus arteriovenous dysplastic lesions [gray] and other etiologies [black]). Data were derived from all studies that met selection criteria except DeBarros et al.,[6] where days to rebleeding was not reported.

To date, the overall failure rate of embolization remains high in some series, and its widespread application has not been universally achieved. We hypothesized that certain etiologies of bleeding would be more effectively treated by the use of embolization than would others. We therefore set out to systematically examine the published literature using the techniques of meta-analysis to identify those patients who might benefit from the use of embolization in the treatment of LGIB. A thorough review of the published literature identified 25 articles for subsequent analysis. We applied selection criteria to these data sets to identify the highest quality studies with comprehensive individual data reporting. Critical review

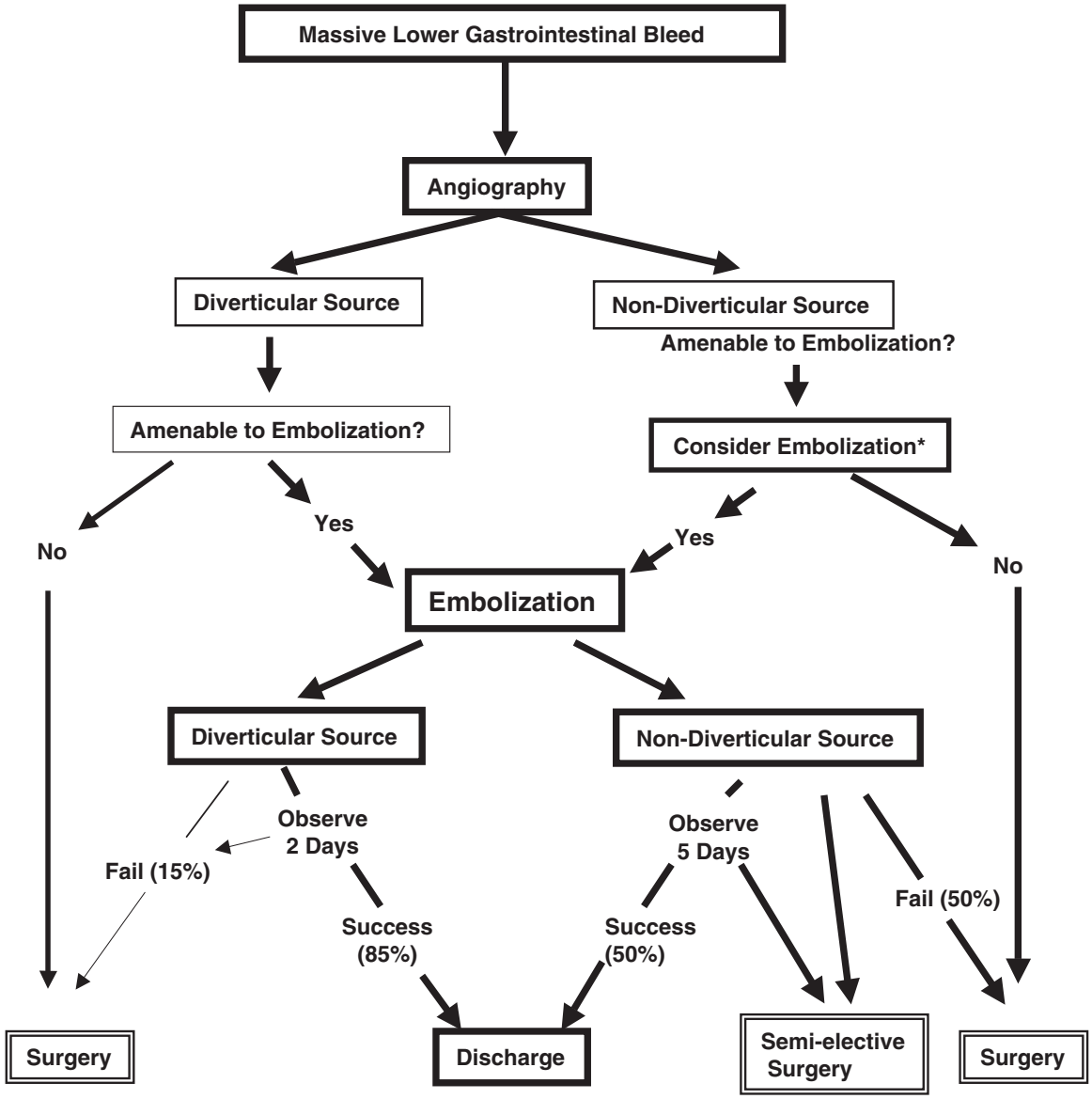

Fig. 6. Suggested treatment approach algorithm.

of the literature identified six published series and our institutional data set that were amenable to subsequent statistical analysis. Initial examination of these data sets involved exploration of sources of anticipated heterogeneity between trials by using multiple logistic regression analysis and using each study's data set as a variable. Importantly, no statistically significant difference based on the covariates of age, microcoil use, or individual study were found on the outcome of rebleeding between these studies, strongly suggesting that the difference in rebleeding rates in diverticular versus nondiverticular bleeding of each study were consistent and that subsequent pooled identified differences were, in fact, valid.

The only statistically significant variable identified by logistic regression was disease process. Embolization is demonstrated more effective for diverticular bleeding than other less common pooled pathologies. Meta-analysis of the data set with both random and fixed-effects models demonstrated that diverticular bleeding was three to four times more likely to be controlled with embolization than other causes of bleeding. These data suggest, therefore, that embolization is most effective for diverticular bleeding and that this efficacy is not dependent on the patient's age or the embolization technique used.

Several limitations exist in this meta-analysis primarily because the available data on this technique are from small retrospective case series, allowing a total sample of 103 patients for meta-analysis. Selection bias was possible based on the studies included in the meta-analysis, particularly because the data

used were from higher-volume centers. Hence, the conclusions made for the success of embolization for diverticular bleeding may not be those encountered where less expertise exists. Moreover, the studies examined were noncontrolled observational studies and therefore may include other potential unknown confounding variables. To address the potential of bias in some of the reported studies, a funnel plot was constructed and appeared symmetric, suggesting no significant evidence of publication bias. However, much debate has focused on the ability of funnel plots in excluding publication bias completely, and it is possible that publication bias was present in the analysis (see Fig. 4). A sensitivity analysis was also undertaken but failed to demonstrate significant differences in outcomes measures either after serial study omission or compared with a single-reference study. Again, the techniques of meta-analysis are often hypothesis generating but can be useful in planning subsequent trials to further elucidate the optimal selection of patients for superselective embolization.

Notwithstanding the above limitations of small sample size and observational design, it is clear that the outcomes of our meta-analysis are internally consistent. In addition, by using the rigors of meta-analysis to the best available data on this topic, we conclude that superselective embolization has a high initial success rate at controlling hemorrhage. The best available data suggest a control rate exceeding 85% at 1 month for diverticular bleeding. The rate of control of bleeding for AVD and other rare causes of benign LGIB is lower, with an overall success rate of less than 55% at 30 days postembolization. These data suggest a controlled randomized study comparing surgical resection and superselective embolization would require a sample size of at least 250 patients in each treatment arm to achieve 80% power with a significance level of 5%.

Based on the results of the meta-analysis, a treatment algorithm is suggested (Fig. 6). All patients, regardless of age, who present with significant LGIB from diverticulosis should be considered for superselective embolization, if technically feasible. A subset of these patients may stop on their own, without embolic therapy, but its inclusion in the treatment algorithm for these patients is associated with a very high overall control rate. Surgery should be reserved for the few for whom embolization fails. Overall, 95% of patients who do not rebleed within 2 days of embolization for diverticular bleeding are most likely not to require reintervention. Moreover, according to these data, at least a 2-day observation period for rebleeding following embolization for diverticular bleeding appears to be justified. Importantly, long-term follow-up of these patients has not identified a large late recurrence rate after 30 days, but this possibility should still be entertained. Embolization for AVD and other nondiverticular LGIB may be considered given the low risk of postembolization ischemia; however, a failure rate of 45% may be encountered. Embolization in this subset of LGIB patients may best be used as a temporary measure to allow bowel preparation and subsequent semielective alternate procedure. Alternatively, early consideration for the use of other therapies following localization may be considered.

REFERENCES

1. Schuetz A, Jauch KW. Lower gastrointestinal bleeding: Therapeutic strategies, surgical techniques and results. Langenbecks Arch Surg 2001;386:17–25.
2. Hendrickson RJ, Diaz AA, Salloum R, Koniaris LG. Benign rectal ulcer. Surg Endosc 2003.
3. Vernava AM 3rd, Moore BA, Longo WE, Johnson FE. Lower gastrointestinal bleeding. Dis Colon Rectum 1997;40:846–858.
4. Bokhari M, Vernava AM, Ure T, Longo WE. Diverticular hemorrhage in the elderly—is it well tolerated? Dis Colon Rectum 1996;39:191–195.
5. Leitman IM, Paull DE, Shires GT 3rd. Evaluation and management of massive lower gastrointestinal hemorrhage. Ann Surg 1989;209:175–180.
6. DeBarros J, Rosas L, Cohen J, Vignati P, Sardella W, Hallisey M. The changing paradigm for the treatment of colonic hemorrhage: Superselective angiographic embolization. Dis Colon Rectum 2002;45:802–808.
7. Patel TH, Cordts PR, Abcarian P, Sawyer MA. Will transcatheter embolotherapy replace surgery in the treatment of gastrointestinal bleeding? Curr Surg 2001;58:323–327.
8. Bandi R, Shetty PC, Sharma RP, Burke TH, Burke MW, Kastan D. Superselective arterial embolization for the treatment of lower gastrointestinal hemorrhage. J Vasc Interv Radiol 2001;12:1399–1405.
9. Defreyne L, Vanlangenhove P, De Vos M, et al. Embolization as a first approach with endoscopically unmanageable acute nonvariceal gastrointestinal hemorrhage. Radiology 2001;218:739–748.
10. Funaki B, Kostelic JK, Lorenz J, et al. Superselective microcoil embolization of colonic hemorrhage. AJR Am J Roentgenol 2001;177:829–836.
11. Evangelista PT, Hallisey MJ. Transcatheter embolization for acute lower gastrointestinal hemorrhage. J Vasc Interv Radiol 2000;11:601–606.
12. Luchtefeld MA, Senagore AJ, Szomstein M, Fedeson B, Van Erp J, Rupp S. Evaluation of transarterial embolization for lower gastrointestinal bleeding. Dis Colon Rectum 2000; 43:532–534.
13. Dobson CC, Nicholson AA. Treatment of rectal hemorrhage by coil embolization. Cardiovasc Intervent Radiol 1999;22: 143–146.
14. Ledermann HP, Schoch E, Jost R, Zollikofer CL. Embolization of the vasa recta in acute lower gastrointestinal hemorrhage: A report of five cases. Cardiovasc Intervent Radiol 1999;22:315–320.
15. Ledermann HP, Schoch E, Jost R, Decurtins M, Zollikofer CL. Superselective coil embolization in acute gastrointestinal hemorrhage: Personal experience in 10 patients and review of the literature. J Vasc Interv Radiol 1998;9:753–760.

16. Nicholson AA, Ettles DF, Hartley JE, et al. Transcatheter coil embolotherapy: A safe and effective option for major colonic haemorrhage. Gut 1998;43:79–84.
17. Peck DJ, McLoughlin RF, Hughson MN, Rankin RN. Percutaneous embolotherapy of lower gastrointestinal hemorrhage. J Vasc Interv Radiol 1998;9:747–751.
18. Skulski R, Snider JM, Buzzard CJ, Ling FS, Mendelsohn AM. Transcatheter closure of a patent foramen ovale following mitral valve replacement. Ann Thorac Surg 1999;68:582–583.
19. Gordon RL, Ahl KL, Kerlan RK, et al. Selective arterial embolization for the control of lower gastrointestinal bleeding. Am J Surg 1997;174:24–28.
20. Encarnacion CE, Kadir S, Beam CA, Payne CS. Gastrointestinal bleeding: Treatment with gastrointestinal arterial embolization. Radiology 1992;183:505–508.
21. Guy GE, Shetty PC, Sharma RP, Burke MW, Burke TH. Acute lower gastrointestinal hemorrhage: Treatment by superselective embolization with polyvinyl alcohol particles. AJR Am J Roentgenol 1992;159:521–526.
22. Okazaki M, Furui S, Higashihara H, Koganemaru F, Sato S, Fujimitsu R. Emergent embolotherapy of small intestine hemorrhage. Gastrointest Radiol 1992;17:223–228.
23. Uflacker R. Transcatheter embolization for treatment of acute lower gastrointestinal bleeding. Acta Radiol 1987;28:425–430.
24. Gomes AS, Lois JF, McCoy RD. Angiographic treatment of gastrointestinal hemorrhage: Comparison of vasopressin infusion and embolization. AJR Am J Roentgenol 1986;146: 1031–1037.
25. Palmaz JC, Walter JF, Cho KJ. Therapeutic embolization of the small-bowel arteries. Radiology 1984;152:377–382.
26. Chuang VP, Wallace S, Zornoza J, Davis LJ. Transcatheter arterial occlusion in the management of rectosigmoidal bleeding. Radiology 1979;133:605–609.
27. Matolo NM, Link DP. Selective embolization for control of gastrointestinal hemorrhage. Am J Surg 1979;138:840–844.
28. Bookstein JJ, Naderi MJ, Walter JF. Transcatheter embolization for lower gastrointestinal bleeding. Radiology 1978;127: 345–349.
29. Goldberger LE, Bookstein JJ. Transcatheter embolization for treatment of diverticular hemorrhage. Radiology 1977;122: 613–617.
30. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for Meta-analysis in Medical Research. London: John Wiley and Sons, 2000.
31. Zuckerman GR, Prakash C. Acute lower intestinal bleeding. Part I: Clinical presentation and diagnosis. Gastrointest Endosc 1998;48:606–617.
32. Zuckerman GR, Prakash C. Acute lower intestinal bleeding. Part II: Etiology, therapy, and outcomes. Gastrointest Endosc 1999;49:228–238.
33. Jensen DM, Machicado GA, Jutabha R, Kovacs TO. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. N Engl J Med 2000;342:78–82.
34. Browder W, Cerise EJ, Litwin MS. Impact of emergency angiography in massive lower gastrointestinal bleeding. Ann Surg 1986;204:530–536.
35. Sherman LM, Shenoy SS, Cerra FB. Selective intra-arterial vasopressin: Clinical efficacy and complications. Ann Surg 1979;189:298–302.
36. Rosenkrantz H, Bookstein JJ, Rosen RJ, Goff WB 2nd, Healy JF. Postembolic colonic infarction. Radiology 1982; 142:47–51.

Left Trisegmentectomy With Reconstruction of Segment 6 Hepatic Venous Outflow Using Cryopreserved Vein Graft

Alan W. Hemming, M.D., M.Sc., F.A.C.S., Alan I. Reed, M.D., F.A.C.S.

Liver resections that require hepatic vein reconstruction rarely occur. Options regarding venous reconstruction include primary end-to-end reconstruction, reimplantation into the vena cava, or the use of a variety of autologous or synthetic grafts. Cryopreserved vein grafts have recently become available for use. We describe a left trisegmentectomy with bile duct resection/reconstruction during which the segment 6 hepatic vein was reconstructed into the inferior vena cava using a cryopreserved vein graft. (J GASTROINTEST SURG 2005;9:353–356)

KEY WORDS: Hepatic vein reconstruction, liver resection, vein graft

Involvement of the hepatic veins requiring reconstruction has traditionally been considered a contraindication to resection for advanced tumors of the liver, because the surgical risks are great and the long-term prognosis is poor. Recent advances in liver surgery gleaned from split and live donor liver transplantation that necessitate hepatic vein reconstruction can be applied to hepatic resection in some patients. A variety of techniques have been used to reconstruct the hepatic veins including direct reimplantation into the vena cava or the use of autologous ovarian, external iliac, superficial femoral, or even transposed portal vein as extension grafts.[1–5,6] In cirrhotic patients, ringed Gortex grafts (W.L. Gore & Associates, Inc., Newark, DE) have been used to provide venous outflow from isolated segments of the liver to improve liver function.[1] However, because of the long-term risks of thrombosis and stenosis, Gortex is generally not used when a substantial percentage of the total venous outflow of the remnant liver requires reconstruction. The availability of cryopreserved cadaveric vein grafts offers an alternative for hepatic venous reconstruction and have recently been used to successfully reconstruct hepatic venous outflow in extended right lobe living donor liver transplant grafts.[7]

In the resection setting, we would prefer to reimplant the hepatic vein(s) directly into the vena cava or use short autologous venous extension grafts if necessary. In this article, however, a patient that required a longer venous extension graft using a cryopreserved femoral vein to reconstruct the hepatic venous outflow from segment 6 during a left trisegmentectomy was studied.

A 63-year-old woman presented with a large central hepatic mass on imaging studies (Fig. 1). Tumor markers for Ca (carbohydrate antigen) 19-9 were elevated at 1100 and a percutaneous biopsy of the lesion performed before referral to our institution was consistent with cholangiocarcinoma. A metastatic workup including a colonoscopy, chest CT, and a positron emission tomography (PET) scan revealed no disease outside of the liver. The patient's liver function was normal.

Assessment of the CT scan suggested that it would be possible to perform a left trisegmentectomy, but that the right hepatic vein might require resection and reconstruction to obtain a tumor-free margin. CT volumetry calculated that the future liver remnant was 35% of the total liver volume, therefore, we decided not to perform preoperative left portal vein embolization because the liver remnant volume was believed to be adequate and we also believed that the left portal vein from the resected side of the liver might be used to reconstruct the right hepatic vein.

From the Department of Surgery, University of Florida College of Medicine, Gainesville, Florida.
Reprint requests: Alan W. Hemming, M.D., M.Sc., F.R.C.S.C., University of Florida, Dept of Surgery, P.O. Box 100286, Gainesville, FL 32610-0286. e-mail: hemming@surgery.ufl.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.07.012

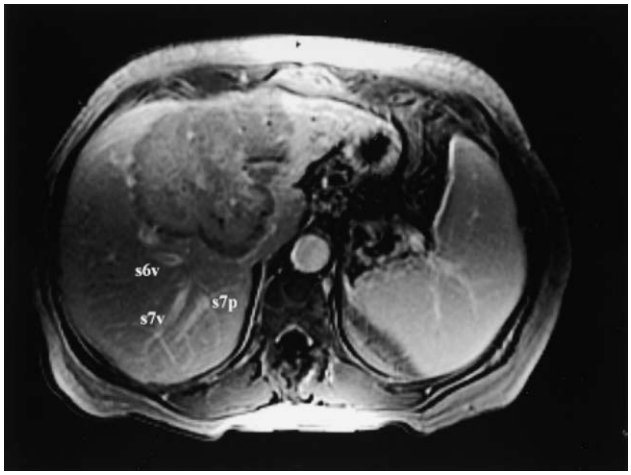

Fig. 1. Computed tomograph scan illustrating a large central hepatic tumor and the relative position of the hepatic vein draining segment 6 (S6V), segment 7 (S7V), and the segment 7 portal vein (S7P).

MATERIAL AND METHODS

Surgery indicated that the tumor was confined to the liver. Intraoperative ultrasound revealed that the tumor involved the middle and left hepatic veins and was in close proximity to, but did not involve, the bifurcation of the hepatic ducts. There was hypertrophy of segments 6 and 7 presumably caused by venous outflow obstruction to the rest of the liver. The proximal (caval side) right hepatic vein seemed to be free of tumor but a large venous branch seeming to drain the hypertrophied segment 6 was patent, but in close proximity to the tumor (Fig. 2). There were no large short hepatic veins draining segment 6 directly into the vena cava, although several small 1–2 mm veins were identified and left undisturbed. A left trisegmentectomy was performed via an anterior approach identifying, but sacrificing, the large segment 6 vein as well as the hepatic duct bifurcation to achieve a tumor-free margin. The transection of the liver parenchyma was performed without portal inflow occlusion and it immediately became evident that segment 6 was intensely venous congested, whereas segment 7 seemed quite normal. A short segment of the segment 6 hepatic vein stump was dissected from the surrounding liver parenchyma and a small vascular clamp applied. Although the segment 6 branch had originally drained into the right hepatic vein, we elected to reconstruct it directly into the vena cava avoiding the possibility of compromising the outflow from segment 7. A segment of Cryolife (Cryolife Inc., Kennesaw, GA) cryopreserved femoral vein was used to reconstruct the segment 6 vein directly to the vena cava (Fig. 3). The graft to hepatic vein anastomosis was performed first allowing maximum mobility and minimal tension when suturing the relatively fragile intraparenchymal hepatic vein. A side-biting vascular clamp was placed on the vena cava maintaining caval

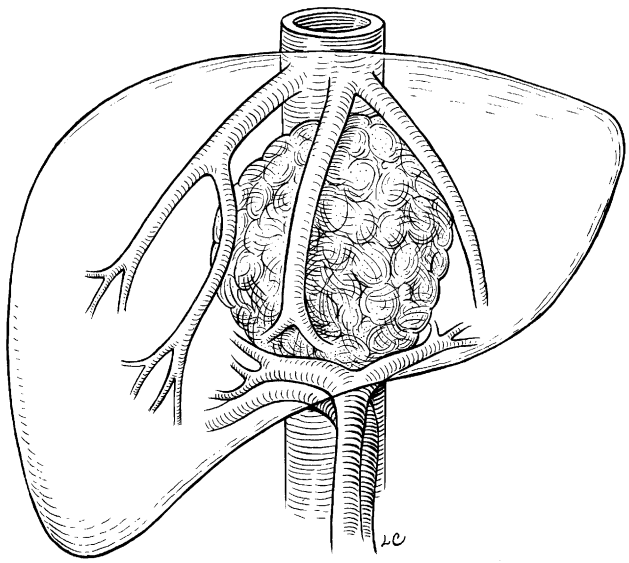

Fig. 2. Position of the tumor in relation to the hepatic veins.

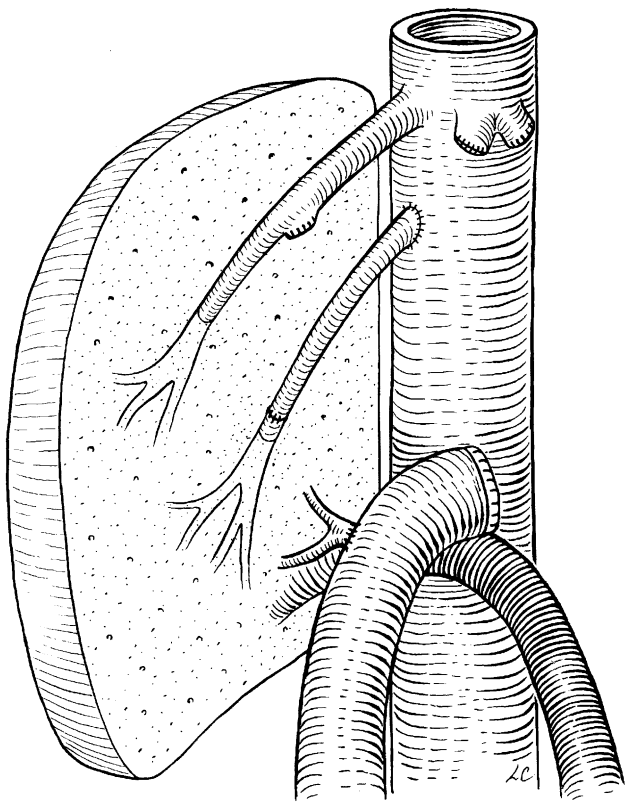

Fig. 3. Venous reconstruction of segment 6 vein after left trisegmentectomy and biliary reconstruction of the posterior segmental hepatic duct.

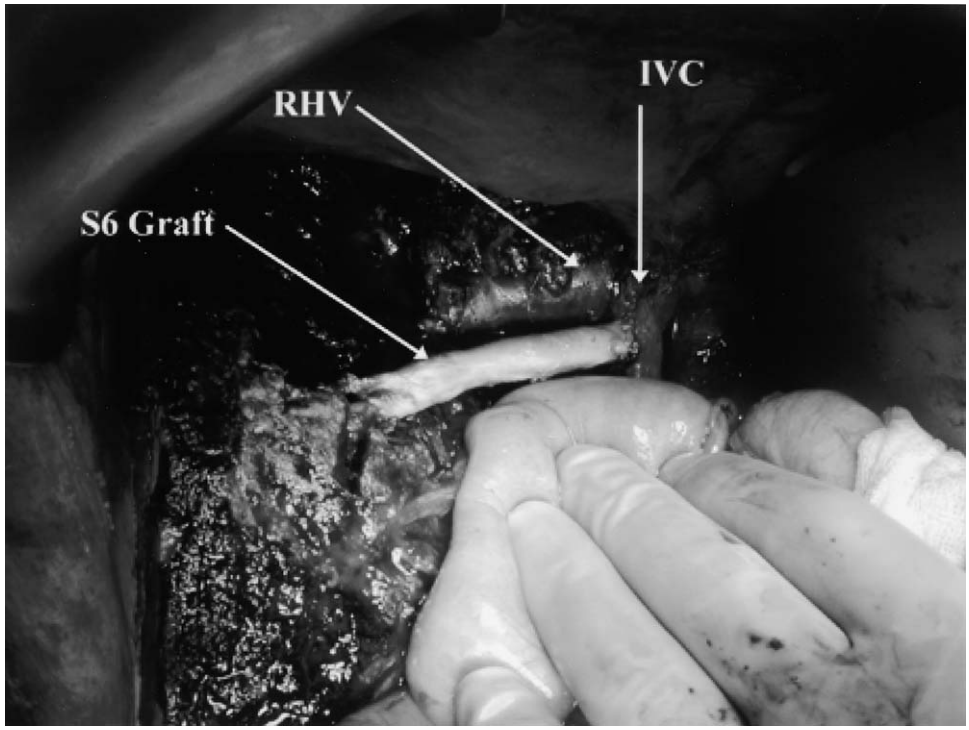

Fig. 4. Operative photograph of the venous reconstruction of the segment 6 hepatic vein with cryopreserved femoral vein after left trisegmentectomy and biliary reconstruction of the posterior segmental hepatic duct. IVC = inferior vena cava; RVC = right vena cava; S6 graft = segment 6 graft.

flow but allowing a 1 cm cavotomy to be created. The graft-to-caval anastomosis was subsequently performed and the vascular clamps removed. The venous congestion immediately resolved. The right posterior segmental hepatic duct was then reconstructed with a Roux-en-Y limb (Fig. 4).

RESULTS

Postoperatively, the patient exhibited a peak bilirubin of 10 mg/dl that had decreased to less than 2.0 mg/dl at the time of discharge on postoperative day 11. It was normal when observed at follow-up 3 weeks later. Triphasic CT scan at 1 year indicated no evidence of recurrent disease, a patent vein graft, and substantial hypertrophy of both segments 6 and 7.

DISCUSSION

The need for graft material to reconstruct a single segmental hepatic vein is rare. Ideally, venous anastomoses should be kept short with no redundancy. We have determined that hepatic veins, even if cut flush with the liver surface, can be anastomosed without an extension graft to either the origin of the same hepatic vein or, if necessary, placed lower down on the inferior vena cava.[1] This case was an exception because the position of the vein precluded direct reimplantation into the vena cava and we believed that the risk of a longer venous graft directly to the vena cava was less than the risk of compromising the venous outflow to segment 7 by reimplanting the segment 6 vein back into the right hepatic vein. We have previously used 6–8 mm ringed Gortex grafts to reconstruct segmental hepatic veins in cirrhotic patients to maximize remnant liver function. The cryopreserved grafts seem to offer advantages over the Gortex grafts with regard to the handling and ease of anastomosis.

The availability of cryopreserved venous grafts offers an alternative to previously existing methods of venous reconstruction of hepatic veins. The availability of these grafts in various diameters and lengths designates their use as attractive, particularly when a long length of graft is required. The question of long-term patency with regard to cryopreserved grafts remains unanswered, however, and longer-term follow-up is required.

REFERENCES

1. Hemming AW, Reed AI, Langham MR, Fujita S, van der Werf WJ, Howard RJ. Hepatic vein reconstruction for resection of hepatic tumors. Ann Surg 2002;235:850–858.

2. Nakamura S, Sakaguchi S, Kitazawa T, Suzuki S, Koyano K, Muro H. Hepatic vein reconstruction for preserving remnant liver function. Arch Surg 1990;125:1455–1459.
3. Kubota K, Makuuchi M, Sugawara Y, Midorikawa Y, Sakamoto Y, Takayama T, Harihara Y. Reconstruction of the hepatic and portal veins using a patch graft from the right ovarian vein. Am J Surg 1998;176:295–297.
4. Kaneoka Y, Yamaguchi A, Isogai M, Hori A. Hepatic vein reconstruction by external iliac vein graft using vascular clips. World J Surg 2000;24:377–382.
5. Hemming AW, Cattral MS. Ex vivo liver resection with replacement of the inferior vena cava and hepatic vein replacement by transposition of the portal vein. J Am Coll Surg 1999; 189:523–526.
6. Kornberg A, Heyne J, Schotte U, Hommann M, Scheele J. Hepatic venous outflow reconstruction in right lobe living-donor liver graft using recipient's superficial femoral vein. Am J Transplant 2003;3:1444–1447.
7. Sugawara Y, Makuuchi M, Imamura H, Kaneko J, Kokudo N. Outflow reconstruction in extended right liver grafts from living donors. Liver Transpl 2003;9:306–309.

Isolated Involvement of the Gallbladder by Crohn's Disease Manifesting as Acute Cholecystitis

Ajay Kumar Sharma, M.D., F.R.C.S., Ibrahim M. Nawroz, M.D., F.R.C.Path, DipFM, Nicholas Evgenikos, M.D., F.R.C.S., Thomas Daniel, M.D., F.R.C.S.

A 79-year-old female presented with acute cholecystitis. Having recovered on conservative management, elective laparoscopic cholecystectomy was performed. The diagnosis of Crohn's disease of the gallbladder was a histopathological surprise. Further detailed investigation indicated this to be the isolated involvement of gallbladder. (J GASTROINTEST SURG 2005;9:357–359) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Acute cholecystitis, Crohn's disease, extraintestinal

Hepatobiliary manifestations are not uncommon with regard to Crohn's disease. However, involvement of the gallbladder regarding this chronic inflammatory granulomatous disease has been rare. Within the English literature, three instances have been indicated[1–3] and within the French literature, one instance has been indicated.[4] We herein report the case record of a patient who seemed to present with acute cholecystitis, but who was later recognized to actually be suffering from Crohn's disease of the gallbladder. This diagnosis was histopathologically surprising.

CASE REPORT

In March 2002, a 79-year-old diabetic female presented with upper abdominal pain, which had lasted for 24 hours, along with constipation, which had endured for 3 days. She experienced tenderness in the right hypochondrium and epigastrium. There was a palpable mass in the right hypochondrium. An ultrasound and CT scan indicated a distended gallbladder along with a gallstone surrounded by fluid collection. Because the fluid collection was multilocular, it was believed to be inappropriate for percutaneous drainage. Initial treatment with intravenous antibiotics and then oral antibiotics was administered. The patient was discharged and was also scheduled for an elective laparoscopic cholecystectomy. In the interim, self-limiting diarrhea developed within the patient for approximately 3 days and was thought to be associated with the antibiotic use. The laparoscopic cholecystectomy was uneventful. The gallbladder was thick-walled with a thickened mesentery. In the postoperative period, diarrhea again developed within the patient for approximately 3 days and was still considered to be related to the antibiotic usage.

The examination of the gallbladder specimen revealed a thick-walled gallbladder with a "cobblestone" appearance of the mucosa. Histopathologic findings were rather surprising and consisted of chronic mucosal inflammation, fissuring, transmural lymphoid aggregates, perivascular epithelioid histiocytic granuloma, neural hypertrophy with perineural lymphoid infiltrate, and epithelioid histiocytic granulomas in cystic lymph node of Lund. No foreign body could be identified in any of the granuloma (Figs. 1–5). There was

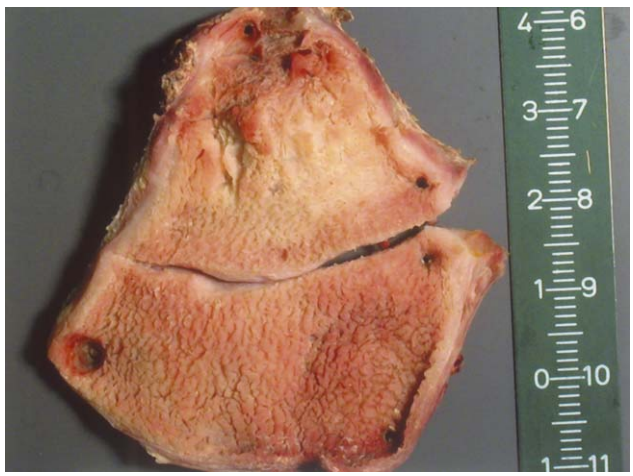

Fig. 1. Thick-walled gallbladder with "cobblestone" appearance of the mucosa.

From the Departments of Surgery (A.K.S., N.E., T.D.) and Pathology (I.M.N.), Queen Margaret Hospital, Dunfermline, United Kingdom. Reprint requests: Thomas Daniel, M.D., Consultant Colorectal Surgeon, Queen Margaret Hospital, Dunfermline, KY12 0SU, United Kingdom. e-mail: Thomas.Daniel@faht.scot.nhs.uk

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.08.012

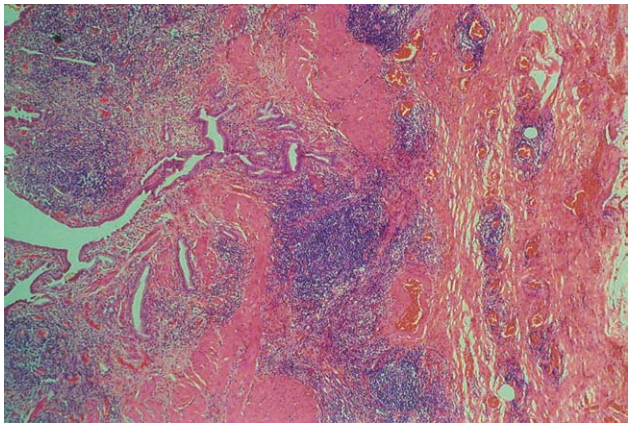

Fig. 2. Transmural chronic inflammation with transmural lymphoid aggregates.

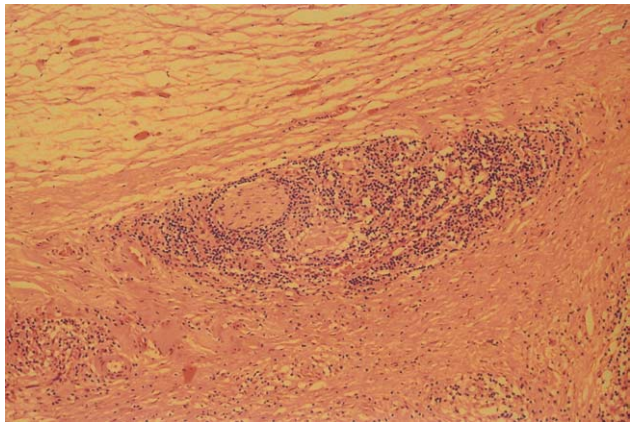

Fig. 4. Neural hypertrophy with perineural lymphoid infiltrate.

no evidence of acid-fast bacillus. These findings were interpreted as Crohn's disease of the gallbladder.

Previous records revealed that roughly 20 years ago the intermittent diarrhea experienced by the patient was extensively investigated by performing a flexible sigmoidoscopy and barium enema. The findings from these tests were interpreted as diverticulosis.

Approximately 18 months after the cholecystectomy for Crohn's disease was performed, the patient did not experience any diarrhea, weight loss, or abdominal pain. Since then, the patient has, however, been admitted for repair of a para-umbilical hernia and, in subsequent period, for sebaceous cysts. An upper gastrointestinal endoscopy and small bowel barium enema study ruled out any evidence of Crohn's disease elsewhere.

DISCUSSION

Crohn's disease patients may present with acute cholecystitis either due to gallstones or not. Gallstones are more common in Crohn's disease than in the general population,[5,6] while acalculus cholecystitis is more common in very sick patients.[7]

Extraintestinal granulomatous lesions are rarely observed in Crohn's disease.[2] The present patient is unique, because the isolated involvement of the gallbladder is the sole presentation. Other instances of gallbladder-related Crohn's disease reported so far have been indicated to be small bowel disease.[1–4] Although analysis on the basis of one anecdotal occurrence is not very scientific to suggest, it is worthwhile to note that a thickened mesentery of the gallbladder in a patient with Crohn's disease, as was illustrated in the index case, may potentially be an indication toward this rare presentation. Interestingly, the macroscopic as well as microscopic findings in the resected specimen of the gallbladder regarding this patient are exactly similar to those

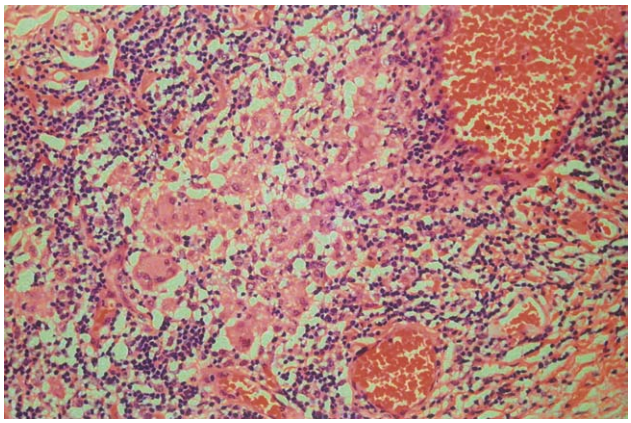

Fig. 3. Perivascular epithelioid histiocytic granuloma.

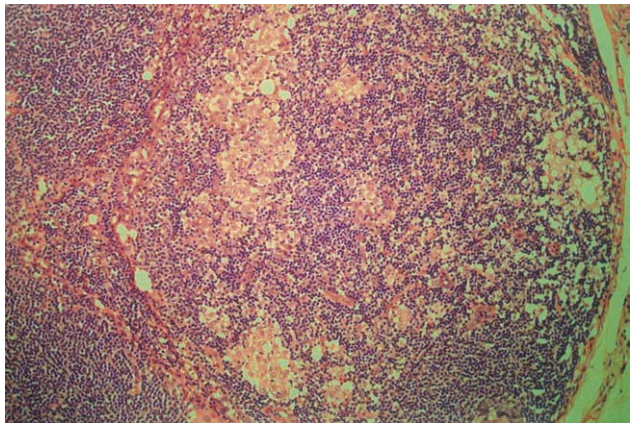

Fig. 5. Cystic lymph node of Lund indicating epithelioid histiocytic granulomas.

observed in a classical case of Crohn's disease involving the bowels.

REFERENCES

1. Rettally CA, Trevino HH, Molina K, Kane SV. Crohn's disease involving the gallbladder. Case report and review of the literature. Am J Gastroenterol 2003;98:509–511.
2. McClure J, Banerjee SS, Schofield PS. Crohn's disease of the gall bladder. Clin Pathol 1984;37:516–518.
3. Post AB, van Stolk R, Broughan TA, Tuthill RJ. Crohn's disease of the gallbladder. J Clin Gastroenterol 1993;16: 139–142.
4. Bouteloup C, Guedon C, Francois A, Hemet J, Lerebours E. Gallbladder involvement in Crohn's disease. Gastroenterol Clin Biol 1997;21:153–155.
5. Lapidus A, Bangstad M, Astrom M, Muhrbeck O. The prevalence of gall stone disease in a defined cohort of patients with Crohn's disease. Am J Gastroenterol 1999;94:1261–1266.
6. Fraquelli M, Losco A, Visentin S, Cesana BM, Pometta R, Colli A, Conte D. Gall stone disease and related risk factors in patients with Crohn's disease: Analysis of 330 consecutive cases. Arch Intern Med 2001;161:2201–2204.
7. Hyams JS, Baker E, Schwartz AN, Ricci A Jr, McGowan G. Acalculous cholecystitis in Crohn's disease. J Adolesc Health Care 1989;10:151–154.

Perioperative Outcome of Laparoscopic Left Lateral Liver Resection Is Improved by Using Staple Line Reinforcement Technique: A Case Report

Esther C.J. Consten, M.D., Ph.D., Michel Gagner, M.D., F.A.C.S., F.R.C.S.C.

Current laparoscopic stapling technology still cannot prevent bile leakage (<55%) along the resection margin. A new staple line reinforcement technique was used in the present case. This technique incorporates an absorbable polymer membrane into the stapler system, such that it buttresses the transected solid organ. The objectives of this novel procedure are to decrease hemorrhage at the staple line and to prevent bile duct leakage after liver resection. A 47-year-old man followed for status post biliopancreatic diversion with duodenal switch presented with epigastric pain. On imaging, he was found to have a lesion in segment 2–3 of the left lobe of the liver, which measured at least 3 cm in diameter. He was admitted to the hospital to undergo a laparoscopic left lateral liver resection. This procedure involved laparoscopic ultrasonography of the liver and transection of the left liver lobe with endoscopic linear staplers. The staple height of 3.5, 60 mm long, reinforced with an absorbable polymer membrane was used for liver transection to catch the portal branches. This required multiple firings in the liver parenchyma and additional division of some tissue using the Harmonic scalpel. The larger branch in the middle of segment 2–3 and the left hepatic vein were both transected with the novel staple line reinforcement technique. Bleeding or any bile leakage in this area could not be visualized. No drains were left. The patient's postoperative course was uncomplicated, and he was discharged on postoperative day 3. Pathology results showed a cavernous hemangioma of 4.5 cm in diameter. Staple line reinforcement with the absorbable polymer membrane has the potential to decrease staple line hemorrhage and bile leakage. (J GASTROINTEST SURG 2005;9:360–364)

KEY WORDS: Laparoscopic surgery, liver lesions, staple line reinforcement, complications, bile duct leak, hemorrhage, ultrasonography

The success of laparoscopic cholecystectomy has driven the application of minimally invasive techniques to other disease processes and led to the application of laparoscopy in solid organs.[1] With the introduction of the first complex laparoscopic liver resection for a 6-cm focal nodular hyperplasia, laparoscopic surgery for the treatment of liver diseases has become more popular. In 1995, excision of a segment 4 hepatic tumor was reported. The first successful laparoscopic left lateral hepatectomy (segments 2 and 3) in a patient with a benign adenoma was performed in 1996.[1–9]

Technological advances and the development of new equipment have facilitated the growing trend of laparoscopic liver resections.[2] However, laparoscopic liver surgery remains a technical challenge. Many comparative studies concerning liver resections favor the laparoscopic approach over open surgery for several reasons: decreased pain and thus reduced postoperative analgesic requirement, shorter hospitalization, faster recovery and time to oral intake, and quicker improvement in serum transaminase levels. These advantages are often exemplified even in patients undergoing cyst or benign tumor resections. However, indications for a laparoscopic resection with a curative intent for liver malignancies are not yet established. Tumor dissemination and inadequate margins are potential disadvantages of the laparoscopic approach.[2] Nevertheless, short-term outcome is comparable to that of conventional surgery with the additional benefits derived from minimally invasive therapy. Moreover, laparoscopic liver surgery provides real benefits to the patient, provided it does not increase the surgical risk. Knowledge of the anatomy and a thorough understanding of the complications associated with laparoscopic liver surgery

From the Department of Surgery, New York Presbyterian Hospital, Weill College of Medicine of Cornell University, New York, New York. Reprint requests: Michel Gagner, M.D., F.A.C.S., F.R.C.S.C., 525 E. 68th Street, Box 294, New York, NY 10021. e-mail: Gagnerm@aol.com or Mig2012@med.cornell.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.07.016

delineate steps to prevent their occurrence and to manage them if they do occur.

Transection of the liver can be performed in several ways; each technique has its risk of bleeding and bile leakage. In the reported case, to prevent bleeding and bile leakage, based on prospective animal studies, we used staple line reinforcement technique to transect the liver. This is a modification of stapling systems used for laparoscopic gastrointestinal surgery that is made in an attempt to reduce the afore-mentioned complications. The addition of an absorbable polymer membrane (Gore Seamguard Bioabsorbable material, Flagstaff, AZ) to reinforce staple lines made with linear cutting stapling devices may help prevent bleeding and the development of bile duct leakage.

CASE REPORT

Medical History

The patient was a 47-year-old man who was followed for status post biliopancreatic diversion with duodenal switch in April 2000. The patient presented with epigastric pain. His comorbidities and family history were unremarkable, and he was not on any medication. A full imaging work-up showed a lesion in segment 2–3 of the liver that measured at least 3 cm in diameter on an abdominal CAT scan (Fig. 1). The lesion appeared to be benign, although a tissue diagnosis could not be obtained preoperatively. Because of the size of the lesion and the pain, the decision was made to explore and resect this lesion. Also, due to the close proximity of the old sleeve gastrectomy, an old abscess cavity from the staple line had to be excluded.

Surgical Procedure

With the patient under general anesthesia, he was positioned on the operating table in supine position with both legs spread unflexed. A 10-mm reusable trocar was inserted under direct vision, followed by a laparoscope at 30 degrees. Adhesions from the previous surgery were lysed, especially between the inferior portion of the liver and the sleeve gastrectomy, between the duodenal ileostomy and the anterior abdominal wall, and the entire border of the left lower liver near the falciform ligament. Subsequently, the patient had four additional trocars inserted. A flexible ultrasound laparoscope of 10 mm (Aloka; 5–7.5 MHz frequency) was introduced. The first lesion (3×4 cm) was explored and was found to be mostly in segment 2 (Fig. 2). A second smaller lesion (1×1 cm), adjacent to the larger one at the tip of segment 2 near the diaphragm, was visualized.

The right lobe of the liver and the gallbladder were also explored with laparoscopic ultrasound and no lesions were found. The patient had two mesentery defects: one at the ileoileostomy and the other at Peterson's defect. The decision was made to close these defects first with a running suture.

We decided to perform a laparoscopic modified left lateral hepatectomy. The liver capsule was incised anteriorly and posteriorly, with use of the Harmonic scalpel. Subsequently, the stapler blue cartridge (staple height 3.5 mm, 60 mm long, reinforced with an absorbable polymer membrane) was used for liver transection to catch the portal branches located mostly inferiorly. This required multiple firings in the liver parenchyma and additional division of some tissue anteriorly using the Harmonic scalpel. The larger branch in the middle of segment 2–3 and the left hepatic vein were both transected with the novel staple line reinforcement technique. There was no major bleeding. The smaller lesion on the surface was separately enucleated with the Harmonic scalpel. With the argon beam coagulator, the entire surface of the liver was coagulated. No bleeding or bile leakage could be visualized in this area. The radical resected lesions were then inserted into a plastic bag and extracted through the umbilicus. Trocar sites of 12 mm were closed, without intra-abdominal drains.

Postoperative Course

The patient's postoperative course was uncomplicated, without pain and fever. He started to ambulate on his first postoperative day. On the next days, he started tolerating a regular diet, and he was discharged 3 days after the surgery. Pathology results showed a resected cavernous hemangioma, 4.5 cm in diameter. Laboratory values, including liver enzymes, showed no abnormalities at 3 days postoperatively.

Three weeks postoperatively, the patient showed no abnormalities at his outpatient clinic visit.

Absorbable Polymer Membrane

An absorbable polymer membrane (Gore Seamguard Bioabsorbable material) is constructed as a buttress mat integrated into the stapler system (Fig. 3). Pressure at staple lines after resections is equally distributed and mechanically closes potential holes. In this way, both hemorrhage and ischemia are thought to be prevented. This implanted absorbable material is a porous fibrous structure composed solely of polyglycolide acid (PGA) trimethylene carbonate (TMC) (67.5%/32.5% by weight). All PGA TMC copolymers are synthesized from various combinations of glycolide and TMC monomers and often are referred

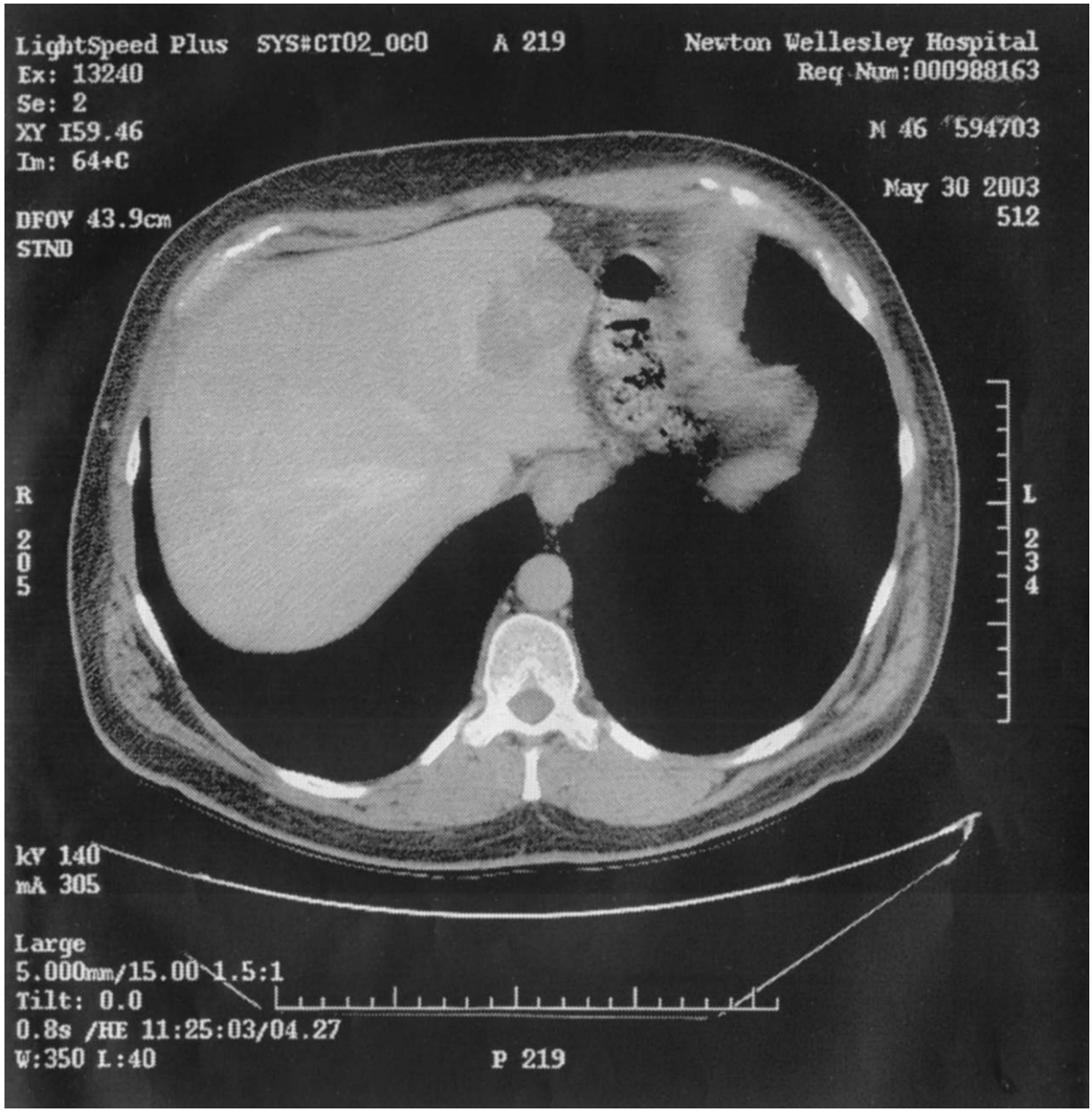

Fig. 1. Computed tomography scan showing the lesion in segment 2–3 of the liver, which measured at least 3 cm in diameter.

to as polyglyconate polymers. Degraded via a combination of hydrolytic and enzymatic pathways, the copolymer has been found to be both biocompatible and nonantigenic, with a history of use in bioabsorbable sutures, membranes, and other implantable devices.[10,11]

DISCUSSION

The majority of laparoscopic hepatic operations are currently performed for diagnostic purposes. Preoperative imaging studies, such as computed tomography scanning, computed tomography arterial portography, and magnetic resonance imaging are more diagnostic for liver lesions but still lack sensitivity for small lesions in the liver.[3–5] Herefore, intraoperative ultrasonography is still important and frequently used to confirm the diagnosis.[4]

The resected liver lesion should be reasonably small; large tumors are more difficult to mobilize, have more dangerous vascular connections, and have a higher risk of bleeding during laparoscopy.

Transection of the liver can be performed in several ways; each technique has its own risk of bleeding

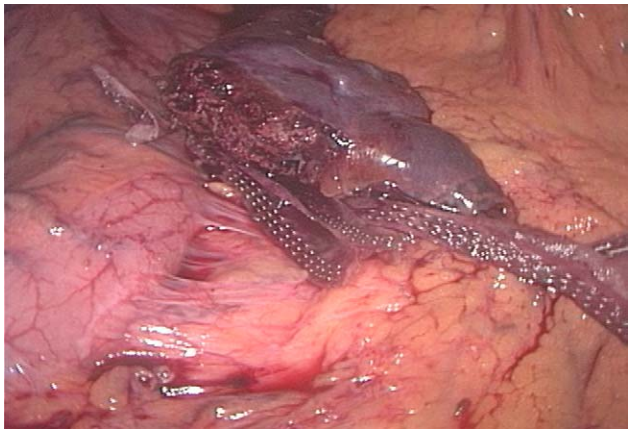

Fig. 2. Macroscopic view of resected left lateral liver segment with the cavernous hemangioma, 4.5 cm in diameter.

and bile leakage. These procedures are difficult to perform laparoscopically. Overtime, the frequency of these complications has not changed considerably, remaining between 4.6% and 55%.

Intermittent clamping might be used; this allows the surgeon the time necessary for meticulous transection. Cavitron Ultrasonic Surgical Aspirator (CUSA) (Valleylab, Boulder, CO) allows selective fragmentation and aspiration of collagen-sparse tissues like liver parenchyma, preserving blood vessels and bile ducts. The argon beam coagulator (Valleylab) is useful for hepatic resections, primarily for superficial hemostasis. However, the plume of argon flows into the peritoneal cavity, and in the presence of CO_2 pneumoperitoneum, it can increase intra-abdominal pressure and might cause hemodynamic instability. Ultrasonic scalpel (Ethicon Endo-Surgery, Cincinatti, OH) works by means of a vibrating blade or scissors and can effectively seal small vessels and bile ducts. The Jet-Cutter (US Surgical, Boulder, CO) is a promising new instrument for use in liver surgery that uses a high-pressure water stream for safe dissection of hepatic tissue.

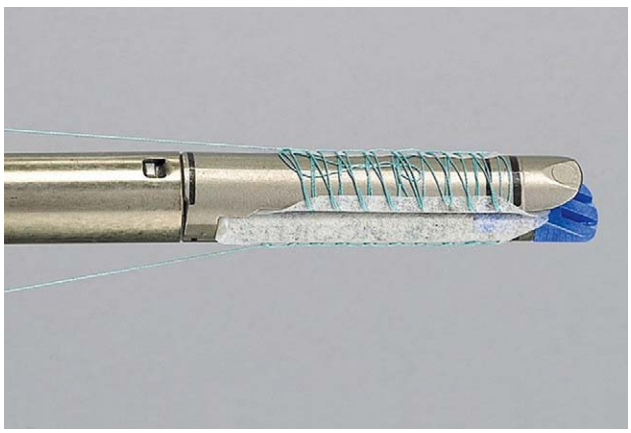

Fig. 3. Bioabsorbable Seamguard (W. L. Gore, Flagstaff, AZ), a buttress mat that, when integrated into the stapler system, covers intestinal anastomoses and transected solid organs.

A novel technique of staple line reinforcement can also be applied for actual liver resections to prevent bleeding and bile leakage. As a result of this, modifications to stapling systems used for laparoscopic gastrointestinal surgery have been developed in an attempt to reduce these complications. One such modification is the addition of an absorbable polymer membrane to reinforce staple lines made with linear cutting stapling devices. These reinforcing strips may help prevent bleeding and the development of anastomotic leaks.

Bioabsorbable staple line reinforcement material provides staple line reinforcement without requiring the implantation of permanent prosthetic material.[12–27] The absorbable polymer membrane (Seamguard) is constructed as a buttress mat integrated into the stapler system (Fig. 3). Pressure at staple lines after resections is equally distributed and mechanically closes potential openings and/or lacerations. In this way, both hemorrhage and ischemia are thought to be prevented. This device has the benefit of easy loading, safety, biocompatibility, and rapid absorption. Moreover, the bioabsorbable material does not carry the risk of animal source contamination and has an extensive history as a suture. It maintains strength for 4–5 weeks and is completely absorbed by 6 months. As such, concerns over possible long-term complications such as migration, erosion, calcification, and infection are eliminated or reduced.

Moreover, it can be speculated that following a reduction in blood loss, there might be lower requirements for blood transfusion, subsequently leading to lower risks for transmitting diseases and allergic reactions. Lower rates of reexploration for postoperative bleeding might also be expected. All of these aspects will probably lead to lesser costs. An average of six to eight loadings of the absorbable polymer membrane is required per patient. The materials cost for staple line reinforcement may add approximately $960 to $1280 to the cost of the operation. Staple line reinforcement with the absorbable polymer membrane might lead to the elimination of more expensive reoperations associated with staple line hemorrhage and bile leakage of longer hospital stays, or of intermittent radiologic procedures for drainage.

However, more randomized studies have to be performed in the near future—not only to prove the benefits but also to find broader indications for use of the absorbable polymer membrane. Until now, the bioabsorbable staple line reinforcement material was intended for use in surgical procedures in which soft

tissue transection or resection (gastric and lung resections) is needed. It seems that this material will also be extremely valuable in resection and reinforcement of abdominal solid organs.

Our patient elected to undergo a radical left lateral liver resection. In this procedure, the novel staple line reinforcement technique was used. This technique incorporated the absorbable polymer membrane in the stapler system, such that it buttressed the transected solid organ. Hemorrhage and bile duct leakage at the staple line were possibly prevented as a consequence. Staple line reinforcement with the absorbable polymer membrane might lead to the elimination of more expensive reoperations associated with staple line hemorrhage and bile leak.

The authors are grateful to Mariano Palermo, M.D., New York Presbyterian Hospital, Weill College of Medicine of Cornell University, Department of Surgery, New York, NY.

REFERENCES

1. Montorsi M, Santambrogio R, Bianchi P, et al. Laparoscopy with laparoscopic ultrasound for pretreatment staging of hepatocellular carcinoma: A prospective study. Laparoscopic Ultrasound 2001;5:312–315.
2. Descottes B, Lachachi F, Durand-Fontanier S, Sodji M, Pech de Laclause B, Valleix D. Traitement laparoscopique des tumeurs solides et kystiques du foie. Étude de 33 cas. Ann Chir 2000;125:941–947.
3. Kamel IR, Choti MA, Horton KM, et al. Surgically staged focal liver lesions: Accuracy and reproducibility of dual-phase helical CT for detection and characterization. Radiology 2003;227:752–757.
4. Descottes B, Glineur D, Lachachi F, et al. Laparoscopic liver resection of benign liver tumors. Surg Endosc 2003;17:23–30.
5. Cherqui D, Husson E, Hammoud R, et al. Laparoscopic liver resections: A feasibility study in 30 patients. Ann Surg 2000; 232:753–762.
6. Mouiel J, Kathkouda N, Gugenheim J, Fabiani P. Possibilities of laparoscopic liver resection. J Hepatobiliary Pancreat Surg 2000;7:1–8.
7. Gramática L Jr, Herrera MF, Mercado-Luna A, Sierra M, Verasay G, Brunner N. Videolaparoscopic resection of insulinomas: Experience in two institutions. World J Surg 2002; 26:1297–1300.
8. Furihata M, Tagaya N, Kubota K. Laparoscopic enucleation of insulinoma in the pancreas. Case report and review of the literature. Surg Laparosc Endosc Percutan Tech 2001;11: 279–283.
9. Fernández-Cruz L, Sáenz A, Astudillo E, et al. Outcome of laparoscopic pancreatic surgery: Endocrine and nonendocrine tumors. World J Surg 2002;26:1057–1065.
10. Brolin RE. Laboratory evaluation of four techniques of stapled gastroplasty. Surgery 1985;97:66–71.
11. Katz AR, Mukherjee DP, Kaganov AL, Gordon S. A new synthetic monofilament absorbable suture made from polytrimethylene carbonate. Surg gynecol obstet 1985;161:213–222.
12. Bourne RB, Bitar H, Andreae PR, Martin LM, Finlay JB, Marquis F. In-vivo comparison of four absorbable sutures: Vicryl, Dexon Plus, Maxon and PDS. Can J Surg 1988;31: 43–45.
13. Sanz LE, Patterson JA, Kamath R, Willett G, Ahmed SW, Butterfield AB. Comparison of Maxon suture with Vicryl, chromic catgut, and PDS sutures in fascial closure in rats. Obstet Gynecol 1988;71:418–422.
14. Metz SA, Chegini N, Masterson BJ. In vivo and in vitro degradation of monofilament absorbable sutures, PDS and Maxon. Biomaterials 1990;11:41–45.
15. Kangas J, Paasimaa S, Makela P, et al. Comparison of strength of poly-L/D-lactide (PLDLA) 96/4 and polyglyconate sutures: In vitro, in the subcutis, and in the Achilles tendon of rabbits. Inc J Biomed Mater Res 2001;58:121–126.
16. Kawamura M, Kase K, Sawafuji M, Watanabe M, Horinouchi H, Kobayashi K. Staple-line reinforcement with a new type of polyglycolic acid felt. Surg Laparosc Endosc Percutan Tech 2001;11:43–46.
17. Miller JI, Landreneau RJ, Wright CE, Santucci TS, Sammons BH. A comparative study of buttressed versus nonbuttressed staple line in pulmonary resections. Ann Thorac Surg 2001;71:319–322.
18. Murray KD, Ho CH, Hsia JY, Little AG. The influence of pulmonary staple line reinforcement on air leaks. Chest 2002; 122:2146–2149.
19. Itoh E, Matsuda S, Yamauchi K, et al. Synthetic absorbable film for prevention of air leaks after stapled pulmonary resection. J Biomed Mater Res 2000;53:640–645.
20. Fischel RJ, McKenna RJ. Bovine pericardium versus bovine collagen to buttress staples for lung reduction operations. Ann Thorac Surg 1998;65:217–219.
21. Hazelrigg SR, Boley TM, Naunheim KS, et al. Effect of bovine pericardial strips on air leak after stapled pulmonary resection. Ann Thorac Surg 1997;63:1573–1575.
22. Shikora SA, Kim JJ, Tarnoff ME. Reinforcing gastric staplelines with bovine pericardial strips may decrease the likelihood of gastric leak after laparoscopic Roux-en-Y gastric bypass. Obes Surg 2003;13:37–44.
23. Chae FH, McIntyre RC, Stiegmann GV. Laparoscopic bariatric surgery. Surg Endosc 1999;13:547–549.
24. Shamji MF, Maziak DE, Shamji FM, Matzinger FR, Perkins DG. Surgical staple metalloptysis after apical bullectomy: A reaction to bovine pericardium? Ann Thorac Surg 2002; 74:258–261.
25. Provencher S, Deslauriers J. Late complication of bovine pericardium patches used for lung volume reduction surgery. Eur J Cardiothorac Surg 2003;23:1059–1061.
26. Ahmed S, Marzouk K, Bhuiya T, Iqbal M, Rossol L. Asymptomatic expectoration of surgical staples complicating lung volume reduction surgery. Chest 2001;119:307–308.
27. Oey I, Waller D. Metalloptysis: A late complication of lung volume reduction surgery. Ann Thorac Surg 2001;71:1694–1695.

Portal Venous Reconstruction in a Living Liver Donor With an Anomalous Hepatic Arterial and Portal Venous Anatomy

Shigeru Marubashi, M.D., Keizo Dono, M.D., Ph.D., Masato Sakon, M.D., Ph.D., Kunihito Gotoh, M.D., Hidenori Takahashi, M.D., Kazuhiko Hashimoto, M.D., Masaru Kubota, M.D., Shinji Yamamoto, M.D., Atsushi Miyamoto, M.D., Ph.D., Hiroaki Nagano, M.D., Ph.D., Shoji Nakamori, M.D., Ph.D., Koji Umeshita, M.D., Ph.D., Morito Monden, M.D., Ph.D.

Hepatic arterial and portal venous anomalies in living liver donors are not uncommon. Modified surgical techniques may be required in such circumstances, although the safety of the living donor must always be given top priority. We describe here a successful portal venous reconstruction in a living donor with an anomalous hepatic arterial and portal venous anatomy in which the right anterior and posterior hepatic arteries encircled the main portal vein. Although such an anomaly of hepatic vessels was not frequently encountered, we should be able to alter the surgical strategy to deal with it. This case illustrates the importance of preoperative hepatic artery and portal venous evaluation in all living donors to identify the feasibility of modifying vessel anastomoses in living donors, as well as recipients, before living donor liver transplantation. (J GASTROINTEST SURG 2005;9:365–368)

KEY WORDS: Liver transplantation, living donor, portal vein, reconstruction

The safety of living liver donors has been emphasized, especially since the death of a living donor for the first time in Japan; several deaths have also occurred in Western countries.[1] Placing the lives of living donors in danger requires great courage. We report the case of a living right lobe liver donor with an unusual arterial anatomy in whom a portal venous reconstruction was inevitable to avoid arterial or portal venous complications in the recipient. This is the first report of a portal vein reconstruction performed in a living liver donor.

CASE REPORT

A 27-year-old man with acute fulminant hepatic failure resulting from a hepatitis B virus infection was transferred to our hospital for evaluation. The patient had been healthy until experiencing a general fatigue 2 weeks before hospital admission. His liver function progressively deteriorated, and he developed encephalopathy 1 week before admission to our hospital. He was intubated, and a sensor catheter for intracranial pressure monitoring was inserted because of a deep hepatic coma that occurred 3 days before admission to our hospital. His height was 170 cm and his weight was 97.1 kg at the time of admission. The health care team, which included hepatologists and transplant surgeons, discussed the case and concluded that an emergent liver transplantation was necessary to save the patient. A thorough explanation was presented to his family to identify a possible living liver donor. The patient had a younger brother who was 20 years old, but this family member decided not to donate part of his liver. As a result, the only volunteer donor candidate was the patient's mother. The mother was 54 years old and was of small stature. The three-dimensional image of a preoperative multi–detector-row computed tomography (MDCT) scan clearly revealed an anomalous hepatic arterial anatomy in which the right posterior hepatic artery passed behind the main portal vein while the right anterior hepatic artery passed in front of the main portal vein (Figs. 1, 2). The estimated volume of her right liver lobe [calculated using the following equation: 706.2 × body surface area (m^2) + 2.4^2)] was 580 mL (40.7% of the

From the Department of Surgery and Clinical Oncology, Osaka University, Graduate School of Medicine, Suita, Osaka, Japan.
Reprint requests: K. Dono, M.D., Department of Surgery and Clinical Oncology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita City, Osaka 565-0871, Japan. e-mail: kdono@surg2.med.osaka-u.ac.jp

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.05.019

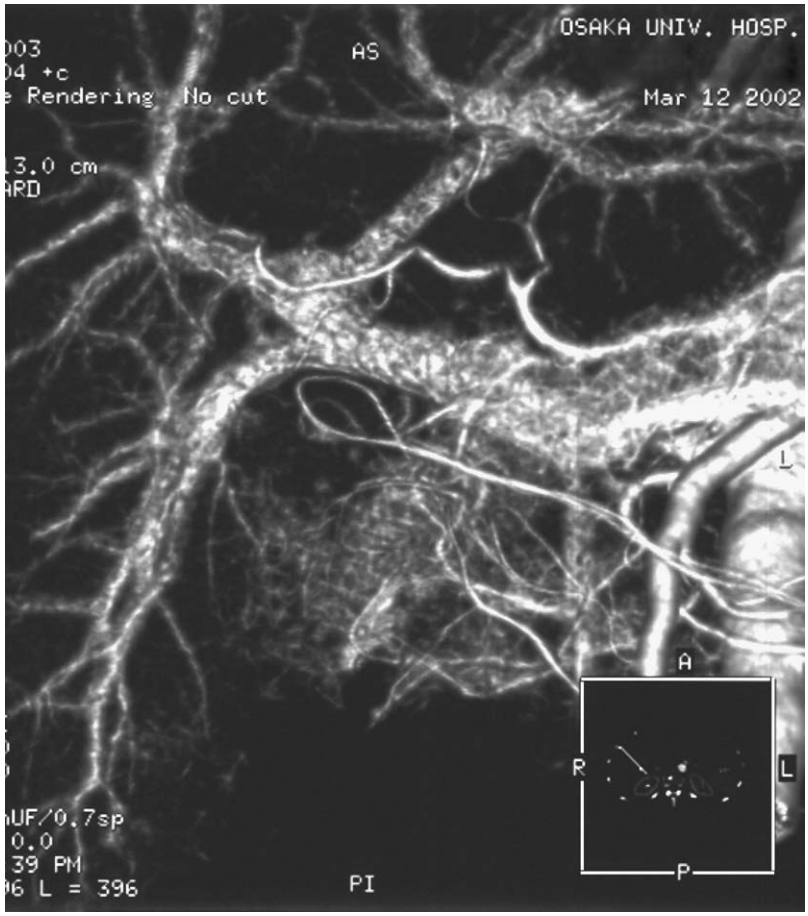

Fig. 1. Three-dimensional image from a multidetector-row CT scan. The right posterior hepatic artery passes behind the main portal vein, while the right anterior hepatic artery passes in front of the main portal vein. The right posterior portal vein branched off from the main portal vein and then divided into the right anterior portal vein and the left portal vein.

recipient's standard liver volume). The estimated volume of her left liver lobe was 385 ml (27.0% of the recipient's standard liver volume). Given the size of the recipient, a right lobe graft was thought to be necessary. The right hepatic artery was left in place because the posterior and anterior branches of the right hepatic artery were too small to reconstruct and maintain patency, even using a microscope to perform the arterial anastomosis. Thus, division and anastomosis of the donor's main portal vein after the extraction of the right lobe graft was adopted as the planned surgical strategy. A detailed explanation of the procedure and the risk to the donor was presented to the donor and other family members, and written informed consent was obtained before transplantation.

OPERATIVE TECHNIQUE

An emergent living donor liver transplantation (LDLT) was performed because of the patient's serious condition. The donor's portal vein was identified and exposed distally until the posterior and anterior branches of the right portal vein became visible, and the left portal vein was encircled distally to the trifurcation. The right hepatic artery was then exposed in the region of the portal vein. The right lobe, minus the middle hepatic vein, was then dissected. After the administration of heparin sodium (1500 units), the artery was cut at the level of the right hepatic artery (Fig. 2A) and the portal vein was transected proximal and distal to the trifurcation (Fig. 2B). The right liver lobe, weighing 602 g, was removed, and the donor's main portal vein and left portal vein were anastomosed using 6-0 Proline running sutures in an end-to-end fashion (Fig. 3).

The donor's postoperative course was uneventful. The hepatic artery and portal venous flow were examined by Doppler sonography during and after the operation; the donor's blood flow remained normal with no signs of stenosis or thrombus formation. CT examinations showed a normal-looking portal vein

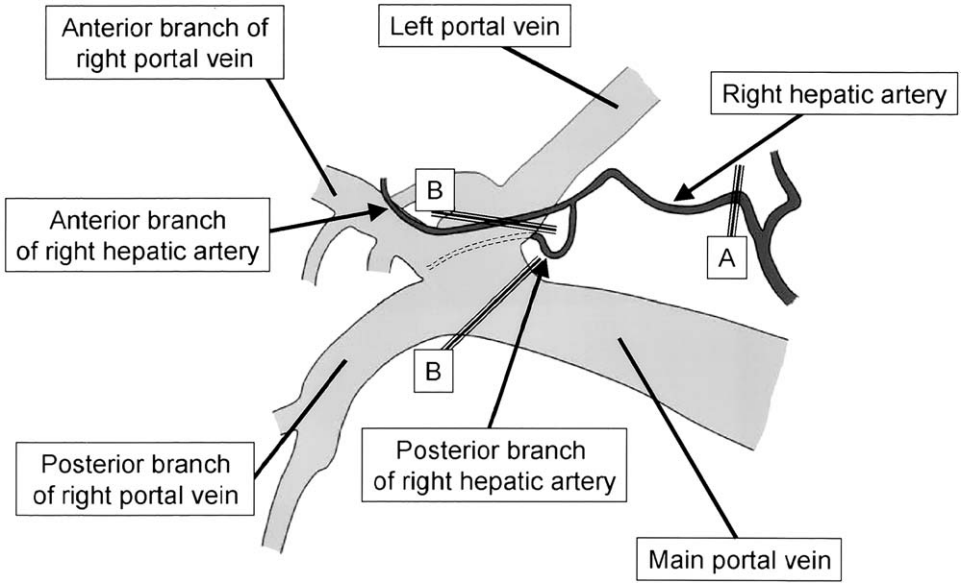

Fig. 2. Schematic view showing the three-dimensional relationship between the hepatic artery and the portal vein. The donor portal vein was transected (**B**), while the donor right hepatic artery was cut (**A**).

on postoperative days 30, 60, and 180. The donor is presently healthy and has not experienced any liver problems in the 2 years that have passed since the surgery.

The arterial and portal venous flows of the graft were also closely monitored during and after LDLT in the recipient. Although the blood flow through the hepatic vessels was excellent and showed no signs of complications, the recipient developed sepsis and died 2 months after the surgery.

DISCUSSION

Arterial and portal venous anatomies are quite important in adult-to-adult LDLTs. According to Gruttadauria et al.,[3] anomalous hepatic arteries were observed in 42% of 701 cases. The arterial anomaly presented here, in which the right anterior and posterior hepatic arteries encircled the main portal vein, belongs to type 5 of their classification system; in their series, the incidence of type 5 anomalies was 2.1%[3] and was not considered to be rare.[4] Although both arteries could have been separately anastomosed using the aid of a microscope, double arterial reconstruction in right liver lobe transplantations has been associated with an increased risk of hepatic arterial thrombosis compared with single simple reconstructions.[5,6]

Anomalies of the portal vein and its reconstruction in right lobe LDLT are also critical in many living donor cases. According to the classification of portal venous anomalies by Cheng et al.,[7] the present case belongs to the type III anomalous portal venous branching (APVB) classification. Lee et al.[8] reported that an anomalous portal venous anatomy was observed in 19 (8.9%) of 214 cases, with type III APVB anomalies accounting for 7 (3.3%) of the cases; in their series, a double anastomosis in donors with type III APVB anomalies increased the risk of portal vein thrombosis.

Portal vein reconstruction in association with a major hepatectomy is often performed for the treatment of primary hepatic cancer. Ebata et al.[9] reported that complications related to the portal vein reconstruction were not encountered in 52 consecutive cases requiring a hepatectomy with portal vein resection for the treatment of hilar cholangiocarcinoma. At our institution, we have performed more than 100 cases of portal vein reconstruction for hepatopancreatobiliary malignancies in the past 20 years and have not encountered any postoperative portal venous complications, such as portal venous thrombosis. Thus, reconstruction of the portal vein appears to be a safe technique with a very low morbidity rate.

In the case presented here, we decided to transect the donor portal vein and anastomose it in an end-to-end fashion, requiring one anastomosis of the portal vein and one anastomosis of the hepatic artery in the recipient, rather than securing the donor portal vein and producing two orifices in the right portal vein and two branches in the right hepatic artery requiring anastomoses. Although some physicians may disagree with the idea of placing the donor at risk by resecting the partial portal vein, because the safety of the living donor is of fundamental importance, we believe that

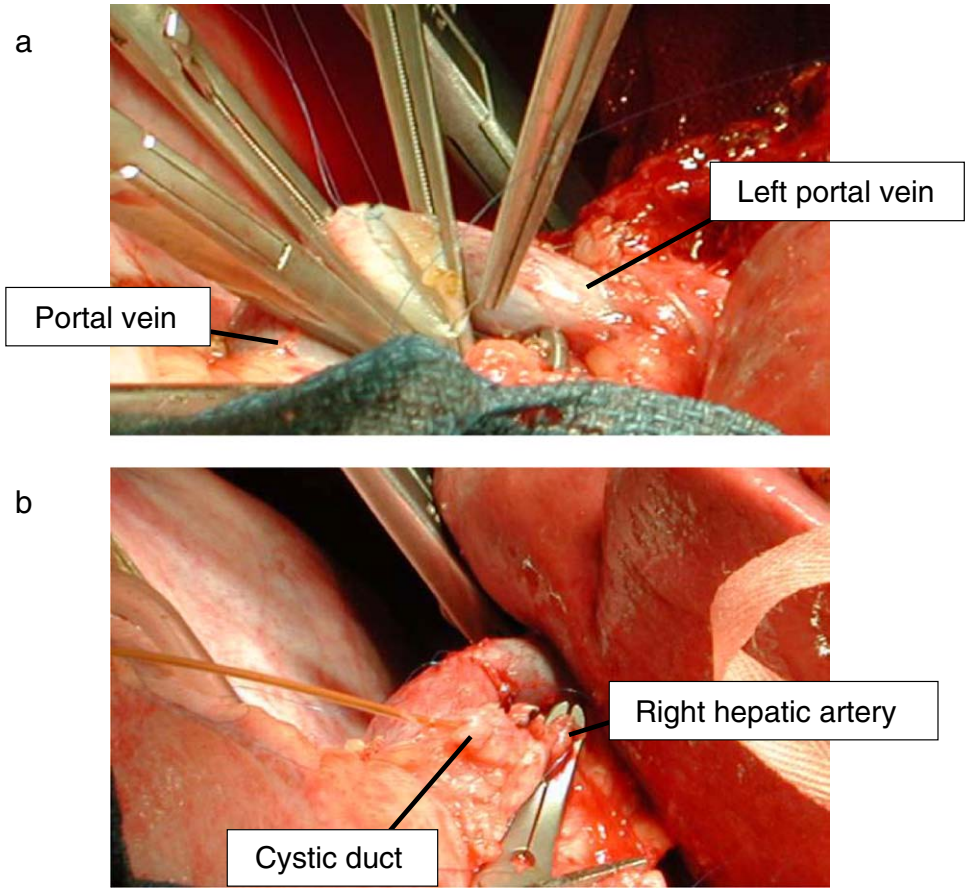

Fig. 3. (**a**) Reconstruction of the donor portal vein using 6-0 Proline running sutures. (**b**) Portal vein after declamping. Sufficient blood flow was confirmed using intraoperative Doppler sonography.

the portal venous reconstruction procedure performed in this report was justified because the risk of postoperative complications after the portal vein reconstruction was very low and the quality of the donated graft would have been poorer if double portal vein branch and double arterial branch reconstructions had been required, as discussed earlier. In this case, because the vascular anomaly was identified preoperatively, informed consent was obtained from the donor before the procedure. This case illustrates the importance of preoperative hepatic artery evaluations in addition to portal vein evaluation in all living donors to identify the feasibility of modifying vessel anastomoses in living donors, as well as recipients.

REFERENCES

1. Umeshita K, Fujiwara K, Kiyosawa K, et al. Operative morbidity of living liver donors in Japan. Lancet 2003;362:687–690.
2. Urata K, Kawasaki S, Matsunami H, et al. Calculation of child and adult standard liver volume for liver transplantation. Hepatology 1995;21:1317–1321.
3. Gruttadauria S, Foglieni CS, Doria C, Luca A, Lauro A, Marino IR. The hepatic artery in liver transplantation and surgery: Vascular anomalies in 701 cases. Clin Transplant 2001; 15:359–363.
4. Sugawara Y, Kaneko J, Akamatsu N, Makuuchi M. Arterial anatomy unsuitable for a right liver donation. Liver Transpl 2003;9:1116–1117.
5. Marcos A, Killackey M, Orloff MS, Mieles L, Bozorgzadeh A, Tan HP. Hepatic arterial reconstruction in 95 adult right lobe living donor liver transplants: Evolution of anastomotic technique. Liver Transpl 2003;9:570–574.
6. Soliman T, Bodingbauer M, Langer F, et al. The role of complex hepatic artery reconstruction in orthotopic liver transplantation. Liver Transpl 2003;9:970–975.
7. Cheng YF, Huang TL, Lee TY, Chen TY, Chen CL. Variation of the intrahepatic portal vein: Angiographic demonstration and application in living-related hepatic transplantation. Transplant Proc 1996;28:1667–1668.
8. Lee SG, Hwang S, Kim KH, et al. Approach to anatomic variations of the graft portal vein in right lobe living-donor liver transplantation. Transplantation 2003;75:S28–S32.
9. Ebata T, Nagino M, Kamiya J, Uesaka K, Nagasaka T, Nimura Y. Hepatectomy with portal vein resection for hilar cholangiocarcinoma: Audit of 52 consecutive cases. Ann Surg 2003;238:720–727.

Bile Duct Replacement Using an Autologous Femoral Vein Graft: An Experimental Study. Preliminary Results

Pablo Capitanich, M.D., Javier Herrera, M.D., Mario L. Iovaldi, M.D., Roque Balbuena, M.D., Gabriel Casas, M.D., Patricio Malizia, M.D., Maximiliano Bun, M.D., Norberto Mezzadri, M.D.

The repair of common bile duct injuries is a complex procedure with a significant rate of postoperative morbidity and mortality. The aim of this study was to demonstrate the usefulness of the autologous vein graft in replacement of the bile duct. Twelve male Sprague-Dawley rats weighing 350 ± 550 g were used in the study and were divided at random into two groups: the control group (60) and the experimental group in which a 3-mm segment of the bile duct was resected and the biliary tract was replaced by a segment of vein aided by stent (G1). Both groups were subdivided into pairs of rats to study at 30, 60, and 120 days. All of the animals underwent radioisotope cholangiography, a repeat laparotomy, and blood tests for further pathologic study. The clinical evaluation and biochemical nuclear medicine and pathologic studies showed no evidence of cholestasis. The histologic study of the graft showed replacement of the endothelium by biliary-appearing epithelium. The use of an autologous vein graft with a supporting stent proves to be a feasible and alternative procedure for bile duct reconstruction. Further experimental studies should be carried out to validate these findings so they can be implemented in clinical cases. (J GASTROINTEST SURG 2005;9:369–373)

KEY WORDS: Bile duct, autologous vein graft, replacement of bile duct

Biliary tract reconstruction is a challenging issue faced by surgeons.[1] Despite the advantages of laparoscopic procedures, the widespread application of the laparoscopic cholecystectomy has brought about an increase in the incidence of combined vascular and biliary injuries.[2,3] The prevalence of bile injuries in open cholecystectomy varies between 0% and 0.4%,[4,5] whereas for laparoscopic cholecystectomy, after the learning curve is surpassed, it remains well above those values (0.6%).[5,6]

Complications are likely to appear during repair of bile duct injuries and bile reconstruction in liver transplantation, and a great deal of expertise and training is necessary to obtain satisfactory results. The purpose of this work was to evaluate the usefulness of the femoral vein graft to replace the bile duct as an additional therapeutic resource.

MATERIAL AND METHODS

Twelve healthy male Sprague-Dawley rats weighing 350 ± 550 g were used in this experimental study, after the exclusion of 10 rats that died during the 24-hour postoperative period due to hemodynamic reasons. Two groups were formed: a control group (G0) and the group with bile duct replacement (G1).

After a 14-hour fasting period, the animals were anesthetized using a 25 mg/kg dose of thiopental, following which a left inguinal transverse incision was performed; 5–7 mL of venous blood was collected for further biochemical analysis, and a 5-mm segment of femoral vein was removed to be used as an autologous graft. The incision was sutured with linum 70 interrupted stitches.

Abdominal midline laparotomy was performed in the G0 group. After careful exploration, the abdominal wall was sutured in layers: the muscle was sutured

From the Departments of Surgery (P.C., J.H., M.L.I., P.M., M.B., N.M.), Radiology (R.B.), and Pathology (G.C.), Hospital Alemán, Buenos Aires, Argentina.
Reprint requests: Pablo Capitanich, M.D., Department of Surgery, Hospital Alemán, Av. Pueyrredon 1640, C1118AAT Buenos Aires, Argentina. e-mail: pcapitanich@hospitalaleman.com.ar

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.09.024

using polyglactin-910 (Vicryl), and the skin was sutured using 7.0 linen interrupted stitches.

All of the animals in the G1 group underwent a midline laparotomy; the bile duct was exposed, and a 3-mm segment was resected. The biliary tract was replaced using an autologous femoral vein graft aided by the use of a 0.7-mm tubular fluorinated ethylene propylene (FEP) polymer catheter (Johnson & Johnson Intl., Brussels, Belgium) as a stent. The femoral vein graft was then anastomosed to the proximal and distal stumps using a microsurgical technique with 10-0 nylon suture (magnification ×32) (Fig. 1). The abdominal wall was sutured following the same procedure as for the G0 group.

The animals were returned to individual cages in the hospital laboratory (Laboratory of Experimental Medicine, Hospital Alemán, Buenos Aires) for postoperative recovery at 21 ± 2° C with a 12-hour light/dark cycle (7:00 AM–7:00 PM). During the experiment, all of the animals were given food and water ad libitum. Their regular diet consisted of balanced rat food (16–18 % protein; Cargill, Argentina). Both groups were subdivided into paired sets of rats for histologic study at 30, 60, and 120 days, thus forming three subgroups of four animals each (G0 and G1: two animals per group).

After a set period, all of the animals were anesthetized; radioisotope cholangiography and laparotomy were performed, and blood samples were collected. For the biliary scintigraphy, the animals were administered ^{99m}Tc intravenous mebrofenin, a derivative of iminodiacetic acid. This radiopharmaceutical (drug plus radioisotope) is extracted from the blood by the hepatocytes and may or may not be conjugated in the hepatic cells to be later eliminated toward the small bowel lumen, thus allowing the assessment of hepatobiliary function and the intrahepatic and extrahepatic permeability of the excretory tract.

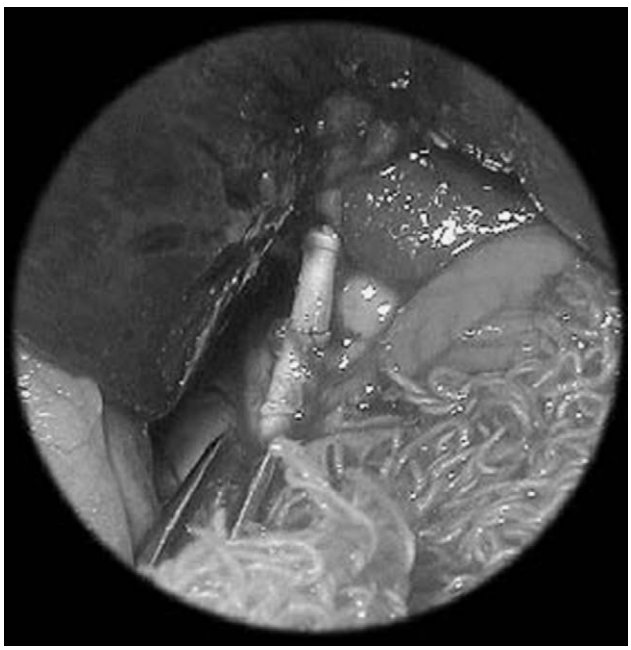

Fig. 1. Femoral vein graft after implantation.

Each animal was administered 0.5 mL mebrofenin with 2 mCi ^{99m}Tc in one of the tail veins, so that the gamma camera could obtain sequential images at 30 to 60 seconds during 30 minutes and then a static image at 45 minutes.

After a 14-hour fasting period, the animals were killed with an overdose of 40 mg/kg intraperitoneal thiopental, after which the bile duct was extracted and liver biopsy samples were collected in both groups for further histopathologic study. All experiments were conducted in accordance with the regulations of the Ethics Committee and the Teaching and Research Committee at Hospital Alemán, Buenos Aires, and the recommendations of the National Institutes of Health *Guide for the Care and Use of Laboratory Animals.*

Clinical, humoral testing, nuclear medicine imaging, and histopathologic parameters were assessed to determine cholestasis. All the rats were examined on a daily basis to complete the clinical follow-up for jaundice or scleral icterus, which suggests cholestasis.

Blood samples were obtained in the study to measure serum total bilirubin (STB), GOT (AST), and GPT (ALT) using the ultraviolet test; the kinetic method with para-nitrophenylphosphate substrate was used to assess alkaline phosphate (ALP) levels.

All of the biopsy samples taken for histopathologic examination were fixed in 10% phosphate-buffered formalin before routine processing through paraffin-embedded blocks. Sections that were 3 μm thick were cut and stained with hematoxylin and eosin. A sample of the vein graft was also examined before implantation, to compare evolutionary changes. Liver biopsies were assessed to identify any signs of cholestasis such as dilated canaliculi, bile thrombi, feathery degeneration, and swollen hepatocytes.

Statistical analysis was performed using the Student's *t* test, with significance set at $P < 0.05$.

RESULTS

Twelve of the 22 Sprague-Dawley rats survived without hemodynamic complications at 24 hours after the surgery, and six were distributed into each experimental group (G0 and G1). There was no significant difference between the preoperative and postoperative STB, GOT, GPT, and ALP values in the two groups (Table 1).

Table 1. Preoperative and postoperative serum values in both groups

		Group 0			Group 1			
	References	Preoperative	Postoperative	Variation	Preoperative	Postoperative	Variation	*P*
Serum total bilirubin (mg/dL)	0.1–0.3	0.1 ± 0.0	0.1 ± 0.0	0.002 ± 0.05	0.1 ± 0.1	0.2 ± 0.1	−0.005 ± 0.16	0.60
GOT	273–469	187 ± 35	198 ± 35	−11.50 ± 60.37	200 ± 109	180 ± 54	19.67 ± 116.70	0.57
GPT	50–98	50 ± 3	66 ± 37	−16.33 ± 37.36	57 ± 11	65 ± 8	−8.67 ± 15.68	0.65
Alkaline phosphate (IU/L)	142–298	433 ± 113	340 ± 93	92.67 ± 90.93	349 ± 48	332 ± 106	16.67 ± 81.66	0.16

The hypothesis test was applied to analyze the perioperative variations.

The sequential images provided by biliary scintigraphy revealed activity in the small bowel lumen at 15 minutes in all of the rats from both the experimental and control groups, thus indicating no abnormalities in their liver function and permeability of their excretory tract (Fig. 2).

Only one of the rats in the experimental group presented with dilatation of the vein graft at 60 days postoperatively (Fig. 3). This can be attributed to the early migration of the stent, resulting in a stenosis of the distal anastomotic site. In all of the other rats, the stent also migrated at the time of repeat laparotomy.

This was the only rat that presented with an area below the liver with simultaneous activity to the intestine passage during radioisotope cholangiography, which was interpreted as an initial delay in the elimination of the marker without alteration of permeability.

Microscopic examination demonstrated that in five of the vein grafts in the experimental group (G1), the endothelial lining had been entirely replaced by biliary-type epithelium (polygonal and columnar

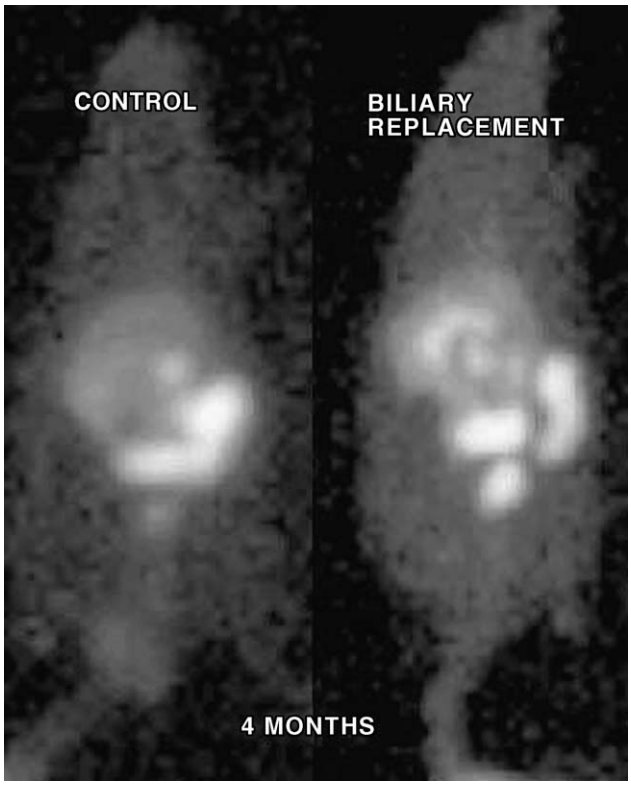

Fig. 2. Static radiosotopic cholangiography at 45 minutes. Presence of marker in the intestinal lumen in the control and biliary replacement groups at 4 months.

Fig. 3. Vein graft at 60 days with dilatation and evidence of permeability.

cells). The remaining graft showed a partial substitution. This has been interpreted as an intermediate stage between the loss of endothelium and its replacement with columnar epithelium (Figs. 4–7).

The hepatic biopsy performed in all of the 12 animals (6 in G0 and 6 in G1) showed signs of mild congestion with no signs of cholestasis.

DISCUSSION

Roux-en-Ycholangiojejunostomy,choledochoduodenostomy, end-to-end anastomosis, and reconstruction of lateral lesions using a T-tube are some of the techniques most widely used to repair major bile duct injuries. Roux-en-Y hepaticojejunostomy has proved to be a technique with low signs of cholangitis and excellent long-term results if performed in medical centers that specialize in complex hepatobiliary surgery.[1]

The field of hepatic transplantation offers a similar situation. The standard management of bile duct reconstruction is Roux-en-Y hepaticojejunostomy and end-to-end anastomosis. Because the jejunal limb is not very versatile, it makes biliary reconstruction difficult in the living related liver transplant with the presence of multiple small-caliber bile ducts. Li et al.[7] propose the use of an autologous vein graft, stating that such a technique would preserve the function of the papilla of Vater, thus preventing reflux and possible associated cholangitis. In this experimental study, the control group received an end-to-end anastomosis of the biliary tract after a complete section. This fact increases the probability of cholestasis in the control group, showing uniform results.

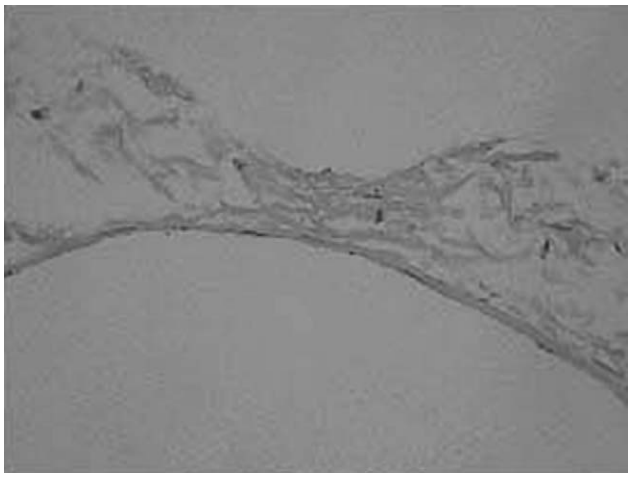

Fig. 4. Femoral vein covered with endothelial cells (hematoxylin and eosin stain; original magnification, ×140).

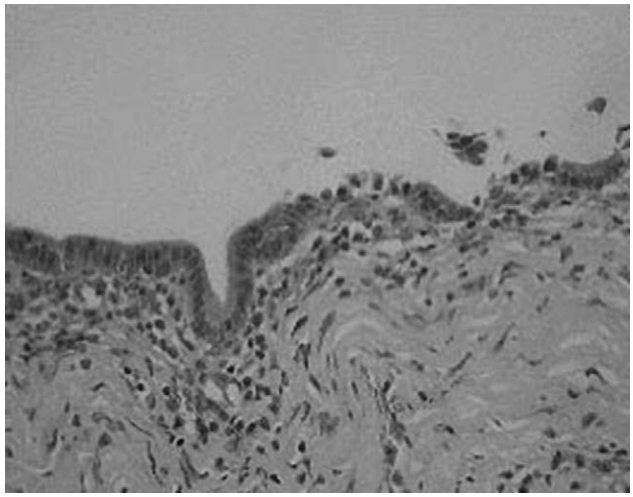

Fig. 5. Vein graft at 120 days postoperatively, covered by endothelial cells: polygonal (*right*) and columnar (*left*) cells (hematoxylin and eosin stain; original magnification, ×140).

Other authors have discussed the substitution of the graft endothelium with biliary epithelium in previous experimental models.[7–9] In their search for alternative therapies for bile duct injuries, other researchers[10] have tried Dacron prosthetic material in pigs with limited success as a definitive surgical repair; they concluded that granulation tissue after spontaneous removal of the prosthesis may be covered with biliary epithelium.

In their experimental study in dogs, Gomez et al.[11] conclude that the ductility and flexibility of thin-walled FEP-ringed Gore-Tex vascular grafts (W.L. Gore & Associates, Inc., Flagstaff, AZ) allows any

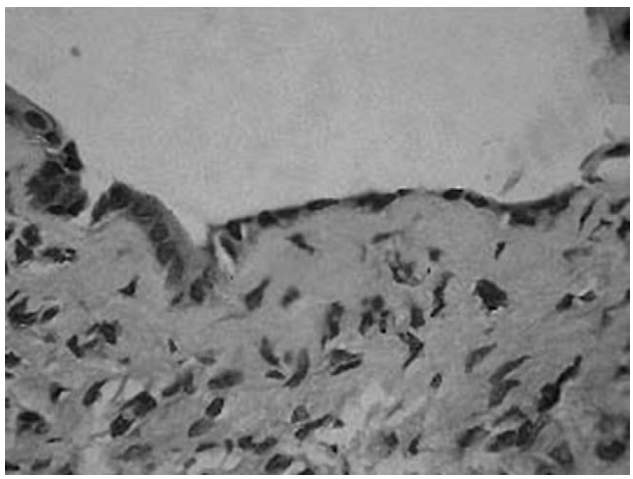

Fig. 6. Vein graft at 60 days postoperatively, covered by columnar epithelium with glandular structures and presence of moderate subendothelial lymphocytic infiltrate (hematoxylin and eosin stain; original magnification, ×140).

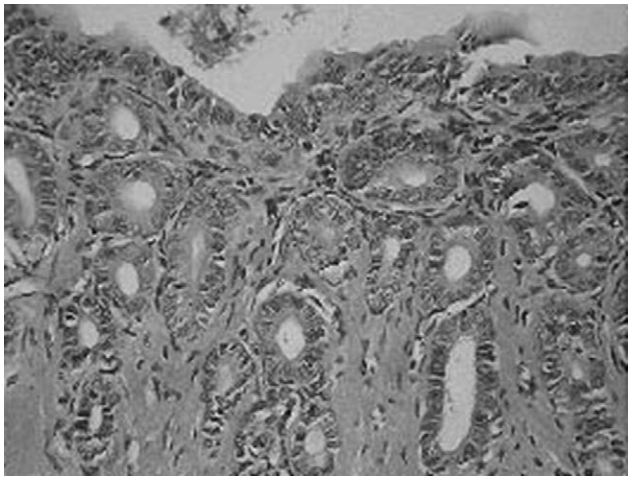

Fig. 7. Bile duct covered by columnar epithelium, showing numerous glandular structures (hematoxylin and eosin stain; original magnification, ×140).

type of required anastomosis to be performed. However, those prostheses were used mostly in choledochoduodenostomy, except for one case of end-to-end anastomosis. Moreover, their study lacked a control group for reference.

In the present study, clinical, humoral, and histologic examinations and radioisotope cholangiograms were performed, revealing no signs of cholestasis. No changes in perioperative or postoperative humoral variations were observed. However, both the control and the experimental groups showed an increase in the basal postoperative ALP level, in relation to the international values used for reference. Such a variation may be justified by surgical trauma or stress.[12]

Heistermann et al.[13] performed a similar study in a porcine model with 6-month follow-up. They showed that the group treated without stents had severe complications, whereas the group treated with stents had the same good results as ours.

The present study is the first experimental study in rats with 4-month follow-up using an autologous vein graft aided by stents, and the results demonstrate that the biliary replacement by an autologous vein graft is a feasible technique. However, the limited number of samples leads us to conclude that these results are preliminary, yet stimulating, in order to implement the use of an autologous femoral vein graft with stent as an alternative technique once its validity has been fully proved.

The authors thank Mariana Feldman, Laboratory of Experimental Medicine, for her support and assistance.

REFERENCES

1. Lillemoe KD, Melton GB, Cameron JL, et al. Postoperative bile duct strictures: Management and outcome in the 1990s. Ann Surg 2000;232:430–441.
2. Buell JF, Cronin DC, Funaki B, et al. Devastating and fatal complications associated with combined vascular and bile duct injuries during cholecystectomy. Arch Surg 2002;137:703–710.
3. Chapman WC, Abecassis M, Jarnagin W, Mulvihill S, Strasberg SM. Bile duct injuries 12 years after the introduction of laparoscopic cholecystectomy. J GASTROINTEST SURG 2003; 7:412–416.
4. Morgernstern L, Wong L, Berci G. Twelve hundred open cholecystectomies before the laparoscopic era: A standard for comparison. Arch Surg 1992;127:400–403.
5. The Southern Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 1991;324:107–108.
6. Deziel DJ, Millikan KW, Economou SG, Doolas A, Ko S, Airan MC. Complications of laparoscopic cholecystectomy: A national survey of 4,292 hospitals and an analysis of 77,604 cases. Am J Surg 1993;165:9–14.
7. Li JY, Zhang F, Moon W, et al. Biliary tract reconstruction using an autologous vein graft in rats. J Reconstr Microsurg 2000;16:51–55.
8. Karaayvaz M, Ugras S, Güler O, Aydin M, Alkan I, Yigit MF. Use of an autologous vein graft and stent in the repair of common bile defects: An experimental study. Surg Today 1998;28:830–833.
9. Wittrin G, Clemens M, Arndt M, Rühland D. Choledochusersatz durhr ein autologes. Venetransplantat Res Exp Med 1978;173:95–103.
10. Kasui K. Experimental biliary reconstruction with a Dacron graft which preserves the function of papilla Vater. Hokkaido Igaku Zasshi 1996;71:599–609.
11. Gomez NA, Alvarez LR, Mite A, et al. Repair of bile duct injuries with Gore-Tex vascular grafts: Experimental study in dogs. J GASTROINTEST SURG 2002;6:116–120.
12. Shinozaki T, Watanabe H, Takagishi K, Pritzker K. Allotype immunoglobulin enhances alkaline phosphatase activity: Implications for the inflammatory response. J Lab Clin Med 1998;132:320–328.
13. Heistermann HP, Palmes D, Hierlemann H, et al. Reconstruction of bile duct lesions by an autologous vein graft and a bio-degradable endoluminal stent in an animal model: Technique and clinical impact. Zentralbl Chir 2003;128: 952–957.

Analysis of Preoperative Prognostic Factors for Long-term Survival After Hepatic Resection of Liver Metastasis of Colorectal Carcinoma

Atsushi Sasaki, M.D., Yukio Iwashita, M.D., Kohei Shibata, M.D., Toshifumi Matsumoto, M.D., Masayuki Ohta, M.D., Seigo Kitano, M.D.

Hepatic resection is the most effective therapy for liver metastasis of colorectal carcinoma. To clarify indications for this therapy, the clinicopathologic and follow-up data of 103 consecutive patients who underwent hepatic resection for metastases of colorectal carcinoma were analyzed. Factors influencing overall survival rate were investigated by multivariate analysis. Thereafter, patients who underwent resection were stratified according to the number of independent risk factors present, and their outcomes were compared with those of 14 nonresection patients with fewer than six liver tumors and without extrahepatic metastasis. The overall survival rate of the 103 resection patients was 43.1%. The clinicopathologic factors shown to affect on long-term survival after hepatic resection were the interval between colorectal and hepatic surgery (<12 months), preoperative carcinoembryonic antigen level (≥10 ng/ml), and number of hepatic metastases (four or more). The 5-year overall survival rates were 75.0% with no risk factors (n = 16), 53.6% with one risk factor (n = 46), 23.0% with two risk factors (n = 36), and 0% with three risk factors (n = 5). Survival rates did not differ between resection patients with three risk factors and nonresection patients. Therefore, hepatic resection may be appropriate for patients with fewer than three risk factors. (J GASTROINTEST SURG 2005;9:374–380)

KEY WORDS: Colorectal carcinoma, liver metastasis, hepatic resection, risk factor, prognosis

The incidence of colorectal carcinoma has increased worldwide, and synchronous or metachronous liver metastasis occurs in about 30% of cases. Hepatic resection is considered the most effective therapy for metastasis of colorectal carcinoma to the liver, and the overall survival rate after hepatic resection is reported as 26%–51%.[1–10] Several clinicopathologic factors predictive of patient survival after hepatic resection have been identified: status of the primary colorectal carcinoma (tumor stage and grade),[1,2,4,6,8,9] interval between colorectal and hepatic surgery,[1,2,4,5,9] number of hepatic metastases,[1,3–9] distribution of hepatic tumors,[3,7] size of the liver tumor,[3,4,5] preoperative serum carcinoembryonic antigen (CEA) level,[10] and nodal metastasis in the hepatic hilum.[1,3,8] Most investigators agree that the interval between colorectal and hepatic surgery, number of hepatic tumors, and status of the primary colorectal cancer are the most important predictors of long-term survival.

Several investigators have proposed staging of colorectal liver metastasis; stages would predict postoperative survival of patients.[3,4,9,11] Fortner et al.[11] listed the risk factors as invasion of a major intrahepatic vessel or bile duct, distribution of the hepatic tumors, invasion of perihepatic organs, and distant metastasis including nodal metastasis. Gayowski et al.[3] listed factors such as the number of metastatic tumors (solitary versus multiple), size of metastasis (larger or smaller than 2 cm in diameter), location of the liver tumor (one or both lobes), major vessel invasion, and extrahepatic metastasis. Ueno et al.[9] proposed a preoperative staging system based on the primary tumor features (degree of tumor budding and nodal status), time to the diagnosis of liver metastases, and number of liver tumors. Unfortunately, all three of these staging systems include many factors and are too complex for preoperative use. The search continues

From the Department of Surgery I, Oita University Faculty of Medicine, Oita, Japan.
Reprint requests: Atsushi Sasaki, M.D., Ph.D., Department of Surgery I, Oita University Faculty of Medicine, 1-1 Hasama-machi, Oita 879-5593, Japan. e-mail: sasakia@med.oita-u.ac.jp

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.09.031

for a simple preoperative staging system for liver metastasis of colorectal carcinoma.

The prognosis of patients with colorectal liver metastasis who undergo nonsurgical treatment or who do not undergo treatment remains very poor, despite advances in chemotherapy.[12–15] The median survival time of patients who receive nonsurgical treatment is reportedly less than 20 months.[12–15] In a randomized controlled study of the outcomes of patients who underwent various treatments for multiple (<15) resectable colorectal liver metastases, Wagman et al.[14] observed no significant difference between resection and nonresection patients. Their results and results of other investigations into risk factors have led to the notion that careful selection of patients for hepatic resection of metastases from colorectal cancer is necessary to improve long-term survival, but the indications for hepatic resection for liver metastasis of colorectal cancer have not been well established. Absolute contraindications for resection of liver metastases from colorectal carcinoma have not been clearly defined, but most investigators agree that patients should not be offered hepatic resection if they have uncontrolled primary disease or such widespread hepatic involvement that residual liver function after resection would be inadequate.[16] Aggressive surgical management of multiple colorectal liver metastases has reportedly improved survival of selected patients.[17,18]

In the present study, we attempted to clarify the preoperative risk factors affecting long-term survival after hepatic resection for colorectal liver metastasis and to propose a staging system for predicting long-term postoperative results. In addition, to clarify the indications for resection in cases of liver metastasis of colorectal carcinoma, we compared the long-term survival of resection patients stratified by risk factors with that of nonresection patients.

MATERIAL AND METHODS

During the period of January 1985 through December 2003, 125 patients with liver metastases from colorectal cancer underwent hepatic resection at the Department of Surgery I, Oita University Faculty of Medicine. Twenty-two patients were excluded from the study: three (2.4%) who died of postoperative complications within 30 days, two who had obvious residual tumor at the time of surgery, seven who underwent hepatic resection and thermal ablation therapy for residual hepatic tumors, seven who had extrahepatic metastasis before or at the time of hepatic resection, one who was lost to follow-up, and two for whom clinicopathologic data were unclear. All 103 patients were regularly followed at our outpatient clinic and monitored for recurrence by assessment of serum tumor markers every 2 months and by ultrasonography or contrast-enhanced computed tomography scanning every 4 to 6 months.

We investigated 10 clinicopathologic variables pertaining to patient characteristics, clinical data, and histopathologic findings such as gender, age, interval between colorectal and hepatic resection, number of hepatic metastases, tumor diameter, preoperative CEA level, site of primary tumor, Dukes classification, tumor differentiation of primary tumor, and extent of surgical resection (Table 1). The extent of surgical resection was defined according to Couinaud's classification system; minor hepatic resection as resection of less than two segments and major hepatic resection as resection of two or more segments. Patient outcomes were determined on the basis of clinical data obtained from files as of January 31, 2004. Thus, the mean and median follow-up periods of the 103 patients after hepatic resection were 37.8 and 24.0 months, respectively (range, 1–226 months). The prognostic significance of clinicopathologic factors in relation to cancer-related overall survival rates was investigated by univariate and multivariate analyses. Data were censored in the analysis of overall survival if a patient was living or had died of unrelated disease and in the analysis of disease-free survival if a patient was living or had died of unrelated disease without recurrent colorectal carcinoma. Survival rates were calculated by the Kaplan-Meier method and compared statistically by univariate log-rank analysis. Variables with a value of $P < 0.1$ in univariate analysis were used in subsequent multivariate analysis based on Cox's proportional hazards model.

During the same period, 27 patients with colorectal liver metastasis and no extrahepatic metastasis received nonsurgical treatment at our hospital. Fourteen of these patients who had fewer than seven liver metastases were compared on the basis of clinicopathologic factors and outcome after admission with the 103 resection patients stratified by the number of risk factors. In the comparisons of clinicopathologic factors and treatment methods, continuous variables were analyzed by Kruskal-Wallis test, and nominal variables were analyzed by Fisher's exact probability test. A value of $P < 0.05$ was considered significant in all analyses. Statistical analysis was performed with JMP software (JMP, SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

The 103 patients who underwent hepatic resection with a curative intent included 56 men and 47

Table 1. Results of univariate analysis of clinicopathologic factors affecting overall survival rate after hepatic resection

Clinicopathologic variable	No. of patients	5-Year survival rate (%)	Univariate analysis: *P* value	MULTIVARIATE ANALYSIS	
				Relative risk (CI)	*P* value
Gender					
Male	56	41.1	0.89	—	—
Female	47	46.6			
Age (yrs)					
≤60	32	40.7	0.47	—	—
>60	71	45.0			
Interval (mos)*					
<12	66	33.1	0.03	2.12	0.04
≥12	37	61.2		(1.04–4.74)	
No. of metastasis					
<4	97	45.8	<0.01	3.22	0.04
≥4	6	0		(1.06–8.11)	
Tumor diameter (cm)					
<5	76	47.7	0.14	—	—
≥5	27	32.6			
Preoperative CEA (ng/ml)					
<10	42	65.2	0.01	2.17	0.04
≥10	61	30.0		(1.05–4.95)	
Primary site					
Colon	71	40.4	0.85	—	—
Rectum	32	48.5			
Dukes stage					
A or B	44	48.0	0.32	—	—
C	59	39.6			
Tumor differentiation					
Well	48	39.4	0.21	—	—
Nonwell	54	45.9			
Surgical procedure†					
Minor	60	40.4	0.66	—	—
Major	43	47.9			

CEA = carcinoembryonic antigen; CI = confidence interval.
*Interval between colorectal and hepatic surgery.
†Minor hepatic resection as resection of less than two segments and major hepatic resection as resection of two or more segments.

women with a mean age of 64.0 years. The mean interval between colorectal and hepatic surgery was 13.4 months (range, 0–103 months). The mean number and size of hepatic tumors were 1.6 (range, 2–6) and 42.4 mm (range, 10–130 mm), respectively. Sixty-seven patients had one metastatic liver tumor, 19 had two, 11 had three, 3 had four, 2 had five, and 1 had six. The mean preoperative serum level of CEA was 91.9 ng/ml (range, 0–1637 ng/ml; median, 17.6 ng/ml). The primary tumor was located in the colon in 71 (68.9%) patients and in the rectum in 32 (31.1%) patients. According to the Dukes classification system, 44 (42.7%) of the primary tumors were stage A or B and 59 (57.3%) were stage C. Histologically, there were 48 well-differentiated primary tumors (including one papillary adenocarcinoma) and 54 non–well-differentiated primary tumors (50 moderately differentiated and 3 poorly differentiated tumors and 1 adenosquamous carcinoma). Forty-three patients underwent major hepatic resection and 60 underwent minor hepatic resection (limited resection, 38; segmentectomy, 18; segmentectomy plus limited resection, 4).

Survival Analyses

Of the 103 patients who underwent hepatic resection with a curative intent, 45 patients had died by January 31, 2004. The causes of death were colorectal cancer (n = 39), liver failure unrelated to viral infection (n = 2), liver cirrhosis related to hepatitis viral infection (n = 1), acute myocardial infarction (n = 1), pneumonia (n = 1), and necrotizing myositis (n = 1). The 5-year overall and disease-free survival

rates of the 103 patients were 43.1% and 30.0%, respectively. Univariate analysis identified a short interval between colorectal and hepatic resection (<12 months), increased number of hepatic metastases (four or more tumors), and elevated preoperative CEA level (≥10 ng/ml) as adverse prognostic factors ($P < 0.1$) for overall survival after hepatic resection. Multivariate analysis also indicated that a short interval between colorectal and hepatic resection (relative risk [RR], 2.12; confidence interval [CI], 1.04–4.74], increased number of hepatic metastases (RR, 3.22; CI, 1.06–8.11), and elevated preoperative CEA level (RR, 2.17; CI, 1.05–4.95) were significant factors affecting overall survival after hepatic resection.

Preoperative Staging for Colorectal Liver Metastasis and Comparison Between Resected and Nonresected Patients

All patients were assigned a score (0–3) according to the number of risk factors present (Table 2). In the resection group, 16 patients had a score of 0, 46 had a score of 1, 36 had a score of 2, and 5 had a score of 3. In the nonresection group, 1 patient had a score of 0, 6 had a score of 1, 12 had a score of 2, and 12 had a score of 3. Survival curves were drawn for resection patients, who were stratified by the number of risk factors present. The 5-year cumulative survival rates after hepatic resection were 75.0% in score 0 patients, 53.6% in score 1 patients, 23.0% in score 3 patients, and 0% in score 3 patients (Fig. 1). The survival rate after hepatic resection was significantly lower in patients with a score of 3 than in patients with other scores ($P < 0.01$ for each, log-rank test).

To clarify the contribution of hepatic resection to survival outcomes, we compared the survival curves of resection and nonresection patients. The nonresection patients had not undergone hepatic resection because of multiple bilobar metastases (n = 8), poor residual liver function (n = 2, due to idiopathic portal hypertension and with liver cirrhosis related to hepatitis C virus infection), refusal of hepatic resection (n = 2), tumor thrombosis in the portal trunk (n = 1), and extensive invasion to the inferior vena cava (n = 1). The preoperative serum CEA level was not determined in one patient in the nonresection group. Clinicopathologic factors are shown according to risk scores and in comparison with those in the nonresection group in Table 3. The number of hepatic metastases was significantly higher ($P = 0.02$) in the score 3 resection group than in the nonresection group. There were no significant differences in other clinicopathologic factors between the score 3 resection group and the nonresection group, and there was no significant difference in survival between the score 3 resection group and the nonresection group (Fig. 1).

Table 2. Proposed criteria for preoperative staging of colorectal liver metastasis without extrahepatic metastasis

Positive risk factor	Score
Interval between hepatic and colorectal surgery	
≥12 mo	0
<12 mo	1
No. of liver metastases	
<4	0
≥4	1
Preoperative CEA level (ng/ml)	
<10	0
≥10	1

CEA = carcinoembryonic antigen.

DISCUSSION

Hepatic resection is accepted as the most effective therapy for patients with colorectal liver metastasis. Patient outcomes after hepatic resection have improved during the past two decades. According to recent studies, the 5-year survival rates after hepatic resection have been about 40%.[5,7,8,10] This improvement in survival is due not only to improvements in surgical techniques and postoperative management but also to selection of patients for resection based on risk factors affecting survival. Many investigators report risk factors for adverse outcome after hepatic resection and propose that these factors be used for patient selection. The interval between colorectal and hepatic surgery,[1,2,4,5,9] number of hepatic tumors,[1,3–9] preoperative CEA level,[10] and status of the primary colorectal cancer[1,2,4,6,8,9] are considered the most important predictors of outcome. As in previous studies, the important predictors of adverse patient outcome in this study were a short interval between colorectal and hepatic resection (<12 months), high number of liver metastases (four or more), and elevated preoperative CEA level (≥10 ng/ml). Many authors include therapeutic factors such as surgical margin[1,2,4–7,10] or histologic features of hepatic tumors[7,19] in their assessment of survival risks. Because the aim of this study was to clarify the preoperative risk factors affecting long-term survival after hepatic resection and to propose a preoperative staging system, we excluded therapeutic factors and histopathologic characteristics of hepatic tumors from the analysis.

Several authors have proposed preoperative staging systems for liver metastasis of colorectal cancer to predict patient survival after hepatic resection.

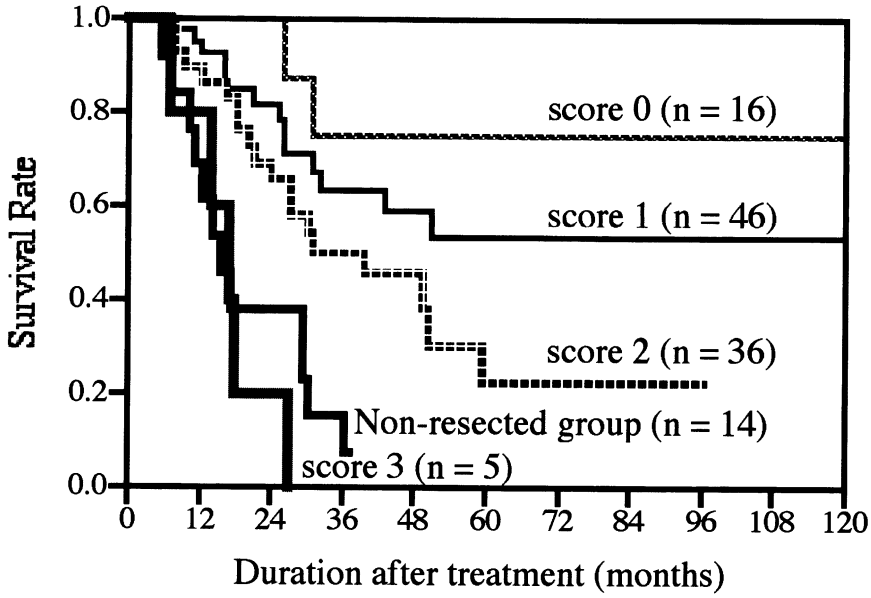

Fig. 1. Cumulative survival curves after admission according to risk factor scores (0–3). The 5-year cumulative survival rates after hepatic resection are 75% for score 0, 53.6% for score 1, 23.0% for score 2, and 0% for score 3 patients. Survival rates did not differ significantly between resection score 3 patients and nonresection patients.

Fortner et al.[11] proposed a three-stage system: stage I indicates hepatic tumor without invasion of major intrahepatic vessels or bile ducts; stage II, regional spread (tumor rupture, direct extension to adjacent organs, histologically positive resection margin) or direct invasion of major vessels or bile ducts; and stage III, presence of lymph node metastases and other intra-abdominal or distant metastases. Gayowski et al.[3] proposed a TNM staging system for colorectal liver metastases based on tumor distribution, number of metastases, tumor size, and presence of disease not confined to the liver. They also included invasion of

Table 3. Patient characteristics in the resection and nonresection groups

	RESECTION GROUPS (n = 103)				
	Score 0 (n = 16)	**Score 1 (n = 46)**	**Score 2 (n = 36)**	**Score 3 (n = 5)**	**Nonresection group (n = 14)**
Gender					
Male	12	26	16	2	7
Female	4	20	20	3	7
Mean age (yr)	63.4	61.9	65.3	69.8	62.1
Mean interval (mo)*	34.4	13.4	5.5	3.0	1.9
Mean No. of liver tumors	1.1	1.3	1.8	4.6	2.9
Mean CEA (ng/ml)	2.6	62.7	174.0	56.3	101.0
Mean tumor diameter (cm)	4.4	4.0	4.5	4.0	5.9
Primary site					
Colon	10	30	27	4	9
Rectum	6	16	9	1	5
Dukes stage					
A or B	9	22	12	1	4
C	7	24	24	4	10
Tumor differentiation					
Well	8	22	17	1	4
Nonwell	8	23	19	4	10

CEA = carcinoembryonic antigen.
*Interval between colorectal and hepatic surgery.

a major vessel or bile duct in the scoring. Nordlinger et al.[4] proposed a prognostic scoring system in which seven variables were considered adverse factors: age greater than 60 years, diameter of the largest lesion greater than 5 cm, extension of the primary cancer into the serosa, lymphatic spread of the primary cancer, disease-free interval less than 2 years, number of liver nodules of four or more, and resection margin less than 1 cm. Because this scoring system includes intraoperative or histologic factors (invasion to major vessels or bile ducts and surgical margin), [3,4,11] it cannot be used for preoperative assessment of hepatic metastasis. Other authors have proposed scoring systems that include only preoperative factors. Fong et al.[20] developed a preoperative clinical scoring system for predicting recurrence after hepatic resection. They listed five adverse preoperative factors: node-positive primary cancer, disease-free interval before the discovery of liver metastases less than 12 months, number of tumors greater than one, preoperative CEA level greater than 200 ng/ml, and diameter of the largest tumor greater than 5 cm. Ueno et al.[9] proposed prognostic staging before hepatectomy on the basis of three factors: primary site aggressiveness (marked tumor budding and/or extended nodal metastasis), time of diagnosis (synchronously or <1 year after the primary surgery), and number of liver metastases of three or more. However, this system was too complicated for clinical use. The three independent risk factors identified in our study, and the associated four-point scoring system, partly resemble the system of Fong and colleagues.[20] In studies incorporating a prognostic scoring system, the 5-year survival rate after hepatic resection was about 60% in the low-score group and about 20% in the high-score group.[3,9,20] The survival results in the equivalent preoperative score group in our study agree with those of the previous survival investigations.[3,9,20]

The indications for hepatic resection for colorectal liver metastasis have remained controversial. The previous studies of hepatic resection did not lead to strict criteria for hepatic resection. There are no established contraindications to resection of colorectal liver metastasis, but the procedure is not generally offered to patients with uncontrolled primary disease or such widespread hepatic involvement that residual liver function after resection would be inadequate.[16] Recent studies show that resection of multiple bilobar hepatic metastases or both liver and pulmonary metastases can result in long-term survival in selected patients.[17,18] Some investigators specify indications for hepatic resection such as good control of the primary tumor, no sign on preoperative images of disseminated disease, and expected complete resection of hepatic metastasis with acceptable postoperative hepatic function.[5,6,8,20] In the present study, the survival rate of score 3 patients did not differ from that of the selected (no extrahepatic metastasis and fewer than seven hepatic tumors) nonresection patients. Despite the small number of patients in our study, our results suggest that hepatic resection should not be offered to patients with three risk factors present.

The prognosis of nonresection patients with colorectal liver metastasis is reportedly very poor. Wagner et al.[12] investigated the natural history of colorectal liver metastases and reported that the 3-year survival rate was 21% in patients with solitary lesions, 6% in patients with multiple unilateral lesions, and 4% in patients with multiple widespread lesions. Steele et al.[15] compared outcomes associated with curative resection, noncurative resection, and no resection and reported that noncurative resection provides no benefit to asymptomatic patients because patients who undergo noncurative resection have a life expectancy similar to that of patients treated nonsurgically. Wagman et al.[14] performed a randomized evaluation of the treatment of colorectal liver metastasis. In their study, patients with multiple surgically resectable liver metastases (<15 metastases, no involvement of portal structures, and <50% liver involvement) were randomized to complete resection with adjuvant chemotherapy or to chemotherapy only. The median survival time did not differ significantly between resection (19.8 months) and nonresection (22.4 months) patients. In their series, the mean number of hepatic tumors was greater in the nonresection group (mean, 2.9; range, 2–7) than in the resection group (mean, 4.5; range, 4–10). No other risk factors were described. In the present study, the survival rate after hepatic resection in patients with a risk score less than 3 was superior to that in resection patients with a score of 3 and in nonresection patients. All resection patients with a score of 3 died within 3 years after hepatic resection.

In conclusion, the three factors adversely affecting survival after hepatic resection for colorectal liver metastasis are a short interval between colorectal and hepatic surgery (<12 months), elevated preoperative CEA level (≥10 ng/ml), and more than four hepatic metastases. Therefore, hepatic resection may be appropriate for patients with fewer than three risk factors.

REFERENCES

1. Registry of Hepatic Metastases. Resection of the liver for colorectal carcinoma metastases: A multi-institutional study of indications for resection. Surgery 1988;103:278–288.
2. Scheele J, Stangl R, Altendorf-Hofmann A, Gall FP. Indicators of prognosis after hepatic resection for colorectal secondaries. Surgery 1991;110:13–29.

3. Gayowski TJ, Iwatsuki S, Madariaga JR, et al. Experience in hepatic resection for metastatic colorectal cancer: Analysis of clinical and pathologic risk factors. Surgery 1994;116:703–711.
4. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Cancer 1996;77:1254–1262.
5. Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. J Clin Oncol 1997;15:938–946.
6. Ambiru S, Miyazaki M, Isono T, et al. Hepatic resection for colorectal metastases: Analysis of prognostic factors. Dis Colon Rectum 1999;42:632–639.
7. Yamamoto J, Shimada K, Kosuge T, Yamasaki S, Sakamoto M, Fukuda H. Factors influencing survival of patients undergoing hepatectomy for colorectal metastases. Br J Surg 1999;86:332–337.
8. Minagawa M, Makuuchi M, Torzilli G, et al. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: Long-term results. Ann Surg 2000;231:487–499.
9. Ueno H, Mochizuki H, Hatsuse K, Hase K, Yamamoto T. Indicators for treatment strategies of colorectal liver metastases. Ann Surg 2000;231:59–66.
10. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759–766.
11. Fortner JG, Silva JS, Golbey RB, Cox EB, Maclean BJ. Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. Treatment by hepatic resection. Ann Surg 1984;199:306–316.
12. Wagner JS, Adson MA, Van Heerden JA, Adson MH, Ilstrup DM. The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment. Ann Surg 1984;199:502–508.
13. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: Impact of surgical resection on the natural history. Br J Surg 1990;77:1241–1246.
14. Wagman LD, Kemeny MM, Leong L, et al. A prospective, randomized evaluation of the treatment of colorectal cancer metastatic to the liver. J Clin Oncol 1990;8:1885–1893.
15. Steele G Jr, Bleday R, Mayer RJ, Lindblad A, Petrelli N, Weaver D. A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: Gastrointestinal Tumor Study Group Protocol 6584. J Clin Oncol 1991;9:1105–1112.
16. Hugh TJ, Kinsella AR, Poston GJ. Management strategies for colorectal liver metastases. Part II. Surg Oncol 1997;6:31–48.
17. Bolton JS, Fuhrman GM. Survival after resection of multiple bilobar hepatic metastases from colorectal carcinoma. Ann Surg 2000;231:743–751.
18. Ambiru S, Miyazaki M, Ito H, et al. Resection of hepatic and pulmonary metastases in patients with colorectal carcinoma. Cancer 1998;82:274–278.
19. Sasaki A, Aramaki M, Kawano K, Yasuda K, Inomata M, Kitano S. Prognostic significance of intrahepatic lymphatic invasion in patients with hepatic resection due to metastases from colorectal carcinoma. Cancer 2002;95:105–111.
20. 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;230:309–321.

Laparoscopic Surgery in Patients With Sporadic and Multiple Insulinomas Associated With Multiple Endocrine Neoplasia Type 1

Laureano Fernández-Cruz, M.D., F.R.C.S.(Ed.), Isidro Martínez, M.D., Gleydson Cesar-Borges, M.D., Emiliano Astudillo, M.D., David Orduña, M.D., Irene Halperin, M.D., Gemma Sesmilo, M.D., Manuel Puig, M.D.

There have recently been reports of a limited number of laparoscopic procedures in patients with clinically manifest hyperinsulinism. However, the precise role of laparoscopy remains unknown. Between January 1998 and September 2003, 11 consecutive patients (10 women and 1 man; mean age, 40 years; age range, 22–66 years) with sporadic insulinoma and two female patients (25 and 40 years old) with multiple insulinomas associated with multiple endocrine neoplasia type 1 (MEN-1) were operated on using the laparoscopic approach. Endoscopic ultrasonography was used to localize the tumor preoperatively in 90% of patients with sporadic insulinoma. In patients with MEN-1, computed tomography and octreoscan-^{111}In demonstrated multiple tumors. Laparoscopic ultrasonography (LapUS) was performed in all patients for operative decision-making. Of 11 patients with sporadic insulinoma, laparoscopic enucleation (LapEn) was planned in 8 patients, but in 1 patient, the use of LapUS missed the tumor and the patient was converted to open surgery. Mean operating time after LapEn (seven patients) was 180 minutes, and the mean blood loss was 200 ml. The mean hospital stay was 5 days. In three of the 11 patients, laparoscopic spleen-preserving distal pancreatectomy (LapSPDP) was performed; the mean operative time was 240 minutes, and the mean blood loss was 360 ml. Postoperative complications occurred in three of seven patients after LapEn (three pancreatic fistulas managed conservatively, and one case of bleeding requiring reoperation). LapSPDP was performed in both patients with MEN-1; in one patient with splenic vessel preservation (SVP), the operating time was 210 minutes and blood loss was 650 ml, with a hospital stay of 6 days. In another patient without SVP, the operating time was 150 minutes and blood loss was 300 ml. The latter patient developed a 4-cm splenic infarct managed conservatively, and the hospital stay was 14 days. LapEn and LapSPDP are feasible and safe and achieved cure in patients with sporadic insulinoma and multiple insulinomas associated with MEN-1. However, the risk of pancreatic leakage after LapEn remains high, and LapSPDP without SVP may be associated with splenic infarct. (J GASTROINTEST SURG 2005;9:381–388)

KEY WORDS: Laparoscopic enucleation, laparoscopic resection, insulinoma

Laparoscopic pancreatic procedures are still at the stage of evaluation with regard to their indications and the technical variations used. We and others have reported the feasibility of laparoscopic pancreatic surgery in patients with benign-appearing pancreatic tumors.[1–4] Recently, there have been reports of a limited number of laparoscopic procedures, including distal pancreatectomy with and without splenic preservation and laparoscopic enucleation of sporadic insulinomas in patients with clinically manifest hyperinsulinism.[5–17] Sporadic insulinomas are suitable for the laparoscopic approach on the basic of its characteristics of being solitary, small, resectable, and not metastatic; only occasionally (10%) are they multicentric. However, whenever insulinomas are multiple, multiple endocrine neoplasia type 1 (MEN-1) should be suspected.[18]

Sporadic insulinomas and insulinomas in patients with MEN-1 may arise at different times. Insulinomas occur more often in MEN-1 patients who are

From the Department of Surgery (L.F.-C., I.M., G.C.-B., E.A., D.O., M.P.), Institut Malaltias Digestivas, and the Endocrine and Diabetes Unit (I.H., G.S.), Hospital Clinic i Provincial de Barcelona, Barcelona, Spain.
Reprint requests: L. Fernández-Cruz, M.D., F.R.C.S.(Ed.), Biliary-Pancreatic and Endocrine Unit, Hospital Clinic i Provincial de Barcelona, University of Barcelona, C/ Villarroel 170, 08036-Barcelona, Spain. e-mail: lfcruz@clinic.ub.es

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.06.009

younger than 40 years and may arise in individuals before the age of 20 years. In non–MEN-1 patients, insulinomas generally occur in those older than 40 years. Insulinomas may be the first manifestation of MEN-1 in 10% of patients, and approximately 4% of patients presenting with insulinomas will have MEN-1.[18] By 1991, Demeure et al.[19] had collected and reviewed 60 patients in the English literature. These authors suggested that patients with insulinomas associated with MEN-1 need a different surgical approach than that required for patients with sporadic insulinomas.

The aim of this report was to review our single-institution experience with the laparoscopic approach in patients with sporadic and multiple insulinomas associated with MEN-1. In this study, we emphasis the use of laparoscopic ultrasonography (LapUS) to detect tumors intraoperatively, facilitating operative decision-making.

PATIENTS AND METHODS

Between January 1998 and September 2003, 11 consecutive patients (10 women and 1 man; mean age, 40 years; age range, 22–66 years) with sporadic insulinoma were operated on at our institution. All patients presented with neuroglycopenic symptoms that developed after a fast or exertion and improved after glucose intake. The diagnosis was confirmed with a supervised 72-hour fasting test. In addition, circulating concentrations of C-peptide were raised in all patients. Preoperative imaging studies were performed in all patients. Computed tomography (CT) was performed in all patients and the results correctly diagnosed the tumor in only four patients. Endoscopic ultrasonography (EUS) was performed in all patients and detected the tumor in 10 patients. In one patient, EUS was not conclusive and suggested the presence of a tumor at the periphery of the gland or possibly an enlarged lymph node in this area. The tumors were presumably localized in the head of the pancreas in one patient (20 mm), in the neck of the pancreas in one patient (15 mm), in the body tail of the pancreas in six patients (mean size, 18 mm; range, 15–20 mm), and in the tail of the pancreas in two patients (16 and 18 mm, respectively).

Two other patients with organic hyperinsulinism were diagnosed with MEN-1. One patient, a 25-year-old woman, had a family history of hyperparathyroidism (in her aunt and cousin). Genetic studies confirmed a MENIN gene mutation in these family members. This patient underwent a subtotal parathyroidectomy for primary hyperparathyroidism in December 2000. She presented with organic hyperinsulinism in January 2001. Spiral CT scanning was able to localize one isodense tumor of 10 mm in the body of the pancreas and one hypodense tumor of 18 mm in the tail of the pancreas. Regionalization studies with intra-arterial calcium stimulation testing showed the presence of the tumor in the splenic vascular region. Octreoscan-^{111}In showed a positive spot at the pancreatic zone.

The second patient was a 40-year-old woman with a family history of a brother (with hyperparathyroidism), a sister, and two nephews; in all of the family members, the MEN-1 gene mutations were identified. She presented with the first manifestation of MEN-1 in February 1999 with acromegaly from a pituitary tumor, undergoing a selective hypophysectomy via the transphenoidal approach. Two years later, she presented with primary hyperparathyroidism with asymptomatic hypercalcemia. She underwent a subtotal parathyroidectomy resulting in normocalcemia. In February 2002, she presented with organic hyperinsulinism. CT was used to detect a pancreatic tumor of 7 cm in the tail of the pancreas. Octreoscan-^{111}In showed a positive spot at the pancreatic zone.

Evaluation criteria included operative factors such as estimated blood loss, operative time, and intraoperative complications. Evaluated postoperative data included length of hospital stay and postoperative complications, with a specific focus on pancreatic leak, intra-abdominal abscess, splenic complications, and other major infectious complications (e.g., pneumonia, wound infection). Postoperative pancreatic leaks were defined as a drain amylase level (measured after the third postoperative day) more than 3 times the upper limit of the normal serum amylase level in the absence of clinical sequelae. A clinical leak was defined as a biochemical leak in the presence of clinical sequelae such as fever or elevated white blood cell count, intra-abdominal abscess, or the need for percutaneous drainage or reoperation. Color Doppler ultrasound (CDUS) studies were performed with a Toshiba (Nasu, Japan) Powervision or a Sequoia (Acuson, Siemens, Mountain View, CA) instrument with a 2- to 4-MHz transducer. CDUS studies were carried out in the postoperative period when clinically indicated: unexplained fever, abdominal pain, or elevated white cell count. The CDUS study included a complete abdominal examination. The spleen evaluation included size, echostructure, and presence of fluid collections, which were evaluated by real-time ultrasonography.

RESULTS

With our approach, the patient is placed in half-lateral position with the left side up for tumors located

in the body tail of the pancreas or with the right side up for tumors in the head of the gland, and reverse Trendelenburg. The surgeon and assistant stand on the left of the patient, whereas the camera person and the scrub nurse stand on the opposite side, when tumors are localized in the left side of the pancreas. Four 10- to 12-mm trocars are inserted in the abdominal wall: 3–4 cm above the umbilicus, in the xiphoid area, subcostal on the midaxillary line, and in the subcostal midclavicular line. Two television monitors were used. CO_2 pneumoperitoneum was used. Abdominal pressure was monitored and maintained at less than 14 mm Hg. A 30° laparoscope was used. The liver was explored visually and with LapUS (7.5-MHz probe, 10 mm in diameter; B-K Medical, Gentolfe, Denmark).

For left-sided pancreatic lesions, the first step is to start with section of the lienorenal ligament and dissection on the subjacent fascia lateral to the spleen. The splenocolic ligament is divided using harmonic scalpel. The splenic flexure of the colon is mobilized downward. The gastrocolic omentum is opened wide up to the level of the mesenteric vessels. The body tail of the pancreas is then visualized. Exposure of the anterior aspect of the pancreas is performed by dividing the adhesions between the posterior surface of the stomach and the pancreas. Care must be taken to preserve the short gastric vessels. For lesions on the head and neck of the gland, the gastrocolic omentum is opened up to the level of the body tail of the pancreas. LapUS was used in all cases to facilitate operative decision-making (Figs. 1 and 2), enucleation, or pancreatic resection.

In the group of 11 patients with sporadic insulinoma, LapUS confirmed the presence of the tumor in 10 patients. However, in one patient, LapUS missed the tumor. A pedunculated insulinoma was enucleated by open surgery at the inferior border of the pancreas.

In seven patients, laparoscopic enucleation was completed. The localization of the tumors for enucleation is depicted in Fig. 3. LapUS was also particularly helpful in cases of enucleation to safely perform dissection between the tumor and normal parenchyma. The dissection started using cautery in the plane surrounding the tumor; small pancreatic vessels feeding the tumor were coagulated with a LigaSure device (Tyco, U.S. Surgical [Valleylab, Boulder, CO]) or clipped with titanium clips. Harmonic scalpel (Ultracision; Ethicon, Somerville, NJ) was used to remove tumors located at the lateral border of the pancreas. The specimen was extracted using a nonpermeable nylon bag through an enlarged trocar incision. A silicon drain was left in the bed of insulinoma. Mean operative time after laparoscopic enucleation was 180 minutes (range, 120–300 minutes), and the mean blood loss was 200 ml (range, 100–300 ml). The postoperative course was uneventful in four patients, with a mean hospital stay of 5 days. However, three patients developed a low-volume pancreatic fistula with output of 50–200 ml; they were discharged home 5 days after surgery with the drain in situ. One of these patients experienced the development of bleeding from the intra-abdominal drain, and she was rehospitalized. A reoperation, using the open approach, was performed after 7 days; bleeding from

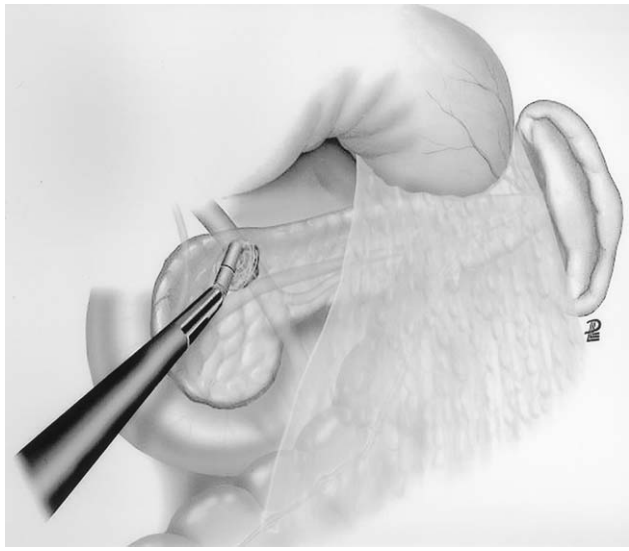

Fig. 1. Patient placed in half-lateral position with the right side up for tumor located in the head of the pancreas. The gastrocolic omentum is opened up to the level of the body tail of the pancreas allowing laparoscopic ultrasonographic study.

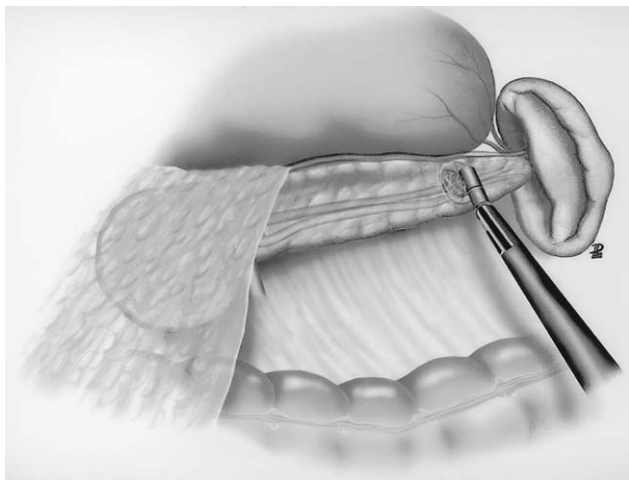

Fig. 2. Patient placed in half-lateral position with left side up for tumor located in the body-tail of the pancreas. The anterior aspect of the pancreas is exposed for laparoscopic ultrasonographic study.

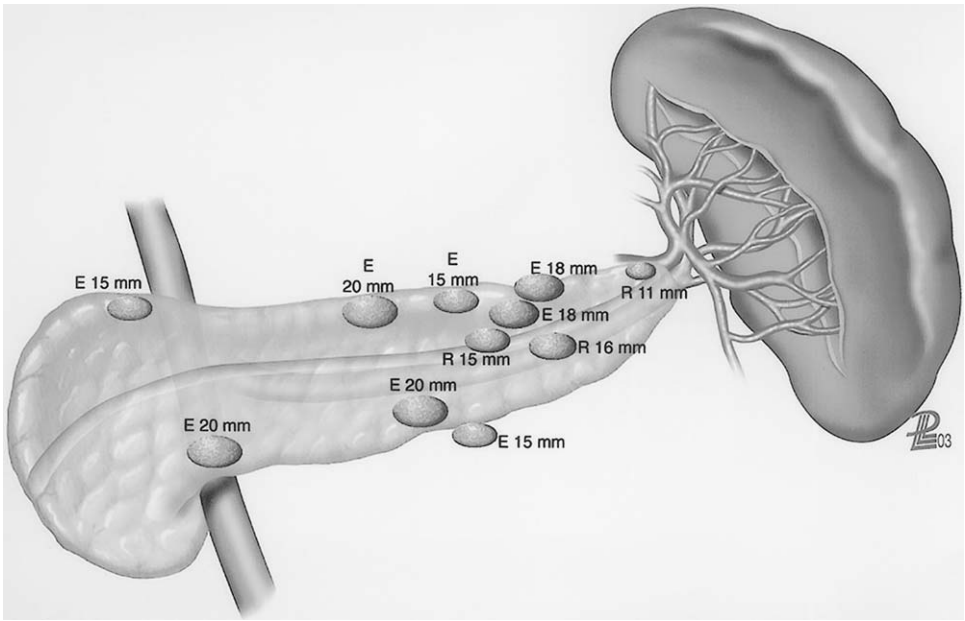

Fig. 3. Distribution of 11 sporadic insulinomas. Each tumor is depicted according to size (mm, diameter), location in the pancreas, and whether resection (R) or enucleation (E) was performed.

small vessels at the edge of the opening of the gastrocolic omentum was found (Table 1).

In three patients, resection of the gland was performed (the amount of pancreas resected was estimated at 40% if the gland was divided to the left border of the portal vein; 60%, along the right border of the vein; and 70%, at the level of the gastroduodenal artery). In one patient, the tumor was located in the tail of the gland in close proximity to the splenic hilum. In another patient, the tumor in the tail of the gland was in close proximity to the Wirsung duct. In both patients, a spleen-preserving distal pancreatectomy (40% and 60% of the volume of the gland, respectively) with splenic vessel preservation was performed. This technique has been previously described.[4,20] In a third patient, the insulinoma was on the posterior wall of the pancreas and bleeding occurred after dissection along the splenic vein. A spleen-preserving distal pancreatectomy (60% of the volume of the gland) with ligation of the splenic vessels with titanium clips was performed; the spleen was kept vascularized by the short gastric and left gastroepiploic vessels, according to the Warshaw technique[21] (Table 1).

After laparoscopic spleen-preserving distal pancreatectomy, the mean operating time was 240 minutes (range, 150–300 minutes), and the mean blood loss was 360 ml (range, 300–500 ml). No postoperative complications were observed, and the mean hospital stay was 5 days.

In all patients with sporadic insulinoma, the tumors were benign. The majority of patients returned to

Table 1. Laparoscopic surgery in patients with sporadic and multiple (MEN-1) insulinoma

	Patients (n)	Pancreatic fistula (n)	Splenic complications (infarct) (n)	Mean hospital stay (days)
Enucleation	8*	3†	—	5
SPDP/SVP (40%)	1	—	—	5
SPDP (60%)	1	—	—	5
SPDP/SVP (60%)	1	—	—	5
SPDP (80%)	1	—	1	14
SPDP/SVP (80%)	1	—	—	6

SPDP = spleen-preserving distal pancreatectomy without splenic vessel preservation; SPDP/SVP = spleen-preserving distal pancreatectomy with splenic vessel preservation.

*One patient was converted to open surgery.

†One patient, after discharge, developed intra-abdominal bleeding, was rehospitalized, and underwent reoperation 7 days after surgery.

previous activities between 2 and 3 weeks after surgery. Laparoscopic enucleation and laparoscopic resection achieved a cure in all patients at the mean follow-up of 28 months (range, 6–42 months).

Laparoscopic spleen-preserving distal pancreatectomy (80% of the volume of the gland, to the right border of the gastroduodenal artery) was performed in two MEN-1 patients with multiple tumors diagnosed preoperatively. LapUS was particularly helpful for determining the optimal site of transsection. In both patients, the head of the pancreas was free of macroscopic tumor. In one patient, laparoscopic pancreatic resection with spleen salvage was associated with splenic vessel preservation (operating time, 210 minutes; blood loss, 650 ml). The postoperative course was uneventful, and the patient was discharged home 6 days after surgery. The resected pancreatic specimen of $22 \times 6 \times 3$ cm contained a tumor in the tail of the gland of 7×6 cm in diameter accompanied by multiple macronodules measuring $1 \times 1 \times 0.8$ cm, $1 \times 0.6 \times 0.6$ cm, and $0.6 \times 0.6 \times 0.6$ cm. In another patient, laparoscopic spleen-preserving pancreatectomy was performed with ligation of both the splenic artery and the splenic vein. The spleen was kept vascularized by the short gastric vessels (Warshaw technique)[21]; the operating time was 150 minutes and blood loss 300 ml. Three days after surgery, this patient experienced fever (38°C) and left upper quadrant pain. CDUS showed an area of splenic infarct of 4 cm on the inferior lobe of the spleen. Chest radiography showed a small pleural effusion. Antibiotic treatment was administrated to prevent splenic abscess. The patient was discharged home 14 days after surgery (Table 1). The resected pancreatic specimen ($10.5 \times 5.6 \times 5$ cm) contained two visible macroadenomas of 18 and 10 mm in diameter and numerous microadenomas (more than eight) with a diameter ranging between 2 and 4 mm. Both MEN-1 patients remain asymptomatic and normoglycemic at 26 and 22 months.

DISCUSSION

Sporadic insulinomas represent up to 70–80% of clinically symptomatic neuroendocrine pancreatic tumors and occur in all age groups, with a peak incidence during the third to fifth decades. Because of characteristic neuroglycopenic symptoms, insulinomas are usually diagnosed when they are still small, resectable, and not metastatic. Insulinomas are located in the pancreas in almost all patients. Approximately 81%–90% of insulinomas are less than 2 cm, and the lesions are distributed equally throughout the head, body, and tail of the pancreas.[22] This is the typical tumor that is suitable for the laparoscopic approach. However, an insulinoma may be occult and difficult to localize both before and during surgery.[23,24]

Notwithstanding recent refinements in imaging techniques for patients with insulinoma, preoperative diagnostic studies still have the same limitations when assessing the number and exact locations of the tumors. EUS is the most sensitive modality for detecting insulinomas, with preoperative detection rates of 86–93%.[25] In recent years, spiral CT scanning has become more successful in localizing insulinoma and may also provide additional information regarding suspected malignancy. The accuracy rate of ^{111}-pentatreotide scintigraphy is 20%–70%.[26] Most believe that preoperative imaging is of limited benefit when an operative procedure is combined with intraoperative ultrasonography.[27–31] The laparoscopic approach and LapUS provide information similar to that obtained by means of open intraoperative ultrasonography[13] and can identify lesions that are undetectable by preoperative imaging techniques. Preoperative imaging might be unnecessary in patients using open surgery; however, when using the laparoscopic approach, despite the advantages of LapUS, it is still worthwhile to attempt preoperative imaging, as it provides useful information for patient positioning and port placement. In our series of 11 patients with sporadic insulinoma, EUS was able to localize the tumor in the pancreas: one in the head of the pancreas, one in the neck, six in the body tail, and two in the tail of the gland. Conversion was necessary in one patient in whom EUS misinterpreted the insulinoma as an enlarged lymph node at the border of the pancreas (later not found by LapUS). This was a pedunculated tumor at the inferior border of the gland found easily at operation and successfully removed by enucleation.

The surgical strategy in patients with sporadic insulinoma should be restricted to remove the solitary tumor in about 90% of patients.[22] The use of enucleation or resection will depend on the localization of the tumor in the pancreas and the findings from LapUS. The clear indications for tumor enucleation are tumors located at the periphery of the gland and tumors on the surface of the parenchyma totally or partially covered by a thin layer of pancreatic tissue. However, when the tumor is located in the distal part of the tail of the pancreas, it may be more convenient to remove that part of the gland containing the adenoma. Also, when the tumor is in close proximity to the Wirsung duct or lying on the splenic vein, resection should be indicated to avoid pancreatic fistula or profuse bleeding.

The reported success rates for laparoscopic resection of insulinoma range from 60% to 100%.[6,11,14,15,32] In most reports, the reasons for conversions were a failure of LapUS to localize the tumor intraoperatively or tumor location in difficult-to-access sites. In our series, the success rate of laparoscopic resection of insulinoma was 90% (Table 2).

The operating times of laparoscopic resection of insulinomas in our series (mean, 180 minutes for enucleation and 240 minutes for pancreatic resection) are not different from those of other reports. In some series, the estimated blood loss in patients who underwent laparoscopic resection of insulinomas was reported to be less than 100 ml.[15] In our series, the mean blood loss was 200 ml after enucleation and 360 ml after pancreatic resection.

Concerning postoperative complications, in patients with insulinoma undergoing open surgery, significant morbidity follows enucleation or resection. Pancreas-related complications have occurred in 12–43% of patients and have included abscesses, pseudocysts, and fistula formation.[33,34] Analysis of the series reported in the literature shows that pancreatic fistula after laparoscopic resection of insulinoma occurred at a rate of 0%–50%; in the majority of patients, the pancreatic fistulas were low volume and not life threatening. In our series, the incidence of pancreatic fistula was observed only in patients undergoing enucleation and they were defined as biochemical leaks. In some series using open surgery, a higher incidence of pancreatic fistulas has been reported in patients undergoing enucleation compared with pancreatic resection.[35,36]

It seems that the incidence of postoperative complications is similar in open surgery and laparoscopic surgery. However, the use of laparoscopic resection minimizes parietal damage, the hospital stay is relatively short, and an early return to previous activities was observed in most patients.

MEN-1 is a well-characterized but phenotypically variable disorder.[18] More than half of patients (60%) with the genomic mutation have biochemical primary hyperparathyroidism by the age of 20, and nearly all (95%) will have hyperparathyroidism by age 35. Early surgical intervention for hyperparathyroidism has become well accepted. Pituitary disease occurs in approximately 20% of MEN-1 patients, and treatment consists of medical therapy or selective hypophysectomy via the transphenoidal approach if feasible. In MEN-1, pancreaticoduodenal disease such as gastrinoma, nonfunctioning islet cell tumors, and insulinomas occur in 60%, 50%, and 10% of affected patients, respectively.[16] The management of hypoglycemia from an insulin-secreting tumor is not controversial, and enucleation or resection should be undertaken.

Techniques such as helical CT or magnetic resonance imaging may detect large pancreatic tumors.[37] One of our patients had a tumor in the tail of the pancreas that was 7 cm. In another patient, helical CT was particularly helpful in detecting multiple tumors. Somatostatin receptor scintigraphy (or octreotide scanning) is a complementary test that images approximately 80% of MEN-1 pancreatic tumors and may indicate distant metastasis.[38] Octreotide scanning was positive in our two patients at the midbody of the pancreas. EUS is the most sensitive imaging modality for small neuroendocrine pancreatic tumors. The sensitivity may be as high as 93% when combined with somatostatin receptor scintigraphy imaging. Because the source of insulin (or proinsulin) secretion may be multifocal or the patient may harbor concomitant nonfunctioning tumors, it is wise to try to determine the origin preoperatively. The intra-arterial calcium injection (Imamura) test may regionalize the hypersecretion and thereby make preoperative decision easier.[39,40] In one of our patients, this test regionalized the lesions to the pancreatic body tail.

According to Gauger and Thompson,[38] the surgical approach is based on the premise that patients with MEN-1 and neuroendocrine disease of the pancreas can potentially be cured of their syndrome or nonfunctioning tumors provided the tumor has not metastasized to the liver and the operation is sufficiently extensive to excise all sites of disease.

In most reports, enucleation or limited resection did not result in the development of recurrent hyperinsulinsm up to 15 years.[41,42] However, others reported recurrence rates of 40% at 10 years after

Table 2. Success rates of laparoscopic resection for insulinomas

	Gagner and Pomp[2]	Berends et al.[11]	Iihara and Obara[15]	Gramática et al.[14]	Present series
No. of patients	5	10	7	9	13
Laparoscopic procedures (n)					
Enucleation	1	5	4	4	7
Distal pancreatectomy	3	1	2	5	5
Converted to open surgery	1	4	1	—	1
Success rate (%)	80	60	86	100	90

enucleation.[43] Enucleation alone of an insulinoma in patients with MEN-1 would likely lead to missed tumors and failed operation. More than 75% of patients with insulinoma and MEN-1 had multiple pancreatic tumors. It seems that subtotal distal pancreatectomy, preserving the spleen, combined with enucleation of any tumors identified in the pancreatic head should be the standard operation.

We believe that patients with MEN-1 insulinomas may benefit from the choice of the laparoscopic approach according to the principles developed during the past 20 years regarding use of the standard open approach.[38] During the operation, intraoperative LapUS may recognize other tumors not seen in preoperative localization studies. In addition, LapUS identifies the demarcation between normal pancreas and macroscopic disease pancreas and is useful for determining the optimal site of transection.

Our experience with two MEN-1 patients with insulinomas supports the adoption of laparoscopic spleen-preserving distal pancreatectomy. We encourage spleen salvage in young patients without suspicion of malignancy, but with suspect or verified malignancy, the spleen should be removed to facilitate clearance of lymph nodes along the splenic vessels.[44] However, preservation of the spleen may be associated with splenic complications such as splenic infarction, when splenic vessels are sacrified and the spleen is kept nourished by the short gastric and left gastroepiploic vessels. This complication occurred in one of our patients and was managed conservatively with antibiotics to prevent splenic abscess.

In conclusion, surgical strategy of MEN-1 patients with hyperinsulinism should be different from those of sporadically occurring insulinomas. However, the laparoscopic approach may benefit both groups of patients. Using the criteria of Cushiery and Jakimowicz,[45] the probable benefit of minimally invasive surgery over conventional open surgery depends on the ratio of access trauma to procedural trauma. Laparoscopic enucleation or laparoscopic pancreatic resection for solitary, small, benign insulinomas is better achieved using the laparoscopic approach (rather than laparotomy) in terms of parietal damage of the abdomen. LapUS is mandatory for operative decision-making. Laparoscopic pancreatic resection (subtotal pancreatectomy) is feasible and safe in MEN-1 patients with left-sided pancreatic lesions, thereby avoiding long abdominal incisions. Spleen salvage should be attempted with splenic vessel preservation. However, there are still some problems with these procedures. The risk of pancreatic leakage after laparoscopic enucleation remains high, and spleen-preserving distal pancreatectomy without splenic vessels preservation may be associated with splenic complications. On the other hand, laparoscopic pancreatic resection using an endoscopic linear stapler proved to be safe and an easy method of preventing pancreatic leakage. Laparosocopic surgical cure can be achieved in patients with solitary and multiple insulinomas associated with MEN-1.

REFERENCES

1. Cushieri A, Jakimowicz JJ, van Spreeuwel J. Laparoscopic distal 70% pancreatectomy and splenectomy for chronic pancreatitis. Ann Surg 1996;223:280–285.
2. Gagner M, Pomp A. Laparoscopic pancreatic resection: Is it worthwhile? J Gastrointest Surg 1997;1:20–26.
3. Patterson EJ, Gagner M, Salky B, et al. Laparoscopic pancreatic resection: Single-institution experience of 19 patients. J Am Coll Surg 2001;193:281–287.
4. Fernández-Cruz L, Saenz A, Astudillo E, et al. Outcome of laparoscopic pancreatic surgery: Endocrine and nonendocrine tumors. World J Surg 2002;26:1057–1065.
5. Pietrabissa A, Shimi SM, Vander G, Cushieri A. Localization of insulinoma by infragastric inspection of the pancreas and contact ultrasonography. Surg Oncol 1993;2:280–285.
6. Gagner M, Pomp A, Herrera MF. Experience with laparoscopic resections of islet cell tumors. Surgery 1996;120:1051–1054.
7. Sussman LA, Christie R, Whittle DE. Laparoscopic excision of distal pancreas including insulinoma. Aust N Z J Surg 1996;66:414–416.
8. Chapuis Y, Bigourdan JM, Massault PP, Pitre J, Palazzo L. Exérèse vidéo-laparoscopique des insulinomas: Étude de cinq observations. Chirurgie 1998;123:461–467.
9. Tihanyi TF, Morvat K, Nehez L, et al. Laparoscopic distal resection of the pancreas with preservation of the spleen. Acta Chir Hung 1997;36:359–361.
10. Burpee ST, Jossart G, Gagner M. The laparoscopic approach to gastroenteropancreatic tumors. Acta Chir Aus 1999;31:207–213.
11. Berends FJ, Cuesta MA, Kazemier G, et al. Laparoscopic detection and resection of insulinomas. Surgery 2000;128:386–390.
12. Collins R, Schlinkert RT, Roust L. Case report: Laparoscopic resection of insulinoma. J Laparoendosc Adv Surg Tech 1999;9:429–431.
13. Lo CY, Lo CM, Fan SM. Role of laparoscopic ultrasonography in intraoperative localization of pancreatic insulinoma. Surg Endosc 2000;14:1131–1135.
14. Gramatica L, Herrera MF, Mercado-Luna A, et al. Videolaparoscopic resection of insulinoma: Experience in two institutions. World J Surg 2002;26:1297–1300.
15. Iihara M, Obara T. Minimally invasive endocrine surgery: Laparoscopic resection of insulinomas. Biomed Pharmacother 2002;56:227–230.
16. Tagaya N, Ishikawa K, Kubota K. Spleen-preserving laparoscopic distal pancreatectomy with conservation of the splenic artery and vein for a large insulinoma. Surg Endosc 2002;16:217–218.
17. Vezakis A, Davides D, Larvin M, McMahon MJ. Laparoscopic surgery combined with preservation of the spleen for distal pancreatic tumors. Surg Endosc 1999;13:26–29.
18. Thakker RV. Molecular genetics and patient management of multiple endocrine neoplasia type 1. In Fardon JR, ed. Best Practice Research Clinical Endocrinology and Metabolism. Endocr Surg 2001;15:189–212.

19. Demeure M, Klonoff D, Karam J, Duh Q, Clark O. Insulinomas associated with multiple endocrine neoplasia type 1: The need for a different surgical approach. Surgery 1991;110: 998–1005.
20. Fernández-Cruz L, Herrera M, Sáenz A, et al. Laparoscopic pancreatic surgery in patients with neuroendocrine tumors: Indications and limits. In Fardon JR, ed. Best Practice Research Clinical Endocrinology and Metabolism. Endocr Surg 2001;15:161–176.
21. Warshaw L. Conservation of the spleen with distal pancreatectomy. Arch Surg 1998;123:550–553.
22. Boukhman MP, Karam JM, Shaver J, et al. Localization of insulinomas. Arch Surg 1999;134:818–823.
23. van Heerden JA, Grant CS, Czako PF, Service FJ, Charboneau JW. Occult functioning insulinomas: Which localizing studies are indicated? Surgery 1992;112:1010–1014.
24. Pasieka JL, McLeod MK, Thompson NW, Burney RE. Surgical approach to insulinomas assessing the need for preoperative localization. Arch Surg 1992;127:442–447.
25. Zimmer T, Scherübl H, Faiss S, et al. Endoscopic ultrasonography of neuroendocrine tumors. Digestion 2000;62(Suppl 1): 45–50.
26. Proye Ch, Malvaux P, Pattou F, et al. Noninvasive imaging of insulinomas and gastrinomas with endoscopic ultrasonography and somatostatin receptor scintigraphy. Surgery 1998;124:1134–1144.
27. Böttger TC, Jungiger T. Is preoperative radiographic localization of islet cell tumors in patients with insulinoma necessary? World J Surg 1993;17:427–432.
28. Lo CY, Lam KY, Kung AW, et al. Pancreatic insulinomas. A 15-year experience. Arch Surg 1997;132:926–930.
29. Pedrazzoli S, Pasquali C, d'Andrea A. Surgical treatment on insulinoma. Br J Surg 1994;81:672–676.
30. Norton JA, Cromak DT, Shauker TH, et al. Intraoperative ultrasonographic localization of islet cell tumors: A prospective comparison to palpation. Ann Surg 1988;207:160–168.
31. Huai JC, Zhang W, Niu HO, et al. Localization and surgical treatment of pancreatic insulinomas guided by intraoperative ultrasound. Am J Surg 1998;175:18–21.
32. Lo CY, Chan WF, Lo CM, Fan ST, Tam PKH. Surgical treatment of pancreatic insulinomas in the era of laparoscopy. Surg Endosc 2004;18:297–302.
33. Grant CS. Insulinoma. Surg Oncol Clin North Am 1998;7: 819–844.
34. Hellman P, Anderson M, Rastad J, et al. Surgical strategy for large or malignant endocrine pancreatic tumors. World J Surg 2000;24:1353–1360.
35. Glickman MH, Hart MJ, White TT. Insulinomas in Seattle, 39 cases in 30 years. Am J Surg 1980;140:119–125.
36. Menegaux F, Schmitt G, Mercadier M, Chigot JP. Pancreatic insulinoma. Am J Surg 1992;165:243–248.
37. van Nieuwenhove Y, Vandaele S, Op de Beeck B, Delvaux G. Neuroendocrine tumors of the pancreas. Surg Endosc 2003; 17:1658–1662.
38. Gauger PG, Thompson NW. Early surgical intervention and strategy in patients with multiple endocrine neoplasia type 1. In Fardon JR, ed. Best Practice Research Clinical Endocrinology and Metabolism. Endocr Surg 2001;15:213–223.
39. Brown CK, Bartlett DL, Doppman JL, et al. Intraarterial calcium stimulation and intraoperative ultrasonography in the localization of insulinomas. Surgery 1997;122:1189–1194.
40. Aoki T, Sakon M, Ozhato H, et al. Evaluation of preoperative and intraoperative arterial stimulation and venous sampling for diagnosis and surgical resection of insulinoma. Surgery 1999;126:968–973.
41. Norton JA, Wells SA Jr. The surgical management of patients with multiple endocrine neoplasia type 1. World J Surg 1994; 18:488–494.
42. Bartsch DK, Langer P, Wild A, et al. Pancreaticoduodenal endocrine tumors in multiple endocrine neoplasia type 1: Surgery and surveillance. Surgery 2000;128:958–966.
43. O'Riordan D, O'Brien M, van Heerden JA, Service FJ, Grant CS. Surgical management of insulinomas associated with multiple endocrine neoplasia type I. World J Surg 1994; 18:488–494.
44. Åkerström G, Hessman O, Skogseid B. Timing and extent of surgery in symptomatic and asymptomatic neuroendocrine tumors of the pancreas in MEN 1. Langenbek's Arch Surg 2002;386:558–569.
45. Cushiery SA, Jakimowicz JJ. Laparoscopic pancreatic resections. Semin Laparosc Surg 1998;S:168–179.

Duodenal Cancer Arising From the Remaining Duodenum After Pylorus-Preserving Pancreatoduodenectomy for Ampullary Cancer in Familial Adenomatous Polyposis

Yoshiaki Murakami, M.D., Kenichiro Uemura, M.D., Masaru Sasaki, M.D., Masahiko Morifuji, M.D., Yasuo Hayashidani, M.D., Takeshi Sudo, M.D., Taijiro Sueda, M.D.

We herein report a rare occurrence of duodenal cancer arising from the remaining duodenum after pylorus-preserving pancreatoduodenectomy for ampullary cancer in familial adenomatous polyposis (FAP). In this patient, proctocolectomy and ileoanal anastomosis for FAP had been performed 11 years earlier. During the current admission, the patient was diagnosed with adenocarcinoma in the Vater's ampulla using imaging and pathological examinations. In addition, a pylorus-preserving pancreatoduodenectomy was performed. The tumor was a well-differentiated tubular adenocarcinoma and no other polyps were identified in the duodenum by pathological examination. However, 1 year after surgery, a polypoid lesion measuring 15 × 15 mm was indicated in the remaining duodenum by endoscopic surveillance. This lesion was completely resected by endoscopic mucosal resection and the resected specimen revealed well-differentiated tubular adenocarcinoma in an adenomatous lesion. This report suggests that resection of the total duodenum is essential for duodenal neoplasms in FAP to prevent a recurrence in the remaining duodenum. (J GASTROINTEST SURG 2005;9:389–392)

KEY WORDS: Familial adenomatous polyposis, duodenal cancer, pylorus-preserving pancreatoduodenectomy

Familial adenomatous polyposis (FAP) is characterized by numerous colorectal adenomatous polyps that develop into colorectal cancer by the age of 40–50 years. Therefore, prophylactic total colectomy is recommended for patients with FAP. Additionally, it is well known that periampullary or duodenal adenomas develop in more than 90% of patients with FAP.[1] Although progression to duodenal cancer in these duodenal adenomas is reported to occur in less than 5%,[2,3] one of the main causes of death in patients with FAP who have undergone prophylactic total colectomy is duodenal cancer.[4] Pancreatoduodenectomy is the best treatment of choice for duodenal cancer and, recently, pylorus-preserving pancreatoduodenectomy has been recommended for patients with duodenal cancer in FAP because this procedure procures a more desirable functional outcome and reduces bile reflux into the stomach, which causes the development of gastric adenoma.[5] However, because 2–3 cm of duodenal mucosa is left by the pylorus-preserving procedure, duodenal cancer arising from the remaining mucosa in the duodenum is anticipated.[6] In the previous literature, reports of recurrence in that tissue have not been indicated. We herein address the occurrence of duodenal cancer arising from the remaining duodenum after pylorus-preserving pancreatoduodenectomy for ampullary cancer in FAP.

CASE REPORT

A 40-year-old female was admitted to our hospital with right upper abdominal pain. She had been treated by proctocolectomy and ileoanal anastomosis for FAP at the age of 29. Her father and sister had died of colon cancer and her son had undergone a

From the Department of Surgery, Division of Clinical Medical Science, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan.
Reprint requests: Yoshiaki Murakami, M.D., Dept of Surgery, Division of Clinical Medical Science, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. e-mail: mura777@hiroshima-u.ac.jp

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.07.010

total colectomy because of FAP. Upon admission, a physical examination indicated normal vital signs and there was no tumor or tenderness regarding palpation of the abdomen. Laboratory evaluation was unremarkable except for slight anemia. Serum levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were within normal ranges. Abdominal ultrasonography and computed tomography revealed no tumor in the abdomen. Endoscopy of the upper gastrointestinal tract revealed numerous polyps in the stomach but not in the duodenum and a papillary tumor in the ampulla of Vater. A biopsy of the gastric polyps indicated no malignancy, but a papillary tumor in the ampulla of Vater was pathologically diagnosed as a well-differentiated tubular adenocarcinoma. Endoscopic retrograde pancreatocholangiography revealed a slight dilatation of the common bile duct and a filling defect was seen in the common bile duct and main pancreatic duct near the ampulla of Vater (Fig. 1). Superior mesenteric and celiac angiography revealed no abnormality. With regard to a diagnosis of ampullary cancer, pylorus-preserving pancreatoduodenectomy was performed on July 2, 1999. The procedure left 3 cm of the duodenum. Reconstruction of the alimentary tract was accomplished by pancreatogastrostomy, duodenojejunostomy, and hepaticojejunostomy. The resected specimen revealed a papillary tumor measuring 3 × 2 cm in the ampulla of Vater. Upon subsequent pathological examination, the tumor indicated itself as a well-differentiated tubular adenocarcinoma in an adenoma with papillary growth. The adenocarcinoma was localized in the mucosa and metastasis to the regional lymph nodes was not located. No other polyps were seen in the duodenum. The postoperative course of the patient was uneventful. The patient was discharged 4 weeks after surgery.

After discharge, an endoscopic examination of the upper gastrointestinal tract was performed in the patient twice a year. One year after surgery, on August 9, 2000, a polypoid lesion measuring 15 × 15 mm was identified in the remaining duodenum (Fig. 2). Biopsy analysis diagnosed this lesion as a well-differentiated tubular adenocarcinoma. Because the patient refused surgical resection and the tumor was localized in the mucosal layer by endoscopic ultrasonography, endoscopic mucosal resection was performed. The resected specimen revealed a well-differentiated tubular adenocarcinoma in an adenomatous lesion that had invaded the mucosal layer. After endoscopic mucosal resection, endoscopic surveillance on the upper gastrointestinal tract was continued. However, no recurrent lesions in the remaining duodenum 2 years after endoscopic mucosal resection have been indicated.

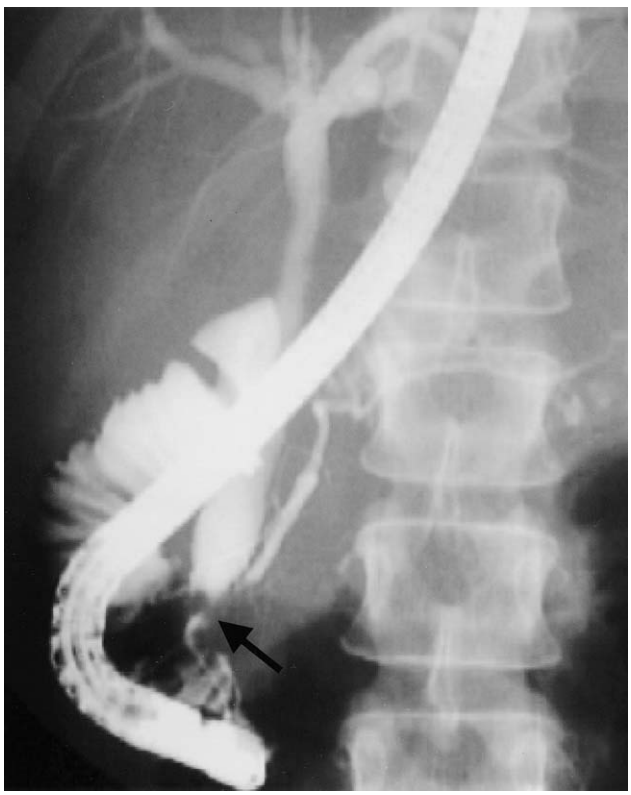

Fig. 1. Endoscopic retrograde cholangiopancreatography illustrating a filling defect (*arrow*) in the common bile duct and main pancreatic duct near the ampulla of Vater.

DISCUSSION

According to recent reports, duodenal polyps are observed in more than 90% of patients with FAP[1] and the lifetime risk of duodenal cancer is estimated at

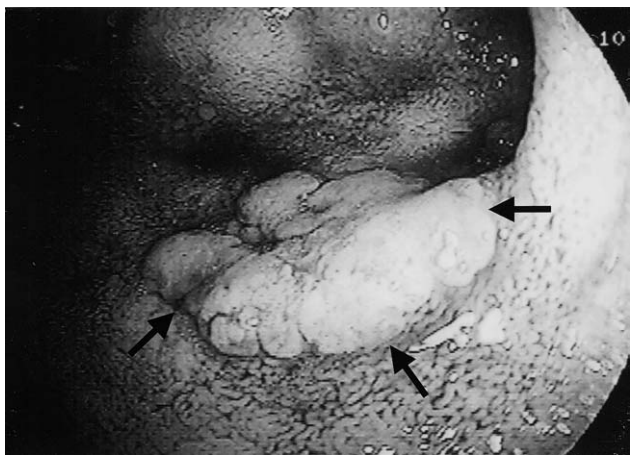

Fig. 2. Endoscopy illustrating a polypoid lesion (*arrows*) measuring 15 × 15 mm in the remaining duodenum, which was successfully resected by endoscopic mucosal resection.

2%–4% in these patients.[2,3] In addition, the relative risk of periampullary or duodenal cancer is 250 times that of the general population[7] and the leading causes of death in patients with FAP after prophylactic total colectomy include duodenal cancer (22%) and desmoid tumor (31%).[4] The risk of duodenal cancer is related to an age greater than 40 years, a familial history of duodenal cancer, and periampullary localization.[8]

Although the most suitable treatment with regard to invasive duodenal cancer in FAP is extensive surgical treatment such as pancreatoduodenectomy, local treatment, including endoscopic electrocoagulation, endoscopic mucosal resection, and transduodenal local resection have been advocated for noninvasive duodenal neoplasms including severe dysplasia and carcinoma in situ. These procedures are useful with regard to the temporary relief of the cancer threat and cause relatively minor complications. However, the recurrence rate of adenoma using these procedures is almost 100%, as indicated in several reports.[5,6] For this reason, many authors have recommended pancreatoduodenectomy for these patients.[5,6,9,10] Although this extensive surgical procedure is sometimes accompanied by major morbidity, the postoperative mortality rate associated with pancreatoduodenectomy has decreased markedly during the past decade.[11] In our institute, there has been no mortality in 120 consecutive patients undergoing pancreatoduodenectomy in recent years. Pancreatoduodenectomy is also recommended for patients with noninvasive duodenal neoplasms in FAP because this procedure offers the only chance of cure or prolonged disease-free interval.

Some surgeons have recommended pylorus-preserving pancreatoduodenectomy for patients with duodenal neoplasms in FAP.[5,9,10] The pylorus-preserving procedure exhibits benefits over conventional pancreatoduodenectomy, because pylorus preservation procures a more desirable functional outcome with fewer cases of "dumping," diarrhea, and marginal ulceration, and it also reduces bile reflux into the stomach, which may cause the development of gastric adenomas.[5] However, because 2–3 cm of the duodenum is left by the pylorus-preserving procedure, development of a duodenal cancer in the remaining duodenum is anticipated.

The previous literature does not indicate instances of recurrent duodenal cancer arising from the remaining duodenum. Our study focuses on a patient with duodenal cancer arising from the remaining duodenum after pylorus-preserving pancreatoduodenectomy. In this patient, we selected endoscopic mucosal resection for treatment of the tumor in the remaining duodenum, because the patient refused surgical resection and the tumor was localized in the mucosal layer by endoscopic ultrasonography. If the tumor in the remaining duodenum develops again in the future, surgical resection of the remaining duodenum might be required.

After our experience with this patient, we have performed pylorus-resected pancreatoduodenectomy with preservation of almost total stomach in 3 patients with duodenal neoplasms in FAP. We conclude that resection of the total duodenum is essential for duodenal neoplasms in FAP to prevent a recurrence in the remaining duodenum.

In this instance, pancreatogastrostomy was performed as the method of reconstruction for the remnant pancreas, because the risk of gastric cancer is reported not to be higher in FAP patients than in the general population.[12] However, the risk of gastric adenoma developing may be expected to increase, because bile reflux is accelerated by resection of the pylorus.[13] Endoscopic surveillance to examine the remaining jejunum and stomach is mandatory for patients undergoing pylorus-resected pancreatoduodenectomy.

CONCLUSION

The development of cancer in the remaining duodenum may occur when pylorus-preserving pancreatoduodenectomy is performed for patients with duodenal neoplasms in FAP, as demonstrated in this patient. Pylorus-resected pancreatoduodenectomy should be recommended for patients with duodenal neoplasms in FAP.

REFERENCES

1. Spigelman AD, Talbot IC, Penna C, et al. Evidence for adenoma-carcinoma sequence in the duodenum of patients with familial adenomatous polyposis. The Leeds Castle Polyposis Group (Upper Gastrointestinal Committee). J Clin Pathol 1994;47:709–710.
2. Vasen HF, Bulow S, Myrhoj T, et al. Decision analysis in the management of duodenal adenomatosis in familial adenomatous polyposis. Gut 1997;40:716–719.
3. Jagelman DG, DeCosse JJ, Bussey HJ. Upper gastrointestinal cancer in familial adenomatous polyposis. Lancet 1988;1:1149–1151.
4. Arvanitis ML, Jagelman DG, Fazio VW, et al. Mortality in patients with familial adenomatous polyposis. Dis Colon Rectum 1990;33:639–642.
5. Penna C, Bataille N, Balladur P, et al. Surgical treatment of severe duodenal polyposis in familial adenomatous polyposis. Br J Surg 1998;85:665–668.
6. Farnell MB, Sakorafas GH, Sarr MG, et al. Villous tumors of the duodenum: reappraisal of local vs. extended resection. J Gastrointest Surg 2000;4:13–23.

7. Iwama T, Mishima Y, Utsunomiya J. The impact of familial adenomatous polyposis on the tumorigenesis and mortality at the several organs. Its rational treatment. Ann Surg 1993; 217:101–108.
8. Debinski HS, Trojan J, Nugent KP, et al. Effect of sulindac on small polyps in familial adenomatous polyposis. Lancet 1995;345:855–856.
9. Ruo L, Coit DG, Brennan MF, et al. Long-term follow-up of patients with familial adenomatous polyposis undergoing pancreaticoduodenal surgery. J GASTROINTEST SURG 2002;6: 671–675.
10. Causeret S, Francois Y, Griot JB, et al. Prophylactic pancreaticoduodenectomy for premalignant duodenal polyposis in familial adenomatous polyposis. Int J Colorectal Dis 1998; 13:39–42.
11. Cameron JL, Pitt HA, Yeo CJ, et al. One hundred and forty five consecutive pancreaticoduodenectomies without mortality. Ann Surg 1993;217:430–438.
12. Spigelman AD, Williams CB, Talbot IC, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989;2:783–785.
13. Spigelman AD, Granowska M, Phillips RK. Duodeno-gastric reflux and gastric adenomas: a scintigraphic study in patients with familial adenomatous polyposis. J R Soc Med 1991; 84:476–478.

Transarterial Embolization for Postoperative Hemorrhage After Abdominal Surgery

Jeong Kim, M.D., Jae-Kyu Kim, M.D., Woong Yoon, M.D., Suk-Hee Heo, M.D., Eun-Ju Lee, M.D., Jin-Gyoon Park, M.D., Heoung-Keun Kang, M.D., Chol-Kyoon Cho, M.D., Sang-Young Chung, M.D.

The study goal was to evaluate the efficacy, safety, and clinical outcome of transarterial embolization for postoperative hemorrhage after abdominal surgery. Thirty-three patients were referred for angiography because of gastrointestinal or intra-abdominal bleeding after abdominal surgery. Urgent angiography and transarterial embolization was performed in all 33 patients. The clinical and angiographic features were retrospectively reviewed. Angiography revealed a discrete bleeding focus in 26 (79%) of 33 patients. Transarterial embolization was technically successful in 24 (92%) of 26 patients with a discrete bleeding focus. Rebleeding occurred in four (17%) of 24 patients. They were successfully managed with repeat embolization. There was no procedure-related complication during follow-up period. Angiography has a high detection rate of bleeding site in patients with postoperative hemorrhage after abdominal surgery. Transarterial embolization is considered to be an effective and safe means in the management of postoperative hemorrhage. (J GASTROINTEST SURG 2005;9:393–399)

KEY WORDS: Surgery, complications; Gastrointestinal tract; hemorrhage; arteries; therapeutic blockade

INTRODUCTION

The incidence of postoperative hemorrhage after abdominal surgery has been reported to be from 2% to 18%.[1–7] Recently, the mortality of postoperative hemorrhage was decreased, but it is still a serious and life-threatening conditions associated with high mortality rate up to 28%.[1–8] Early diagnosis and prompt treatment are both therefore necessary to improve the prognosis of the condition.

Angiographic embolization has been known to be an effective nonsurgical treatment for the selected patients with gastrointestinal hemorrhage.[9–12] There have been several reports describing the efficacy of transarterial embolization in patients with postoperative hemorrhage following abdominal surgery in small series.[13–22]

In this study, we retrospectively evaluate the efficacy, safety, and clinical outcome of transarterial embolization in 33 patients with postoperative hemorrhage after abdominal surgery.

MATERIAL AND METHODS

We perform here a retrospective survey of 33 patients who underwent angiography for postoperative gastrointestinal or intra-abdominal bleeding following abdominal surgery between December 1998 and May 2002. The patients who underwent emergent reoperation for hemodynamically unstable bleeding or endoscopic hemostasis were excluded from analysis. The patients consisted of 22 men and 11 women, with an age range from 6 to 79 years (mean age, 49 years). The abdominal surgeries were hepatobiliary pancreatic surgery (n = 11), upper gastrointestinal surgery (n = 10), combined surgery for multiple trauma or advanced gastric malignancy (n = 5), lower gastrointestinal surgery (n = 4), renal transplantation (n = 1), nephrectomy (n = 1), and adhesiolysis (n = 1). The interval from initial surgery to hemorrhage ranged from 5 hours to 60 days, with a median of 10 days. Eleven patients presented with melena, 8 with hematochezia, 6 with hematemesis and melena, 4 with hematemesis, and 4 with bleeding from surgical

From the Departments of Diagnostic Radiology (J.K., J.-K.K., W.Y., S.-H.H., E.-J.L., J.-G.P., H.-K.K.) and Surgery (C.-K.C., S.-Y.C.), Chonnam National University Medical School and Hospital, Gwangju, South Korea.
Corresponding author: Jae-Kyu Kim, M.D. Department of Diagnostic Radiology Chonnam National University Medical School and Hospital, 8 Hak-Dong, Dong-gu, Gwangju, 501-757, South Korea Tel. 82-62-220-5743 Fax. 82-62-226-4380 E-mail: kjkrad@chonnam.chonnam.ac.kr

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.07.015

drain tubes. The interval from hemorrhage to angiography and embolization ranged from 6 hours to 8 days, with a median of 2 days. The mean preprocedure hemoglobin concentration was 6.8 g/dL. Packed red blood cell transfused before angiography ranged from 2 to 45 units, with a median of 10.5 units.

Celiac and superior mesenteric angiography was performed via transfemoral approach. A 5-Fr Yashiro catheter (Terumo, Tokyo, Japan) was generally used to select mesenteric vessels. The angiographic equipment used was either Multistar T.O.P (Siemens, Erlangen, Germany) or Advantx LCA LP+ (GE Medical Systems, Milwaukee, WI). When both celiac and superior mesenteric angiographies failed to reveal a discrete bleeding focus, inferior mesenteric angiography was performed. Active gastrointestinal hemorrhage was proven and localized, following the unequivocal demonstration, by angiogram, of either the extravasation of contrast agent or a pseudoaneurysm. When a bleeding site was identified, transarterial embolization using a guiding catheter (a 5-F Yashiro catheter or 2-F Microferrat microcatheter [Cook, Bloomington, IN]) was performed using coils (Tornado, Cook) or Vortx-18 (Boston Scientific, Target Vascular, Cork, Ireland) as a primary embolic agent and gelatin sponge (Gelfoam, The Upjohn Co., Kalamazoo, MI) as a supplementary agent. In patients with negative angiographic blind embolization of the artery that supplies the bowel segments where active bleeding had been identified on endoscopic or scintigraphic examinations. Technical success was defined as cessation of bleeding on post-embolization angiography. Clinical success was defined as the cessation of clinical symptoms—melena, hematemesis, or hematochezia—after embolization without any further surgical intervention during follow-up period.

RESULTS

The clinical course, angiographic findings, and results of embolization are summarized in Table 1 and 2.

Thirty-three patients, all of whom required transfusion of at least 2 units of packed cells within 12 hours, were referred for angiography because of gastrointestinal or intra-abdominal bleeding following abdominal surgery. Discrete bleeding focus was detected in 26 (79%) of 33 patients and 30 bleeding arteries. Positive angiographic findings included 20 cases with active contrast extravasation (Fig. 1), 5 with a pseudoaneurysm (Fig. 2), and 5 with a combination of contrast extravasation and a pseudoaneurysm. Selective (n = 3) or superselective (n = 27) transarterial embolization of 30 bleeding arteries was performed in 26 patients. The embolized arteries were the pancreaticoduodenal artery (n = 8), gastroduodenal artery (n = 7), jejunal artery (n = 4), ileocolic artery (n = 4), hepatic artery (n = 3), left gastric artery (n = 1), ileal artery (n = 2), and adrenal artery (n = 1), respectively.

Transarterial embolization of bleeding arteries was performed using a combination of coils and gelatin sponge (n = 17), or coils (n = 10), or gelatin sponge (n = 3). In 4 patients, blind embolization was performed in the gastroduodenal artery (n = 2), jejunal artery (n = 1) and hepatic artery (n = 1) when an active bleeding site had been demonstrated by endoscopy or scintigraphy or was suspected following an angiogram. In 1 patient (patient 22), a second blind embolization was performed in gastroduodenal artery due to continuous melena after first embolization, although angiogram had revealed no definite bleeding focus, and the patient survived.

Transarterial embolization was technically successful in 24 (92%) of 26 patients in whom angiograms revealed a discrete bleeding focus. In 2 patients, transarterial embolization was not performed because bleeding vessels could not be selected.

Rebleeding occurred in 4 (17%) of 24 patients within 24 hours after the first embolization. In all 4 patients, rebleeding was found at a different vessel in follow-up angiograms. They were successfully managed by repeat embolization.

Four (12%) of 33 patients with technical failure (n = 2) or without discrete bleeding focus (n = 2) underwent emergency operation. Two patients survived the operation, but the other 2 patients died of transfusion coagulopathy due to massive transfusions.

Clinical success was achieved in 20 (77%) of 26 patients after a single embolization and in 24 (92%) of 26 patients after repeat embolization. 4 of the patients with rebleeding had medical comorbid conditions; there was coagulopathy in 2 patients, underlying Behcet enteritis in 1 patient, and localized infection in abdominal cavity in 1 patient.

Four (17%) of 24 patients died during the follow-up period. The causes of death were, respectively, disseminated intravascular coagulopathy, acute renal failure, adult respiratory distress syndrome, and septic pneumonia.

Postembolization complications such as bowel infarction or liver infarction did not occur in all patients during follow-up period, except the elevation of transaminase and total bilirubin in 4 patients subsequent to hepatic artery embolization.

DISCUSSION

Postoperative gastrointestinal or intra-abdominal hemorrhage is not an uncommon complication after

Table 1. Clinical course of 33 patients with postoperative hemorrhage

Patient	Operation		Interval from operation to bleeding	Transfused PRC (unit)	Interval from bleeding to angiography
1	Subtotal gastrectomy for gastric cancer	EL	19 days	3	1 day
2	Whipple's operation for duodenal cancer	EL	60 days	5	10 hours
3	Antrectomy for duodenal ulcer	EM	6 days	15	3 days
4	Total gastrectomy, partial pancreatectomy, and splenectomy for gastric cancer	EL	7 days	9	1 day
5	Adhesiolysis	EL	2 days	3	7 days
6	Total gastrectomy for gastric cancer	EL	25 days	8	2 days
7	Nephrectomy for graft rejection	EM	9 days	25	3 days
8	Right hepatic lobectomy for liver laceration	EM	1 day	26	1 day
9	Total gastrectomy for gastric cancer	EL	1 day	5	1 day
10	Primary closure of duodenal perforation	EM	3 days	6	2 days
11	Internal drainage of pancreatic pseudocyst	EM	5 days	7	8 days
12	Palliative gastrojejunostomy for pancreatic cancer	EL	1 day	16	3 days
13	Small bowel revision and anastomosis for anastomotic site leakage	EM	30 days	11	3 days
14	Gastrostomy revision for gastrostomy site bleeding	EM	21 days	4	5 days
15	Cholecystectomy with choledocholithotomy for common bile duct stone	EL	10 hours	17	6 days
16	Cholecystectomy for gallstone	EL	8 hours	5	7 days
17	Total gastrectomy for gastric cancer	EL	5 days	2	10 hours
18	Colostomy revision	EL	3 days	8	1 day
19	Whipple's operation for common bile duct cancer	EL	26 days	7	2 days
20	Pancreaticoduodenectomy for pancreatic injury	EM	33 days	3	1 day
21	Internal drainage of pancreatic pseudocyst	EM	5 days	4	10 hours
22	Gastroduodenostomy, small bowel anastomosis, and right nephrectomy for multiorgan injury	EM	10 days	3	6 hours
23	Liver lobectomy for liver laceration	EL	10 hours	11	1 day
24	Primary closure of liver, colon, small bowel, and splenectomy for multiorgan injury	EM	5 days	45	1 day
25	Right hepatic lobectomy and splenectomy for liver and spleen laceration	EM	10 hours	33	1 day
26	Renal transplantation	EL	39 days	19	6 days
27	Cholecystectomy for cholecystitis	EM	8 days	7	1 day
28	Subtotal gastrectomy for gastric cancer	EL	9 days	2	1 day
29	Right nephrectomy and right hepatic lobectomy for liver and renal laceration	EM	1 day	15	12 hours
30	Whipple's operation for pancreatic cancer	EL	2 days	3	1 day
31	Simple closure of duodenal ulcer perforation	EM	4 days	5	1 day
32	Small bowel resection for Behcet enteritis	EM	6 hours	10	2 days
33	Primary closure of duodenal ulcer perforation	EM	4 days	15	2 days

EL = elective, EM = emergency; PRC = packed red blood cell.

major abdominal surgery, particularly in the case of pancreaticoduodenectomy (2%–18%).[1–7] Bleeding may occur early after abdominal surgery due to improperly ligated vessels in the operative area or due to bleeding from the anastomotic site or the cut surface. Late bleeding is often due to a marginal ulcer or from an intra-abdominal source secondary to an anastomotic leak or localized infection.[1–4]

Early diagnosis and prompt treatment are of the utmost importance, given the associated mortality rates of up to 28%.[1–8] When gastrointestinal bleeding is suspected after abdominal surgery, endoscopy is usually employed as the first-line diagnostic procedure. However, exact diagnosis via urgent upper gastrointestinal endoscopy can be severely impaired by excessive blood and clots in the gastroduodenal tract.[23–24] Radionuclide bleeding scans, although known to be sensitive for active bleeding, are neither specific to the etiology nor precise for the location.[25–26] Angiography allows both the diagnosis of precise location and subsequent embolization as a therapeutic option.[9–12] In our study, angiography

Table 2. Results of angiography and outcome after embolization

Patient	Angiography finding	Embolized artery	Embolic agent	Re-bleed	Follow-up on observation period
1	Extravasation	GDA	Coil	No	Alive
2	Pseudoaneurysm	CHA	Coil	No	Alive
3	Extravasation	ASPDA, AIPDA	Coil	No	Died 6 days later of ARDS
4	Both	JA	Both	No	Alive
5	No bleeding focus				Reoperation and alive
6	Both	Did not perform embolization			Reoperation and alive
7	Both	ICA	Gelfoam	No	Alive
8	No bleeding focus	CHA*	Gelfoam	No	Alive
9	Extravasation	GDA	Coil	No	Alive
10	Pseudoaneurysm	IPDA	Both	No	Alive
11	Both	ASPDA, PSPDA	Both	No	Alive
12	Extravasation	IPDA	Gelfoam	No	Alive
13	Extravasation	IA	Both	No	Alive
14	No bleeding focus				Alive
15	No bleeding focus				Reoperation but died 7days later of DIC
16	Extravasation	IPDA	Both	No	Alive
17	Pseudoaneurysm	1. LGA 2. JA	1. Gelfoam 2. Both	Yes	Repeat embolization and alive
18	Both	ICA	Coil	No	Died 14 days later of septic pneumonia
19	Extravasation	GDA	Coil	No	Alive
20	Extravasation	GDA	Coil	No	Alive
21	Extravasation	1. JA 2. IPDA 3. GDA, MCA	1. Both 2. Coil 3. Both	Yes	Repeat embolization and alive
22	No bleeding focus	1. GDA* 2. GDA*	1. Both 2. Both	No	Alive
23	Extravasation	1. RHA, RAA 2. ICA, LHA	1. Both 2. Both	Yes	Repeat embolization and alive
24	Extravasation	ICA, LGA	Both	No	Alive
25	Pseudoaneurysm	Did not perform embolization			Reoperation but died 7 days later of DIC
26	Extravasation	ICA	Both	No	Alive
27	No bleeding focus	JA*	Gelfoam	No	Alive
28	Extravasation	GDA	Both	No	Alive
29	Pseudoaneurysm	RHA, GDA	Coil	No	Alive
30	Extravasation	JA	Both	No	Alive
31	No bleeding focus	GDA*	Coil	No	Died 4 days later of DIC
32	Extravasation	1. JA 2. JA† 3. JA†	1. Both 2. Both 3. Both	Yes	Repeat embolization and alive
33	Extravasation	GDA, IPDA	Both	No	Alive

GDA = gastroduodenal artery; CHA = common hepatic artery; SA = sigmoidal artery; IA = ileal artery; JA = jejunal artery; ASPDA = anterior superior pancreaticoduodenal artery; PSPDA = posterior superior pancreaticoduodenal artery; IPDA = inferior pancreaticoduodenal artery; ICA = ileocolic artery; AIPDA = anterior inferior pancreaticoduodenal artery; LGA = left gastric artery; RHA = right hepatic artery; LHA = left hepatic artery; RAA = Right adrenal artery; LIPA = left inferior phrenic artery.
*Blind embolization.
†Other branch of previously embolized branch of jejunal artery was done.

demonstrated the discrete bleeding focus in 26 (79%) of 33 patients.

The traditional approach for the treatment for patients with postoperative hemorrhage has been surgery. In the past, emergency surgery for high-risk patients with hemodynamic instability and poor general condition had a mortality rate as high as 64%.[27–28] In addition, the surgical approach to the bleeding artery is often hazardous or even unsuccessful owing to the anatomical inaccessibility of these

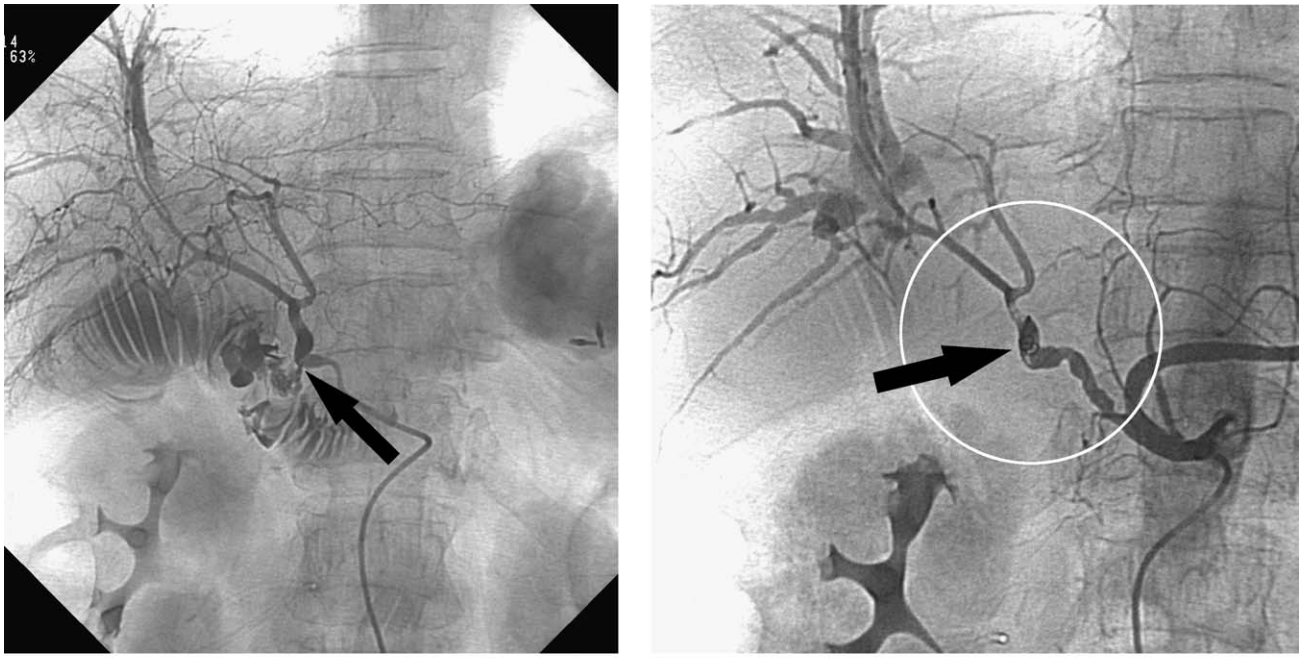

Fig. 1. A 63-year-old woman with massive upper gastrointestinal bleeding after Whipple's operation due to common bile duct malignancy. **A**. Selective common hepatic angiogram shows active arterial contrast extravasation (arrow) from the remnant gastroduodenal artery. **B**. Control angiogram after embolization with two, 2-mm microcoils demonstrates complete occlusion of the gastroduodenal artery (arrow).

arteries and associated inflammatory reaction, especially in patients who have undergone multiple previous abdominal operations.

Transarterial embolization has been known to be very effective for postoperative hemorrhage with low morbidity and mortality rates. However, there is no study in which the safety and efficacy of transarterial embolization is evaluated in a large patient group.[13–22] Shibata et al.[19] treated 8 patients suffering ruptured pseudoaneurysm after pancreatic and biliary surgery with embolization and reported a success rate of 88%. Bulakbasi et al.[21] described 10 patients with massive upper gastrointestinal hemorrhage from the surgical anastomosis treated by subselective embolization with a success rate of 90%. In our study, the clinical success rate was 92% and the mortality rate was 17% during follow-up periods. The causes of death were not, however, exclusively due to bleeding but included disseminated intravascular coagulopathy, acute renal failure, adult respiratory distress syndrome, and septic pneumonia, respectively.

The prevalence of recurrent hemorrhage or failure of embolization requiring surgery or second embolization was about 14-45% in reported series.[11,21,29] In this study, the recurrent bleeding rate was 17%, but in no instance was there technical or diagnostic failure, since bleeding occurred at sites different from the originals due to the coagulopathy, underlying Behcet enteritis, or localized infection. Early rebleeding has associated with either the early recanalization of the embolized arteries via the use of absorbable gelatin sponge or through a refilling of the extensive collaterals, particularly in the duodenum and jejunum. Clinical factors such as coagulopathy, an underlying peptic ulcer, or an ongoing intraabdominal infection play an important role in early failure of transarterial embolization in patients with gastrointestinal hemorrhage.[12]

The efficacy of blind embolization, defined as embolization without angiographic proof of extravasation, is controversial.[30] Dempsey et al.[10] concluded that blind embolization was not helpful in controlling gastrointestinal hemorrhage, but Morris et al.[31] found that the blind embolization of the left gastric artery was effective in preventing rebleeding when an active bleeding site had been demonstrated by endoscopy. In our study, blind embolization was performed in 5 arteries of 4 patients when an active bleeding site had been demonstrated by endoscopy or scintigraphy or was suspicious on angiogram. 4 patients survived during follow-up period, but 1 patient died of underlying coagulopathy due to massive transfusion.

There are several reasons why acute hemorrhage may not be detected by angiography. The rate of bleeding may be below a certain threshold. Colonic bleeding is often intermittent in nature or may have

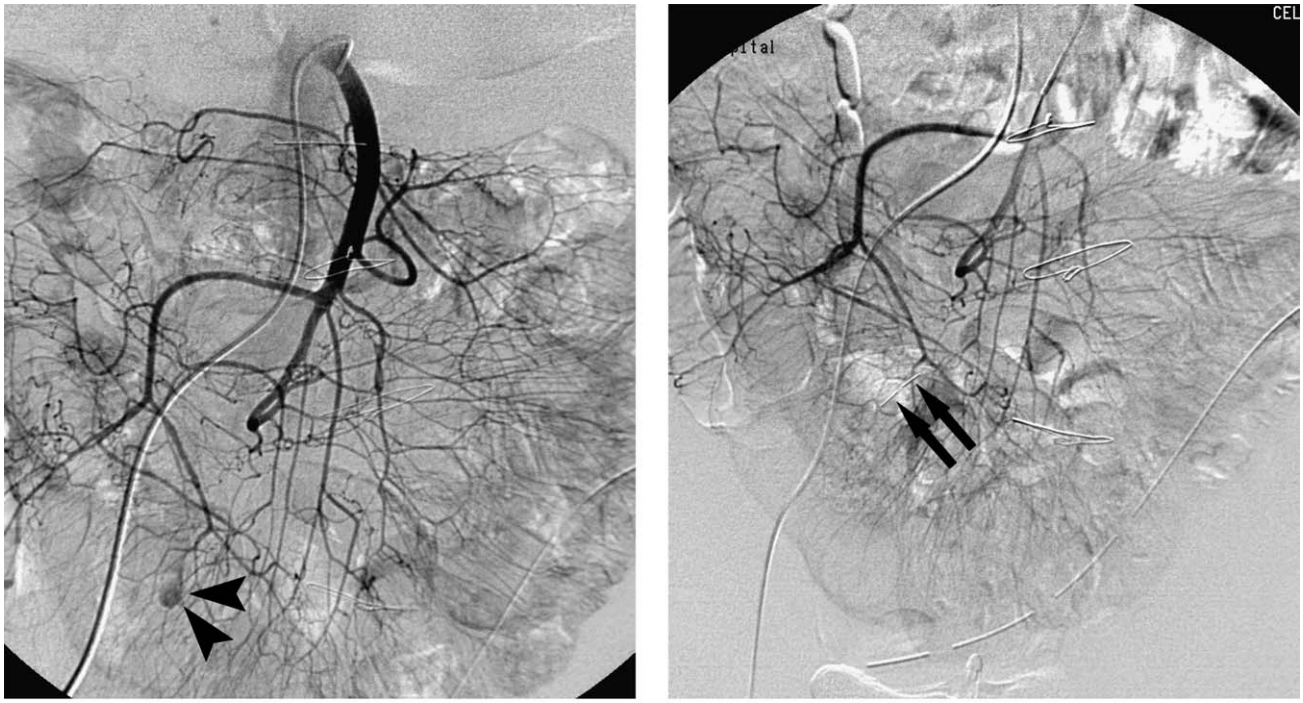

Fig. 2. A 65-year-old woman presented on postoperative day 5 with massive lower gastrointestinal bleeding after revision of colostomy. **A.** Superior mesenteric angiogram shows a pseudoaneurysm (arrowheads) arising from a branch of ileocolic artery. **B**. Late phase of the postembolization angiogram after embolization with two, 2-mm straight type microcoils (arrows) demonstrates complete occlusion.

permanently stopped. Technical difficulties and atherosclerotic changes of vessels may also decrease the sensitivity of the examination in that angiograms are less sensitive for venous or variceal hemorrhage.[32] In this study, the detection rate of angiography was 79%.

The most serious complication of transarterial embolization is irreversible bowel ischemia. Arterial embolization in the upper gastrointestinal tract above the ligament of Treitz is generally considered very safe because of the rich collateral supply to the stomach and duodenum.[30] However, the risk of significant ischemia after embolization is known to increase in patients who previously underwent surgery in the same area or with embolic agents such as liquid agents or very small particles that can advance far into the vascular bed.[33] In contrast to the upper gastrointestinal tract, the colon and, to some extent, the small bowel do not have a rich collateral. This relative lack of a rich network of collaterals has been thought to render the lower gastrointestinal tract more susceptible to ischemic insult. However, significant ischemia may be avoided if the embolic agent can be delivered precisely to the arcade just proximal to the vasa recta supplying the bleeding segment.[34,35]

The liver can tolerate considerable arterial embolization without significant consequence because of collateral pathways and because it has a dual blood supply through the hepatic artery and portal vein.[36] However, in patients with portal vein stenosis, liver infarction or liver ischemia has been reported as the major complication of coil embolization for pseudoaneurysms arising from hepatic arteries.[16] Although levels of transaminase and total bilirubin were elevated in 4 patients after hepatic artery embolization, postembolization complication such as bowel ischemia or liver infarction was not encountered in our study.

Another problem of embolization is technical failure in placing the coaxial catheter sufficiently distal enough to allow the safe embolization of bleeding arteries. This occurs more often in postoperative patients because of anatomical changes from the surgery. Technical failure rates have been reported to be 8–21%,[29,37,38] and the technical failure rate of this study was 8%. The development of newer microcatheters has enabled more peripheral superselective catheterization of distal vessels, permitting more superselective vascular interventions and high success rates.[38–40]

In conclusion, angiography has a high detection rate of bleeding site in patients with postoperative hemorrhage after abdominal surgery. Transarterial embolization is considered to be an effective and

safe method in the management of postoperative hemorrhage.

REFERENCES

1. Dixon JM, Armstrong CP, Duffy SW, Elton RA, Davies GC. Upper gastrointestinal bleeding: a significant complication after surgery for relief of obstructive jaundice. Ann Surg 1984;199:271–275.
2. Yeo CJ. Management of complications following pancreaticoduodenectomy. Surg Clin North Am 1995;75:913–924.
3. Rumstadt B, Schwab M, Korth P, Samman M, Trede M. Hemorrhage after pancreatoduodenectomy. Ann Surg 1998; 227:236–241.
4. Welch CE, Rodkey GV, von Ryll Gryska P. A thousand operations for ulcer disease. Ann Surg 1986;204:454–467.
5. Ikeguchi M, Oka SI, Homyo Y, et al. Postoperative morbidity and mortality after gastrectomy for gastric carcinoma. Hepatogastroenterology 2001;48:1517–1520.
6. Bokey EL, Chapuis PH, Fung C, et al. Postoperative morbidity and mortality following resection of the colon and rectum for cancer. Dis Colon Rectum 1995;38:480–487.
7. Tsiotos GG, Munoz Juarez MM, Sarr MG. Intraabdominal hemorrhage complicating surgical management of necrotizing pancreatitis. Pancreas 1996;12:126–130.
8. Yoon YS, Kim SW, Her KH, et al. Management of postoperative hemorrhage after pancreaticoduodenectomy. Hepatogastroenterology 2003;50:2208–2212.
9. Rosch J, Dotter CT, Brown MJ. Selective arterial embolization: a new method for control of acute gastrointestinal bleeding. Radiology 1972;102:303–306.
10. Dempsey DT, Burke DR, Reilly RS, McLean GK, Rosato EF. Angiography in poor-risk patients with massive nonvariceal upper gastrointestinal bleeding. Am J Surg 1990;159:282–286.
11. Encarnacion CE, Kadir S, Beam CA, Payne CS. Gastrointestinal bleeding: treatment with gastrointestinal arterial embolization. Radiology 1992;183:505–508.
12. Luc D, Peter V, Martine DV, et al. Embolization as a first approach with endoscopically unmanageable acute nonvariceal gastrointestinal hemorrhage. Radiology 2001;218:739–748.
13. Kadir S, Athanasoulis CA. Angiographic diagnosis and control of postoperative bleeding. CRC 1979;12:35–78.
14. Beattie GC, Redhead D, Siriwardena AK. Value of angiographic embolisation for the control of major haemorrhage after oesophagogastric or pancreaticobiliary surgery. Eur J Surg 2001;167:501–503.
15. Beattie GC, MacDonald A, Powell JJ, Redhead D, Siriwardena AK. Angiographic embolization for major haemorrhage after upper gastrointestinal surgery. Br J Surg 2000;87:362–373.
16. Sato N, Yamaguchi K, Shimizu S, et al. Coil embolization of bleeding visceral pseudoaneurysms following pancreatectomy: the importance of early angiography. Arch Surg 1998; 133:1099–1102.
17. Gerard VA, Stephen ON, Marc AB. Successful nonoperative management of bleeding hepatic artery pseudoaneurysm following pancreaticodeodenectomy. Dig Surg 1999;16:528–530.
18. Okuno A, Miyazaki M, Ito H, et al. Nonsurgical management of ruptured pseudoaneurysm in patients with hepatobiliary pancreatic diseases. Am J Gastoenterol 2001;96: 1067–1071.
19. Shibata T, Sagoh T, Ametani F, et al. Transcatheter microcoil embolotherapy for ruptured pseudoaneurysm following pancreatic and biliary surgery. CVIR 2002;25:180–185.
20. Tony N, Simon T, Duncan E, et al. Hepatic artery angiography and embolizatin for hemobilia following laparoscopic cholecystectomy. CVIR 1999;22:20–24.
21. Bulakbasi N, Kurtaran K, Ustunsoz B, Somuncu I. Massive lower gastrointestinal hemorrhage from the surgical anastomosis in patients with multiorgan trauma: treatment by subselective embolization with polyvinyl alcohol particles. CVIR 1999;22:461–467.
22. Ng BL, Thompson JN, Adam A, et al. Selective visceral angiography in obscure postoperative gastrointestinal bleeding. Ann R Coll Surg Engl 1987;69:237–240.
23. Vreeburg EM, Snel P, de Bruijne JW, et al. Acute upper gastrointestinal bleeding in the Amsterdam area: incidence, diagnosis, and clinical outcome. Am J Gastroenterol 1997; 92:236–243.
24. Toyoda H, Nakano S, Takeda I, et al. Transcatheter arterial embolization for massive bleeding from duodenal ulcers not controlled by endoscopic hemostasis. Endoscopy 1995;27: 304–307.
25. Alavi A, Ring E. Localization of gastrointestinal bleeding. Superiority of technetium sulfur colloid compared with angiography. AJR 1981;138:741–748.
26. American Gastroenterological Association medical position statement: evaluation and management of occult and obscure gastrointestinal bleeding. Gastroenterology 2000;118:197–201.
27. Lerut JP, Gianello PR, Otte JB, Kestens PJ. Pancreaticoduodenal resection: surgical experience and evaluation of risk factors in 103 patients. Ann Surg 1984;199:432–437.
28. Smith CD, Sarr KG, van Heerden JA. Completion pancreatectomy following pancreaticoduodenectomy: clinical experience. World J Surg 1992;16:521–524.
29. Rima A, Vincent LO, Eric T, et al. Arterial embolotherapy for upper gastrointestinal hemorrhage: outcome assessment. JVIR 2001;12:195–200.
30. Morris DC, Nichols DM, Connell DG, Burhenne HJ. Embolization of the left gastric artery in the absence of angiographic extravasation. CVIR 1986;9:195–198.
31. Pennoyer WP, Vianati PV, Cohen JL. Mesenteric angiography for lower gastrointestinal hemorrhage. Dis Colon Rectum 1997;40:1014–1018.
32. Lang EK. Transcatheter embolization in management of hemorrhage from duodenal ulcer: long-term results and complications. Radiology 1992;182:703–707.
33. Bandi R, Shetty PC, Sharma RP, et al. Superselective arterial embolization for the treatment of lower gastrointestinal hemorrhage. JVIR 2001;12:1399–1405.
34. Ledermann HP, Schoch E, Jost R, Zollikofer CL. Embolization of the vasa recta in acute lower gastrointestinal hemorrhage: a report of five cases. CVIR 1999;22:315–320.
35. Shimizu Y, Miyazaki M, Shimizu H, et al. Beneficial effects of arterialization of the portal vein on extended hepatectomy. Br J Surg 2000;87:784–789.
36. Uflacker R. Transcatheter embolization for treatment of acute lower gastrointestinal bleeding. Acta Radiol 1987;28:425–430.
37. Gordon RL, Ahl KL, Kerlan RK, et al. Selective arterial embolization for the control of lower gastrointestinal bleeding. Am J Surg 1997;174:24–28.
38. Peck DJ, McLoughlin RF, Hughson MN, Rankin RN. Percutaneous embolotherapy of lower gastrointestinal hemorrhage. JVIR 1998;9:747–751.
39. Matusmoto A, Suhhocki P, Barth K. Superselective gelfoam embolotherapy using a high visible small caliber catheter. CVIR 1988;11:303–306.
40. Okazaki M, Higashihara H, Doganemaru F, et al. A coaxial catheter and steerable guidewire used to embolize branches of the splanchnic arteries. AJR 1990;155:405–406.

Improved Outcomes for Benign Disease With Limited Pancreatic Head Resection

Gudrun Aspelund, M.D., Mark D. Topazian, M.D., Jeffrey H. Lee, M.D., Dana K. Andersen, M.D.

We sought to determine whether duodenum-preserving pancreatic head resections (DPPHRs) offer improved outcomes for benign disease of the proximal pancreas. A single-cohort study was performed of 86 consecutive patients who underwent DPPHR, extended lateral pancreaticojejunostomy with excavation of the pancreatic head (ELPJ), standard or pylorus-sparing Whipple procedure (WHIP), or distal pancreatectomy (DPR). Aspects of cost, complications (mortality and morbidity), and outcomes were assessed during a follow-up period of 6–63 months (mean, 3 years). Twelve DPPHR and 12 ELPJ procedures were performed for benign lesions or chronic pancreatitis (CP), as were 7 of 30 WHIP procedures and 12 of 16 DPRs. Operative time was significantly less than that for WHIP in ELPJ and DPR procedures. Major complications occurred in 40% of WHIPs and 25% of DPPHRs but only 16% of ELPJs ($P < 0.05$). Thirty-day mortality was 2 of 30 for WHIP but 0 for all other procedures. Pancreatic or biliary leak occurred in 3 of 30 WHIPs, 3 of 12 DPPHRs, 1 of 16 DPRs, and 0 of 12 ELPJs. New diabetes occurred in 25% of patients who underwent WHIP but only 8% of both DPPHR and ELPJ patients. Full functional recovery was similar for CP patients in both DPPHR and ELPJ. DPPHR and ELPJ are effective surgical approaches to the treatment of benign tumors and CP and are safer than WHIP with lower morbidity and mortality risks. The incidence of new diabetes is less with both ELPJ and DPPHR. (J GASTROINTEST SURG 2005;9:400–409)

KEY WORDS: Beger procedure, Frey procedure, Whipple procedure, duodenum-preserving pancreatic head resection, chronic pancreatitis, pancreatic surgery

Pancreaticoduodenectomy (the Whipple procedure [WHIP]), with or without pylorus preservation, is frequently used in patients with chronic pancreatitis (CP) or benign tumors (BTs) confined to the pancreatic head.[1,2] Recently, however, two new operations have expanded the surgical options for the treatment of benign proximal pancreatic disease, but these are not performed by most North American surgeons.

The duodenum-preserving pancreatic head resection (DPPHR), described by Beger et al. in 1980,[3] involves subtotal resection of the pancreatic head but spares the duodenum and common bile duct and leaves a rim of pancreatic tissue adjacent to the duodenum. A jejunal loop is then interposed between the left side of the pancreas and the duodenal rim of pancreatic tissue[4] (Fig. 1). DPPHR has been advocated for benign or premalignant lesions of the pancreatic head, including chronic inflammation. The rationale for the Beger procedure is that resection of the antrum, bile duct, and duodenum is neither anatomically nor functionally necessary for the removal of a diseased pancreatic head in the setting of benign disease. Furthermore, preservation of the duodenum results in more physiologic digestion and regulation of insulin and glucagon secretion. These effects may account for the reduction of postoperative exocrine and endocrine insufficiency after DPPHR compared with the WHIP.[5]

The extended lateral pancreaticojejunostomy (ELPJ), described by Frey and Smith in 1987,[6] involves the excavation of the pancreatic head (ELPJ) down to the ductal structures, which spares the duodenum and leaves a rim of tissue around the entire circumference of the pancreatic head.

Presented in part at the Forty-Third Annual Meeting of The Society for Surgery of the Alimentary Tract, San Francisco, California, May 19–22, 2002.

From the Departments of Surgery (G.A., D.K.A.) and Medicine (M.D.T., J.H.L.), Yale University School of Medicine, New Haven, Connecticut. Reprint requests: Dana K. Andersen, M.D., Department of Surgery S3-810, University of Massachusetts Medical School, 55 Lake Avenue N, Worcester, MA 01655. e-mail: dana.andersen@umassmed.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.08.015

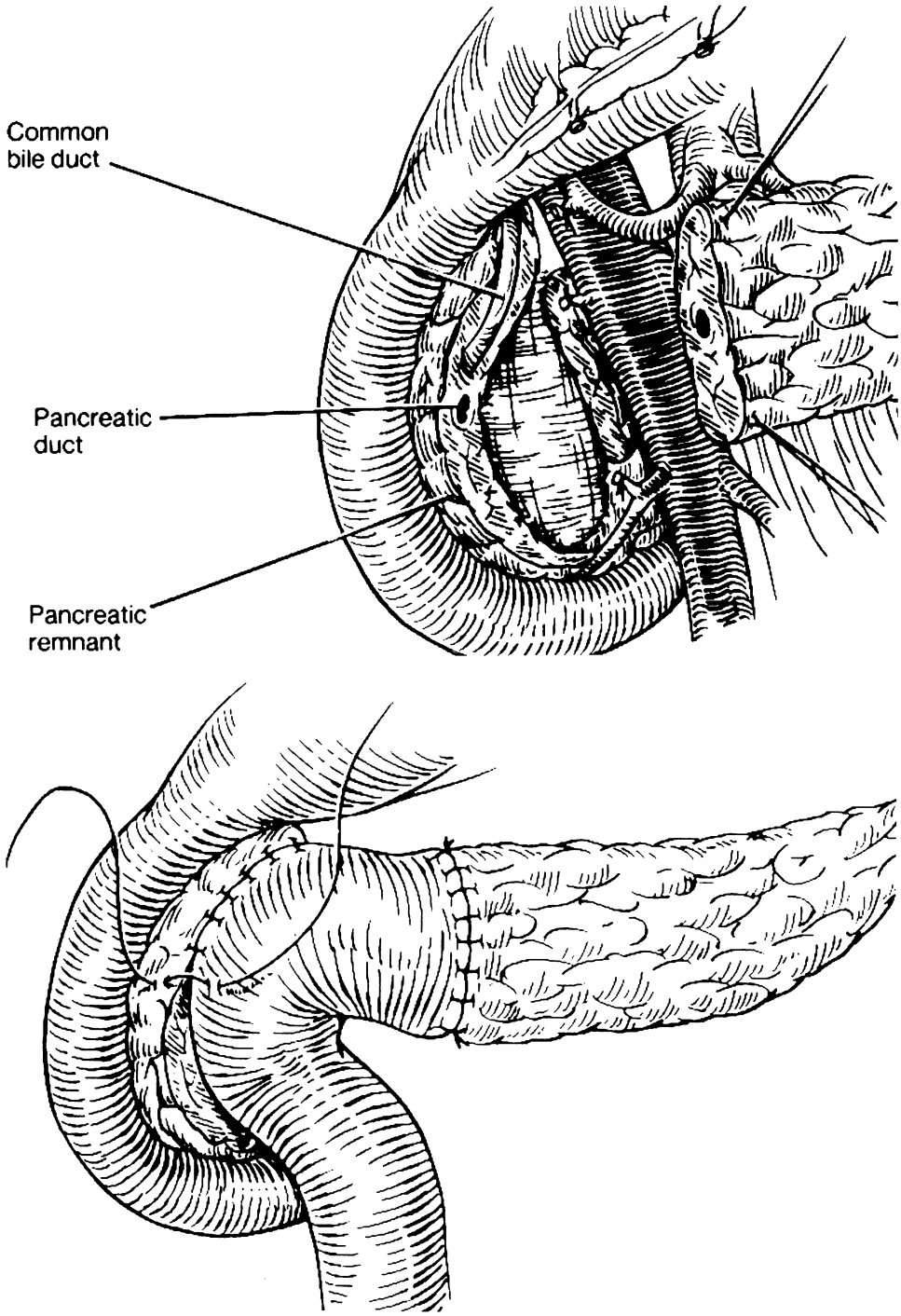

Fig. 1. The duodenum-preserving pancreatic head resection, or Beger procedure. Removal of the central portion of the pancreatic head is performed with preservation of the intrapancreatic common bile duct (*top*). Reconstruction includes an end-to-end pancreaticojejunostomy as well as an end-to-side pancreaticojejunostomy to the same Roux-en-Y jejunal limb (*bottom*). (Reproduced with permission from Bell RH Jr. Atlas of pancreatic surgery. In Bell RH, Rikkers LF, Mulholland MW, eds. Digestive Tract Surgery: A Text and Atlas. Philadelphia: Lippincott Raven, 1996, pp 1014–1015.)

A longitudinal pancreaticojejunostomy from the head to the tail of the pancreas is performed, similar to the "Puestow" procedure, as modified by Partington and Rochelle[7] (Fig. 2). The Frey procedure has been advocated for patients with pain or complications of CP with a dilated main duct in the body and tail of the pancreas.[6,8] A claimed advantage of the Frey procedure is that it is a simpler and less

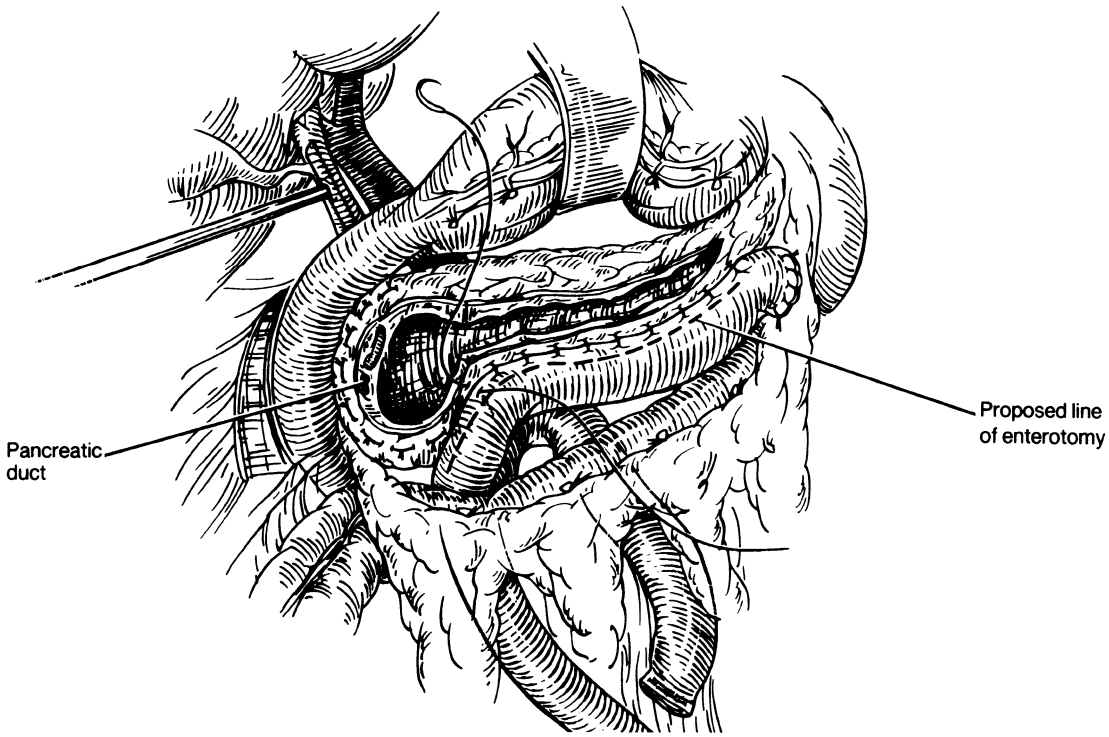

Fig. 2. The extended lateral pancreaticojejunostomy with excavation of the pancreatic head, or Frey procedure. A longitudinal pancreatotomy is carried proximally to the level of the ampulla, and the overlying parenchyma is removed to allow an unobstructed side-to-side, Roux-en-Y, pancreaticojejunostomy. (Reproduced with permission from Bell RH Jr. Atlas of pancreatic surgery. In Bell RH, Rikkers LF, Mulholland MW, eds. Digestive Tract Surgery: A Text and Atlas. Philadelphia: Lippincott Raven, 1996, p 1024.)

time-consuming operation, with lower mortality and morbidity risks than pancreaticoduodenectomy, and carries a decreased incidence of exocrine and endocrine insufficiency compared with the WHIP.[8]

Improved outcomes and lower morbidity have been reported for both the DPPHR and ELPJ compared with the WHIP.[5,9,10] However, direct comparisons of DPPHR and ELPJ have been limited. A randomized study by Izbicki et al.[11] from Hamburg showed equal effectiveness of both operations with fewer complications after the ELPJ, and a short follow-up of a small series of DPPHR patients found no significant changes in exocrine and endocrine function as determined by a set of specific tests.[12]

We reviewed our experience with the DPPHR and ELPJ procedures to evaluate aspects of cost, morbidity, and outcomes and compared these procedures with standard and pylorus-sparing WHIPs and distal pancreatic resection (DPRs) performed contemporaneously over a 54-month period. Our length of follow-up averaged 3 years and ranged from 6 to 63 months.

METHODS

The records of 86 consecutive patients undergoing pancreatic surgery by a single surgeon (D.K.A.) at Yale-New Haven Hospital from March 1997 to September 2001 were reviewed. The operations included 12 DPPHRs, 12 ELPJs, 30 standard or pylorus-preserving pancreaticoduodenectomies (WHIPs), and 16 DPRs, as well as 16 patients with miscellaneous other resectional or decompressive procedures that were not included in the study. Diagnoses were based on the patient's history, transabdominal or endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), computed tomography scan, gross inspection of pancreas at operation, and pathologic examination. All DPPHR and ELPJ patients had preoperative ERCP, and most had EUS. The final diagnoses were CP in 21 patients, cancer (CA) in 28 patients, and BT in 21 patients.

The type of operation performed was based on the histologic diagnosis for each individual patient or on a pattern of disease that strongly suggested either malignant or benign disease. Patients with suspected or proved malignancy located in the head of the pancreas were uniformly recommended to undergo a WHIP. Patients with a diagnosis of CP or with lesions (small cystadenomas and neuroendocrine tumors) that appeared benign on EUS and CT scans were offered either DPPHR or ELPJ. CP patients with diffuse pancreatic duct dilatation were selected for

ELPJ, and patients with marked distortion of the proximal ducts or a BT of the proximal pancreas were selected for DPPHR. Patients with focal lesions distal to the neck of the pancreas were uniformly recommended to undergo a distal pancreatectomy.

Operative time was taken as the total anesthesia time and included intraoperative ultrasound and/or fiberoptic pancreatoscopy in several CA and BT cases. Complications that were considered major included pancreatic or biliary leak (defined as persistent drainage of high amylase or bilious fluid after resumption of an oral diet) portal vein occlusion, intra-abdominal abscess or fluid collection requiring hospitalization, and small bowel obstruction requiring exploration. *Diabetes* was defined as glucose intolerance that required some therapy, such as diet, oral medications, or insulin. Full functional recovery postoperatively was achieved if the patient was pain free and back to work or prior activity level.

Data are expressed as mean ± SEM or medians where appropriate. Analysis of variance and *t* test or Wilcoxon sum rank test were used for statistical comparisons, and $P < 0.05$ was considered significant.

The dissection of the pancreatic head in DPPHR and ELPJ cases was performed in most patients using an ultrasonic aspirator and dissector (Cavitron; Valley Lab, Inc., Norwalk, CT). The use of this instrument for pancreatic dissection, first suggested by Carey,[13] greatly facilitates the exposure of the intrapancreatic portion of the common bile duct (Fig. 3) and allows the excavation and cavitation of the pancreatic head with maximum precision. Initially, the ultrasonic dissector was used only for the DPPHR (Beger) procedures, with electrocautery used for the ELPJ (Frey) excavation. As experience grew with the ultrasonic dissector, we used it for all duodenum-preserving resections and have been pleased with the results.

All patients were treated postoperatively with octreotide 100 μg subcutaneously TID from the immediate postoperative period until a full liquid diet was attained. It is acknowledged that randomized, prospective trials both support and refute the use of octreotide acetate for the prevention of pancreatic leak. Using this protocol, however, we have experienced a 12% combined anastomotic leak rate (10% leak rate for WHIP alone), which is lower than that reported from other high-volume centers.

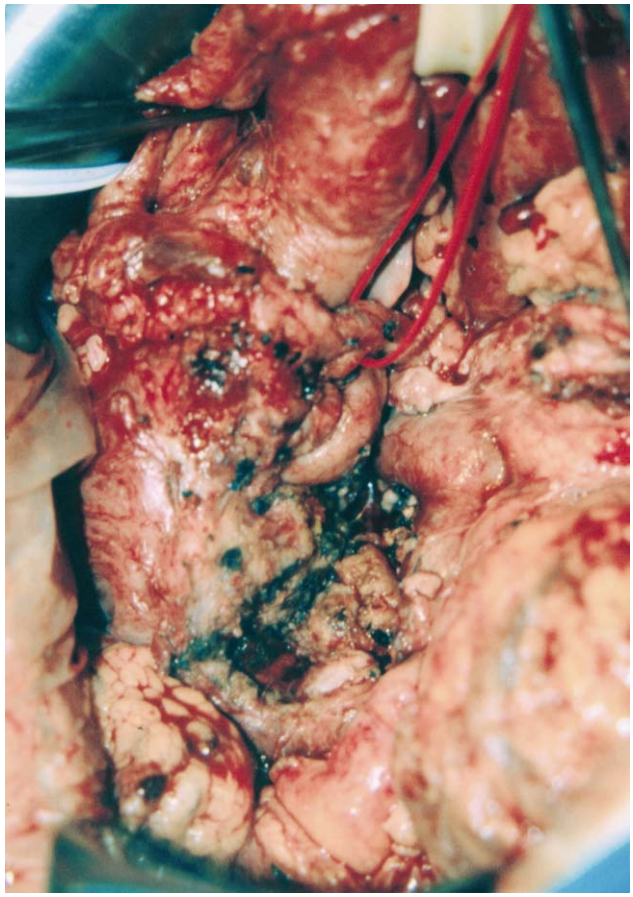

Fig. 3. Operative view of the completed duodenum-preserving pancreatic head resection (Beger) dissection. The intrapancreatic portion of the distal common bile duct is exposed, after identification and preservation of the posterior branch of the gastroduodenal artery (see vessel loop).

RESULTS

Demographics and Indications

Table 1 demonstrates the demographics and operative indications for all clinical groups. Seven of the 30 WHIP procedures were performed for benign diagnoses. This subgroup of patients is tabulated separately under WHIP-benign only. Patients undergoing ELPJ were younger than WHIP patients ($P = 0.002$), but the demographics of the groups were otherwise comparable (Table 1).

Indications for DPPHR included five patients with CP and seven patients with BTs, which included cystadenomas (five), intraductal papillary mucinous tumor (one), and islet cell tumor (one). Two additional patients were offered DPPHR for symptomatic disease diagnosed as CP preoperatively but had the discovery of ductular adenocarcinoma on intraoperative frozen section analysis of the resected portion of the pancreatic head. Both procedures were converted to WHIP, with a single complication of delayed gastric emptying in one patient.

One patient undergoing an ELPJ procedure for a preoperative diagnosis of severe CP was found on

Table 1. Patients, hospital course, and follow-up data

Procedure	DPPHR (n = 12)	ELPJ (n = 12)	DPR (n = 16)	WHIP (total) (n = 30)	WHIP (benign only) (n = 7)
Indications (n)	7 BT, 5 CP	11 CP, 1 CA	8 BT, 4 CA, 4 CP	23 CA, 6 BT, 1 CP	6 BT, 1 CP
Gender, M/F (n)	6:6	7:5	6:10	13:17	4:3
Mean age (yr) (range)	56.2 ± 2.8 (40–70)	44.2 ± 4.5* (28–60)	60.9 ± 3.1 (43–82)	65.3 ± 2.0 (48–82)	61.4 ± 2.1 (54–70)
Operative time (min)	483 ± 26	410 ± 30*	303 ± 35†	513 ± 26	516 ± 68
Blood loss (ml) (range)	860 (250–3200)	650* (250–950)	550 (50–800)	1190 (200–4400)	980 (580–1360)
Nasogastric intubation (days) (range)	5 (3–8)	5 (2–11)	3* (2–5)	6 (3–11)	4 (4–5)
Length of stay (days) (median) (range)	10 (7–30)	11 (7–28)	8‡ (6–9)	12 (6–45)	12 (10–19)
Perioperative death (n) (30 days)	0	0	0	2	1
Major complications (%)	25	16*	31	40	86
New/worsened diabetes (%)	8*	8*	6	25	33
Persistent analgesic use (%)	8	17	6	3	0
Functional recovery (%)	92	75	94	83	71

DPPHR = duodenum-preserving pancreatic head resection; ELPJ = extended lateral pancreaticojejunostomy with excavation of the pancreatic head; DPR = distal pancreatectomy; WHIP = standard or pylorus-sparing whipple procedure.

Morbidity data are expressed as mean ± SEM or median (range).

Indications include benign tumors (BT), chronic pancreatitis (CP), and carcinoma (CA).

Major complications include pancreatic duct leaks in 3 DPPHR, 2 WHIP, and 1 DPR; portal vein occlusion, right hepatic lobe necrosis, and reexploration for bleeding in 1 WHIP each; intra-abdominal fluid collection in 3 WHIP and 1 ELPH; and small bowel obstruction in 1 ELPJ.

Also, improvement or reversal of diabetes mellitus occurred in 1 DPPHR and 1 ELPJ.

*$P < 0.05$ (ANOVA) vs. WHIP.

†$P < 0.05$ (ANOVA) vs. WHIP, DPPHR, and ELPJ.

‡$P < 0.05$ (ANOVA) vs. WHIP and DPPHR.

frozen section analysis to have ductular adenocarcinoma in the excavated portion of the pancreatic head. Conversion to a WHIP procedure was infeasible due to advanced-stage disease, so the Roux-en-Y pancreaticojejunostomy was constructed. The patient's subsequent course included readmission for an intra-abdominal abscess that was successfully managed nonoperatively and eventual death due to progression of malignancy.

Cost

We assessed the following as surrogate measures of cost: operative time, estimated blood loss, and length of hospital stay. The mean operative time was significantly shorter for ELPJ vs. WHIP (410 ± 30 minutes versus 513 ± 26 minutes, $P = 0.002$), but no difference was seen between DPPHR (483 ± 26 minutes) and WHIP. Estimated blood loss was similar for DPPHR and ELPJ, both of which were less than for WHIP.

Length of hospital stay appeared to be affected primarily by two factors: length of nasogastric decompression (or gastric ileus), and the presence or absence of pancreatic and/or biliary leak. The length of nasogastric intubation was similar for all operations. Postoperative hospital stay was less for DPPHR than WHIP (median, 10 vs. 12 days, $P = 0.03$). However, overall length of stay was the same after ELPJ and WHIP.

We experienced no leaks from ELPJ anastomoses but three leaks after DPPHR. In two of the DPPHR patients with leaks, only one anastomosis was performed, an end-to-end pancreaticojejunostomy of the body of the pancreas to the end of the jejunal Roux limb. Midway through our experience, we began to routinely construct a second true anastomosis of the pancreatic rim within the duodenal C-loop to a separate enterotomy of the same jejunal limb. Only one leak has occurred since this modification, so the double-anastomosis technique remains our preferred procedure. A subgroup analysis of those patients with pancreatic or biliary leak (Table 2) revealed that this complication was associated with a threefold prolongation of length of stay (median length of stay 35 days for WHIP with leak [n = 3] versus 11 days without leak [n = 27]; median length of stay, 28 days for DPPHR with leak [n = 3] vs. 10 days without leak [n = 9]).

Table 2. Complications

Operation	Complication	No.	%
Whipple (total) (n = 30)	Pancreatic leak	2	
	Bile leak	1	
	Portal vein occlusion	1	
	Delayed gastric emptying	3	
	Gastrointestinal bleeding	2 (1 Death)	
	Hepatic ischemia	1 (Death)	
	Myocardial infarction	2	
	Intra-abdominal fluid collection	3	
	Wound Infection	2	
	Pneumonia	1	
	Urinary tract infection	1	
	Total	19	63
	Major	12	40
Whipple (benign only) (n = 7)	Abdominal fluid collection	2	
	Bile leak	1	
	Hepatic ischemia	1 (Death)	
	Upper gastrointestinal bleed	1	
	Myocardial infarction	1	
	Urinary tract infection	1	
	Total	7	100
	Major	6	86
DPPHR (Beger) (n = 12)	Pancreatic leak	3	
	Delayed gastric emptying	2	
	Wound infection	1	
	Fever of unknown origin	1	
	Total	7	59
	Major	3	25
ELPJ (Frey) (n = 12)	Delayed gastric emptying	2	
	Small bowel obstruction	1	
	Intra-abdominal fluid collection	1	
	Total	4	33
	Major	2	16
DPR (n = 16)	Myocardial infarction	2	
	Pancreatic leak	1	
	Cerebrovascular accident	1	
	Chylous ascites	1	
	Broken/retained drain	1	
	Total	6	38
	Major	5	31

Mortality

There was no operative mortality. Two perioperative (30 days) deaths occurred after WHIP (one due to gastrointestinal bleed and one due to liver failure). Late deaths have occurred after six WHIPs (all patients with CA) and three ELPJs (one patient with unresectable CA and two patients with alcohol and drug abuse). No perioperative or late deaths occurred after DPPHR.

Morbidity

Our results show lower morbidity and improved outcomes with DPPHR and ELPJ compared with

WHIPs overall or with WHIPs performed for benign disease only. Major complications included pancreatic duct leaks in three DPPHRs, two WHIPs, and one DPR, as well as portal vein occlusion, right hepatic lobe ischemia, and bile leak in one WHIP each (Table 2). Intra-abdominal fluid collections occurred in three WHIPs and one ELPJ, and a small bowel obstruction requiring reoperation occurred after one ELPJ. The rate of pancreatic leak after DPPHR was two of six patients with one anastomosis and one of six patients with two anastomoses. Overall, major complications occurred in 40% of WHIP patients and 25% of DPPHR patients, but only 16% of ELPJ patients ($P < 0.05$ vs. WHIP).

The indication of "benign tumor" had the highest major complication rate of any diagnostic category; 9 of 21 patients (43%) had major complications in this group. These included 5 of 6 (83%) of WHIPs, 3 of 7 (43%) of DPPHRs, and 2 of 8 (25%) DPRs.

The indication of "malignant tumor" was associated with major complications in 8 of 28 patients (29%). These included 6 of 23 (26%) of WHIPs, 1 of 4 (25%) DPRs, and 1 of 1 ELPJ. The indication of "chronic pancreatitis" had the lowest major complication rate; only 3 of 21 patients (14%) had major adverse events. These included 1 of 1 WHIP, 1 of 4 (25%) DPRs, 0 of 5 DPPHRs, and 1 of 11 (9%) ELPJs. We have no explanation for the high rate of complications among our BT group. Pancreatic leak occurred in only 3 of 21 (14%) patients in this category, and all three leaks were in DPPHR patients. The other complications (Table 2) bore no obvious relationship to the indication for surgery.

New diabetes was diagnosed in five WHIP patients, and two WHIP patients experienced worsening of their diabetes. One diabetic patient on oral medications before the ELPJ operation needed insulin therapy postoperatively; however, another ELPJ patient was able to control his diabetes with oral medication only after having required insulin before the operation. One new case of diabetes occurred after DPPHR, but one diabetic patient was able to reduce his treatment after DPPHR. Overall, the incidence of new or worsened diabetes was 25% for WHIP patients but only 8% for both DPPHR and ELPJ ($P < 0.05$ versus WHIP). Persistent analgesic use and failures to achieve full functional recovery were similar in DPPHR, ELPJ, and WHIP groups.

DISCUSSION

The purpose of this analysis was to evaluate the resource needs (cost), mortality and morbidity, and short-term outcomes of three forms of pancreatic head resection considered for treatment of benign disease of the proximal pancreas, when performed in the same university hospital by the same surgical team. To control for continuity of treatment methods, we analyzed 24 consecutive DPPHRs and compared our results with those for 30 consecutive WHIPs and 16 distal resections performed during the same time period. We did not randomize our patients into the various treatment groups, and a selection bias is present because we selectively used a WHIP or distal resection for known or suspected malignancies. To provide a reference for costs, complications, and outcomes, we also compared these proximal pancreatic resections with 16 distal pancreatectomies performed contemporaneously. Our goal was to determine whether, and to what degree, the DPPHR offers benefits for benign pancreatic disease compared with the WHIP.

Our results show that DPPHR and ELPJ result in lower morbidity and similar outcomes for benign disease of the pancreas, compared with the WHIP. Two deaths occurred within 30 days of the WHIP, including one in a WHIP patient with benign disease. No perioperative death occurred after DPPHR or ELPJ. Major complications were significantly fewer after ELPJ; however, three ELPJ patients died late due to recidivism (two patients) or undiagnosed CA (one patient). A longer follow-up and larger experience with ELPJ are needed to confirm this late risk with ELPJ.

The frequency of pancreaticojejunal leak after DPPHR was initially greater than for the WHIP but has not occurred after the ELPJ procedure in our experience. In both DPPHR and WHIP patients, the occurrence of a pancreatic or biliary leak was a major determinant of hospital stay and cost. Rates of full functional recovery were similar after DPPHR, ELPJ, and WHIP.

In our study, new or worsened diabetes occurred after 25% of WHIPs but only 8% of ELPJ and DPPHR operations. In an additional 8% of DPPHR and ELPJ patients, preexisting glucose intolerance or frank diabetes improved after the procedure. We therefore conclude that both the DPPHR and ELPJ procedures are safer than the WHIP procedures and carry a lower risk of the development of diabetes, as observed by others.[5,9–12]

Three recent studies evaluated outcomes after pancreaticoduodenectomy for benign disease with parameters similar to the present study.[14–16] Huang et al.[14] studied 192 patients after classic and pylorus-preserving pancreaticoduodenectomy for CA and benign pancreatic disease, including CP. After an average of 4 years, 71% of CP patients and 82% of patients with other benign pancreatic diseases were

pain free, and 97% of each group had resumed normal physical activity. However, 41% of CP patients and 27% of other benign disease patients reported the presence of diabetes, and around 40% in each group had symptoms of exocrine insufficiency. Similarly, in a retrospective review of 105 patients after classic and pylorus-preserving pancreaticoduodenectomy for CP, Sakorafas et al.[15] found that 89% of patients were relieved of pain after an average 6.6 years of follow-up. Major morbidity occurred in 24%, however, including delayed gastric emptying in 10%, and mortality was 3%. The incidence of diabetes increased from 8% preoperatively to 48% postoperatively, and symptoms of exocrine insufficiency also increased from 17% to 43%. A third study by Jimenez et al.[16] compared the standard pancreaticoduodenectomy with the pylorus-preserving version in 72 patients with CP. In this retrospective review with average follow-up of 3 years, the selection of operation was inconsistent, which makes comparison more difficult,[17] but both operations achieved comparable pain relief. No differences occurred in nutritional parameters, and new diabetes developed in only 10–12% in this study. Major complications occurred in 38% of patients overall, and the only significant difference between the two operations was a paradoxically higher frequency of delayed gastric emptying after pylorus preservation compared with the classic WHIP (33% versus 12%). Overall mortality was 1.4%. Median length of hospital stay after WHIP in all three studies was 12–15 days, which is comparable to our results.

Beger et al. published their long-term follow-up for DPPHR for the treatment of CP first in 1985[4] and more recently in 1999.[18] From 1982 to 1996, 388 patients underwent DPPHR with a hospital mortality rate of less than 1%. Over a median follow-up of 6 years, pain relief was achieved in 91%. New diabetes was diagnosed in 21%, but 11% experienced improvement in endocrine function. Postoperatively, 72% required enzyme supplements compared with 25% preoperatively. These authors also compared the DPPHR and the pylorus-preserving WHIP for CP in a randomized trial of 40 patients with a follow-up of 6 months.[5] Mortality was 0%, and overall morbidity (15–20%) and length of stay (median, 13–14 days) were comparable for both operations. A significant difference was observed in pain relief after DPPHR versus WHIP (94% versus only 67%, respectively), and glucose tolerance deteriorated in the WHIP group as insulin secretory capacity decreased. However, insulin secretion in the DPPHR group increased, resulting in a significant preservation of glucose tolerance in the DPPHR group postoperatively.

Our results are consistent with these prior studies. With regard to the cost and outcomes with the WHIP, our subset of patients who underwent WHIPs for benign disease alone experienced higher complication rates, albeit in a small number of patients.

A randomized trial by Izbicki et al.[11] compared DPPHR and ELPJ for CP with a mean follow-up of 1.5 years. There was no mortality. A significant difference was found in overall morbidity (20% for DPPHR and 9% for ELPJ), but no differences were found in postoperative pain relief (95% and 89% for DPPHR and ELPJ), ability to return to work, or endocrine and exocrine function postoperatively. Operative time was also similar for DPPHR and ELPJ (mean ± SD, 325 ± 77 versus 289 ± 89 minutes). Although the present study used slightly different methods, our results corroborate these findings.

Frey[6,8] originally described his operation in six patients and later published a series of 47 patients who underwent the ELPJ procedure for CP. During an average of 3 years, there were no deaths; however, major morbidity involved 22% of patients. Eighty-eight percent of patients had excellent or improved pain relief. Eleven percent had new or worsened diabetes, but exocrine function remained unchanged. Izbicki et al.[9] conducted a randomized trial comparing the Frey procedure (ELPJ) with pylorus-preserving WHIP for CP. With 30 patients in each group and an average follow-up of 2 years, they found significance differences in postoperative morbidity (19% versus 53% for ELPJ and WHIP, respectively). Postoperative length of stay did not differ but was longer than in our study. In agreement with our study, the operative time for ELPJ (245 ± 62 minutes) was shorter than that for WHIP (328 ± 76 minutes). In Izbicki et al.'s study, two patients developed glucose intolerance after ELPJ, although three patients were able to reduce their insulin requirements compared with preoperatively. In the WHIP group, three patients had new glucose intolerance after the surgery and three additional patients required increased diabetes therapy, for a combined incidence of new or worsened diabetes equal to 20% after the WHIP. Our results are comparable to these findings as well.

Pain relief was observed in around 90% in both groups; however, return to regular daily work or activity and quality of life were significantly greater after ELPJ than after WHIP. From their two randomized trials, Izbicki et al. suggest that the DPPHR and ELPJ procedures offer favorable alternatives to the WHIP, as these techniques provide equally effective pain relief as pancreaticoduodenectomy, with better preservation of pancreatic function and improved quality of life. The apparent preservation of

pancreatic endocrine function by the DPPHR and ELPJ procedures may be related to the conservation of most of the pancreatic uncinate region, which serves as a reservoir of the islet hormone pancreatic polypeptide.[19] This hormone promotes insulin action in the liver, and preservation of pancreatic polypeptide function may explain, in part, the improved glucose homeostasis in patients undergoing "duodenum-preserving" procedures.[20]

The possibility of an underlying pancreatic carcinoma in patients who are diagnosed with CP is well known to pancreatic surgeons and is sometimes used as a justification for using the WHIP for CP. In our series of 26 patients who were identified preoperatively as candidates for either the Frey (ELPJ) or Beger (DPPHR) procedure, two patients undergoing the Beger procedure were found on frozen section analysis to harbor pancreatic CA, and the procedures were successfully converted to WHIPs. One patient in whom a Frey procedure was undertaken was also found to have an unresectable pancreatic CA based on intraoperative frozen section analysis. One other patient selected for a Frey procedure before this series was also found to harbor CA and had a successful intraoperative conversion to a WHIP. Our observed prevalence of CA in patients selected for duodenum-preserving surgery, with a preoperative diagnosis of CP, therefore exceeds 10%. This serves as testimony for the importance of accurate intraoperative frozen section examination of the resected tissue by colleagues who are expert in pancreatic histology. All patients who are selected for duodenum-preserving procedures should be counseled that they may require conversion to a WHIP either intraoperatively or postoperatively, based on frozen section and final histologic analysis.

In summary, our experience suggests that low morbidity and good outcomes are obtained with both DPPHR and ELPJ versions of duodenum-preserving pancreatic head excision. In particular, the risk of postoperative diabetes is significantly less after both the DPPHR and ELPJ procedures. These findings corroborate the observations of European studies and confirm that the early functional recovery and freedom from analgesics (in CP patients) are similar for DPPHR, ELPJ, and WHIP procedures, but the cost and risk of the duodenum-sparing procedures are clearly better than those of the WHIP.[4,5,9,11,12] The morbidity of DPPHR is similar to the WHIP, although length of stay and mortality risk are comparable to those of lesser procedures. The selection of DPPHR versus ELPJ is dictated by the preoperative evaluation of ductal anatomy, as well as the location and extent of any focal lesion. In the setting of obstructive pancreatopathy, the ELPJ is feasible regardless of the degree of duct distortion in the pancreatic head and appears to offer the advantages of reduced morbidity and cost. As described, the ELPJ or Frey procedure is a decompressive procedure, and not a resectional technique (Fig. 4). The DPPHR procedure, on the other hand, may offer a selective advantage in patients with BTs localized to the pancreatic head. The risk of pancreatic leak after DPPHR is comparable to that for the WHIP, however, but may be less when two formal anastomoses are performed, as currently recommended by Beger et al.[18] Removal of the central portion of the pancreatic head is facilitated, in our experience, by the use of the ultrasonic aspirator and dissector. A variation of the Frey procedure recently described by us,[21] in which the pancreatic head is fully excavated with the ultrasonic dissector, may extend the application of the Frey procedure to include some BTs of the proximal pancreas.

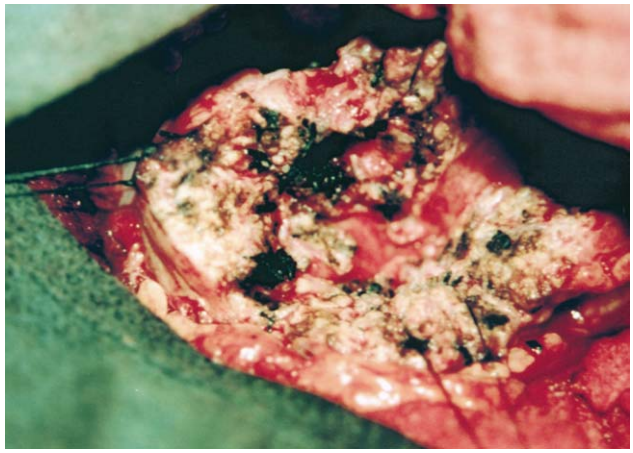

Fig. 4. Operative view of the completed extended lateral pancreaticojejunostomy (Frey) dissection. The head of the pancreas is shown, after excavation down to the dilated proximal ductal network in a patient with obstructive pancreatopathy.

Long-term follow-up is required to determine whether patients with all forms of benign disease benefit preferentially from DPPHR versus ELPJ, but both appear to offer better outcomes than WHIP procedures for benign pancreatic disease.

REFERENCES

1. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomy in the 1990s. Pathology, complications and outcomes. Ann Surg 1997;226:248–257.
2. Strasberg SM, Drebin JA, Soper NJ. Evolution and current status of the Whipple procedure: An update for gastroenterologists. Gastroenterology 1997;113:983–994.
3. Beger HG, Witte C, Kraas E, Bittner R. Erfahrung Mit Einer Das Duodenum Erhaltenden Pankreaskopfresektion Bei Chronisher Pankreatitis. Chirurg 1980;51:303–309.
4. Beger HG, Krautzberger 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.
5. Buchler M, Friess H, Muller MW, Wheatley AM, Beger HG. Randomized trial of duodenum-preserving pancreatic head resection versus pylorus-preserving Whipple in chronic pancreatitis. Am J Surg 1995;169:65–70.
6. Frey CF, Smith GJ. Description and rationale of a new operation for chronic pancreatitis. Pancreas 1987;2:701–707.
7. Partington PF, Rochelle REL. Modified Puestow procedure for retrograde drainage of the pancreatic duct. Ann Surg 1960;152:1037–1043.
8. Frey CF, Amikura K. Local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy in the management of patients with chronic pancreatitis. Ann Surg 1994;220:492–507.
9. Izbicki JR, Bloechle C, Broering DC, Knoefel WT, Kuechler T, Broelsch CE. Extended drainage versus resection in surgery for chronic pancreatitis: A prospective randomized trial comparing the longitudinal pancreatojejunostomy combined with local pancreatic head excision with the pylorus-preserving pancreatoduodenectomy. Ann Surg 1998;228: 771–779.
10. Klempa I, Spatny M, Menzel J, et al. Pankreasfunktion und Lebensqualitat Nach Pankreaskopfresektion bei der Chronishen Pankreatitis. Chirurg 1995;66:350–359.
11. Izbicki JR, Bloechle C, Broering DC, et al. Duodenum-preserving resection of the head of the pancreas in chronic pancreatitis: A prospective randomized trial. Ann Surg 1995; 221:350–358.
12. Eddes EH, Masclee AAM, Gooszen HG, Frolich M, Lamers CBHW. Effect of duodenum-preserving resection of the head of the pancreas on endocrine and exocrine pancreatic function in patients with chronic pancreatitis. Am J Surg 1997;174:387–392.
13. Carey L. Discussion of islet cell tumors. Postgraduate Course on Endocrine Surgery, Annual Clinical Congress of American College of Surgeons, 1995.
14. Huang JJ, Yeo CJ, Sohn TA, et al. Quality of life and outcomes after pancreaticoduodenectomy. Ann Surg 2000;231:890–898.
15. Sakorafas GH, Farnell MB, Nagorney DM. Pancreaticoduodenectomy for chronic pancreatitis. Long-term results in 105 patients. Arch Surg 2000;135:517–524.
16. Jimenez RE, Fernandez-del Castillo C, Rattner DW, Yu-Chiao C, Warshaw AL. Outcome of pancreaticoduodenectomy with pylorus preservation or with antrectomy in the treatment of chronic pancreatitis. Ann Surg 2000;231:293–300.
17. Cameron JL. Whipple or pylorus preservation? A critical reappraisal and some new insights into pancreaticoduodenectomy [editorial]. Ann Surg 2000;231:301.
18. Beger HG, Schlosser W, Friess HM, Buchler MW. Duodenum-preserving head resection in chronic pancreatitis changes the natural course of the disease. A single-center 26-year experience. Ann Surg 1999;230:512–519.
19. Kono T, Wang XP, Fisher WE, Andersen DK, Brunicardi FC. Pancreatic polypeptide (PP). In Martini L, ed. Encyclopedia of Endocrine Diseases. San Diego: Elsevier, 2004, pp 488–496.
20. Slezak LA, Andersen DK. Pancreatic resection: Effects in glucose metabolism. World J Surg 2001;25:452–460.
21. Andersen DK, Topazian MD. Pancreatic head excavation: A variation on the theme of duodenum-sparing pancreatic head resection. Arch Surg 2004;139:375–379.

Focal Hyperthermia Produces Progressive Tumor Necrosis Independent of the Initial Thermal Effects

Mehrdad Nikfarjam, M.B.B.S., Caterina Malcontenti-Wilson, B.Sc., Christopher Christophi, M.D., F.R.A.C.S., F.A.C.S.

Focal hyperthermia, produced using laser, radio frequency, and microwave, is used to treat liver tumors. The exact mechanisms of tissue destruction using focal hyperthermia are, however, unknown. Clinical and experimental studies suggest a progression of injury after cessation of the initial heat stimulus. This study investigates the mechanisms and time sequence of progressive tissue necrosis induced using focal hyperthermia in a murine model of colorectal liver metastases. Focal hyperthermia produced using a neodymium-yttrium aluminum garnet (Nd-YAG) laser source was applied to the normal liver and colorectal cancer liver metastases in inbred male CBA strain mice. The extent of direct lethal thermal injury was assessed histochemically using vital stain for nicotinamide adenine dinucleotide (NADH) diaphorase immediately after laser application. Tissue injury at subsequent time points was assessed using both NADH diaphorase staining and routine histology to determine the temporal relationship between tissue necrosis and time. Thermal injury occurring immediately after the application of 100 joules of energy was greater in the tumor tissue than in the normal liver (mean [standard error of the mean (SEM)]), measuring 23.5 (3.4) and 16.3 (2.6) mm^3, respectively ($P = 0.046$), despite similar tissue temperature profiles. There was a significant increase in tissue necrosis after initial injury that was greater in the normal liver than in the tumor tissue. In the normal liver, the peak volume of necrosis was 137.4 (9.8) mm^3 and occurred at 3 days, whereas in the tumor tissue the peak was 49.0 (3.5) mm^3 at 4.5 days ($P < 0.001$). Focal hyperthermia produces tissue necrosis that occurs in two phases. The first phase is caused by the direct lethal thermal injury followed by a second phase involving a progression of necrosis beyond the initial thermal effects. The normal liver and the tumor tissue responded differently to focal hyperthermia. In the tumor tissue, the direct injury is more pronounced, whereas the progression of injury is more rapid and extensive in the normal liver. (J GASTROINTEST SURG 2005;9:410–417)

KEY WORDS: Colorectal liver metastases, direct and indirect thermal injury, focal hyperthermia, mitochondrial function, progressive necrosis

Surgical resection is currently the preferred option for the treatment of selected patients with colorectal liver metastases.[1–3] Operative mortality associated with hepatic resection has decreased considerably over the last two decades, firmly establishing it as the most effective form of potentially curative therapy for the treatment of liver tumors.[1] Hepatic resection, however, continues to be associated with significant morbidity, particularly in patients with coexistent liver disease and is applicable to only a small number of patients.[1–3] This has lead to the development of local ablative therapies, particularly for the treatment of unresectable liver tumors and patients unable to tolerate major operative interventions. Local ablation can be performed by minimally invasive approaches and may achieve tumor destruction without substantial damage to surrounding functional hepatic parenchyma. It is also potentially curative in selected instances and may be more cost-effective than other palliative therapies.[3–7]

Focal hyperthermia produced using either radiofrequency, microwave, or laser are currently used for local ablation of liver tumors.[3] The mechanisms of action of the various techniques are similar, based on focal heat production to achieve tumor destruction. The major limiting factor of focal hyperthermia for tumor ablation is an inability to consistently achieve complete tumor necrosis, especially at the margins

From the Department of Surgery, University of Melbourne, Austin Hospital, Victoria, Australia.
Reprint requests: Professor Christopher Christophi, M.D., F.R.A.C.S., F.A.C.S., Department of Surgery, University of Melbourne, Austin Hospital, Lance Townsend Building Level 8, Studley Rd., Heidelberg, Melbourne, Victoria 3084; e-mail: surgery-armc@unimelb.edu.au

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.07.008

of larger tumors.[6] An understanding of the underlying mechanisms of tissue injury induced using focal hyperthermia is essential in devising methods to manipulate the processes involved and improve tumor eradication. Ensuring complete tumor destruction may allow focal hyperthermia therapy to eventually achieve similar results to surgical resection.

Clinical and experimental studies suggest the area of tissue injury after focal hyperthermia increases after cessation of the initial heat stimulus.[8–11] The nature of this evolving tissue necrosis after the initial heat stimulus is largely undetermined. This progressive injury may simply represent a delayed identification of lethally damaged cells not detected using standard histological techniques. Alternatively, it may represent a true progression of injury caused by a series of complex cellular mechanisms that are triggered by the initial heat stimulus.

The aim of this study was to investigate the temporal relationship of progressive tissue necrosis in the normal liver and the tumor tissue after the initial injury caused by focal hyperthermia.

MATERIAL AND METHODS

Animals

Male inbred CBA mice, 6–8 weeks of age, were used in these experiments. Animals were housed in standard cages with access to irradiated food and water ad libidum and exposed to a 12-hour light–dark cycle. Animals with and without liver metastases were used in the experiments. All procedures were performed according to the guidelines of the Austin Hospital Animal Ethics Committee.

Liver Metastases Model

A previously characterized model of colorectal liver metastases was used.[12] Dimethyl hydrazine (DMH)-induced primary murine colon adenocarcinoma cells (MoCR) were used for the experiments. The histology, vasculature, and growth kinetics of this cell line closely resembles human colorectal liver metastases.[12–14]

Preparation of Cell Suspension and Induction of Metastases

A cell suspension (1×10^6 cells/ml) was prepared using standard techniques.[12] Mice were anesthetized via intraperitoneal injection of ketamine 100 mg/kg (Parke Davis, Auckland, New Zealand) and xylazine 10 mg/kg (Bayer Australia, Ltd., Pymble, Australia). The spleen was exteriorized through a left subcostal incision and 0.05 ml of colon cancer cell suspension (50,000 cells) was slowly injected into the body of the spleen over 1 minute using a 25-gauge needle. Afterwards, the spleen was compressed for 2 minutes. A splenectomy was then performed to prevent local tumor growth and wounds were closed in layers. Twenty-eight days postoperatively, animals bearing hepatic tumors, with no evidence of extrahepatic disease, were used for subsequent study.

Focal Hyperthermia

A neodymium yttrium-aluminum-garnet (Nd:YAG) wavelength of 1064 nm laser (Dornier medilas fibertom 4100; Medizintechnik GmbH, Munchen, Germany) was used as a focal heat source. Animals were anesthetized as previously described. A bilateral subcostal incision was used to fully expose the liver. A 400 μm bare tip optical quartz fiber was used to deliver laser energy (100 joules) to either the normal liver or the tumor tissue in separate groups of animals. Similarly located 7–8 mm diameter intraparenchymal tumors were chosen for therapy. The liver was removed after the completion of procedures regarding the assessment of the initial injury. In studies performed to determine the progression of injury, it was indicated that the abdomen was closed and that animals were sacrificed at subsequent time points.

Preliminary experiments determined a suitable laser power (2 watts) and treatment exposure duration (50 seconds) that consistently produced a 2–3 mm diameter region of tissue coagulation. The settings with regard to the tumor tissue produced incomplete necrosis that did not extend into the normal liver.

Experimental Groups

Animals with and without metastases were analyzed to determine the time sequence of tissue necrosis after the application of a focal heat stimulus. Animal numbers were based on preliminary studies, estimating a minimum requirement of 10 animals per study group to detect a 10%–15% change in the diameter of necrosis with a power of 0.8 and a value of P less than 0.05.

Study 1: Progression of Necrosis in a Normal Liver. The effect of focal hyperthermia on the normal liver was assessed by inducing laser injury as previously described. One group of animals was sacrificed immediately after laser application to assess the extent of direct lethal heat injury. The remaining animals were recovered and groups were sacrificed thereafter at 24, 48, 72 hours and at 5 days post injury.

Study 2: Progression of Necrosis in Colorectal Liver Metastases. The effect of focal hyperthermia on tumors was assessed by inducing laser injury as

previously described. To evaluate the extent of direct heat injury on the tumor tissue, a group of animals were sacrificed immediately after laser application. Subsequent tumor damage was assessed in the remaining animals at the same time points as indicated for study 1.

Assessment

Macroscopic Assessment of Tissue Necrosis. The maximum diameter of coagulated tissue was measured using a Vernier caliper. Measurements were based on the cross-sectional diameter of coagulated tissue symmetrical to the point of laser fiber insertion.

Histological Assessment of Tissue Necrosis. Formalin-fixed tissue was paraffin embedded, sectioned at 3 mm, and stained with hematoxylin and eosin (H&E). Histological assessment was performed using an Olympus light microscope (BHT; Olympus, Tokyo, Japan) and the mean diameter of necrosis was determined and recorded at various time points in a blinded manner.

Histochemical Assessment of Tissue Necrosis. Nicotinamide adenine dinucleotide diaphorase (NADH diaphorase) staining for mitochondrial activity was performed as a definitive early marker of tissue viability.[15,16] Tissue at the site of laser-induced heat injury was embedded in optimum cooling tissue (OCT) medium (Tissue-Tek, Sydney, Australia), snap frozen, and stored at −80 C, until further processing. Cryostat sections (10 μm) were mounted onto glass slides. Cut sections were incubated for 15 minutes in a humidity chamber at room temperature with a test solution containing 1 ml of reduced NADH (2.5 mg/ml), 2.5 ml nitroblue tetrazolium chloride, 1 ml phosphate-buffered saline, and 0.5 ml of Ringer's solution. Sections were rinsed with distilled water, covered with a permanent aqueous mountant (PMT030; Scytek Laboratories, Logan, UT), and dried at 70 C for 20 minutes. Sections were then mounted in DePeX (Gurr; BDH Laboratory Supplies, Poole, United Kingdom) and cover-slipped for optical clarity. Cells exhibiting mitochondrial activity stained blue. The diameter of necrosis was determined using light microscopy.

Measurement of Volume of Necrosis. Consistent spherical areas of necrosis were produced using the laser heat source, allowing volume calculations based on the formula $4/3\pi r^3$, in which r is the radius of the lesion, as previously described.[11]

Tissue Temperature Measurements. Tissue temperature was assessed immediately after the completion of focal hyperthermia 3 mm from the fiber insertion site. A multiadaptable probe (1 mm diameter) (OxyLab pO_2; Oxford Optronix, Ltd., Oxford, United Kingdom) was used for temperature measurements and repeated 2 minutes after the initial recordings.

Statistical Analysis. Statistically significant differences in necrosis (mean [SEM]) at various time points were identified using the Kruskal-Wallis test and comparisons were assessed using the Mann–Whitney *U* test (SPSS, Inc., Chicago, IL). Differences with regard to necrosis between the tumor tissue and the normal liver were achieved using the Mann–Whitney *U* test. Logistic regression analysis was applied to a plot of tissue necrosis vs. time after focal hyperthermic injury to determine the curve of best correlation (r) (CurveExpert version 1.34; Microsoft Corp., Redmond, WA). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Study 1: Progression of Necrosis in the Normal Liver

Coagulated tissue in the normal liver was visible immediately after laser application and was surrounded by a zone of hyperemia (Fig. 1, a). Upon examining the histology of H&E sections, the outer limit of tissue necrosis was indistinct (Fig. 1, c). Histological changes indicative of early tissue necrosis was evident directly adjacent to the region of heat application at high power, but was less perceptible peripherally. NADH diaphorase staining clearly demarcated the region of tissue necrosis (Fig. 2). This was measured and used to calculate the volume of direct heat-induced tissue injury. The mean volume of liver necrosis immediately after laser application was 16.3 (2.6) mm^3.

The volume of necrosis increased at subsequent time points (Fig. 3, a and b). The mean diameter of tissue necrosis was clearly demarcated in animals sacrificed 24 hours after the initial heat stimulus and thereafter. Macroscopic measurements, routine histology (Fig. 1, b and d) and NADH diaphorase findings were equivalent by 24 hours postinjury. The volume of necrosis at 24 hours (61.4 [6.4] mm^3) was significantly greater than the immediate injury ($P < 0.001$). A further significant increase occurred between 24 and 48 hours (138.9 [11.6] mm^3) ($P < 0.001$). No statistically significant increase was noted thereafter. A logistic model curve correlated best with data points ($r = 0.732$) (Fig. 3, b) and the volume of necrosis reached a peak of 137.4 (9.8) mm^3 at 3 days.

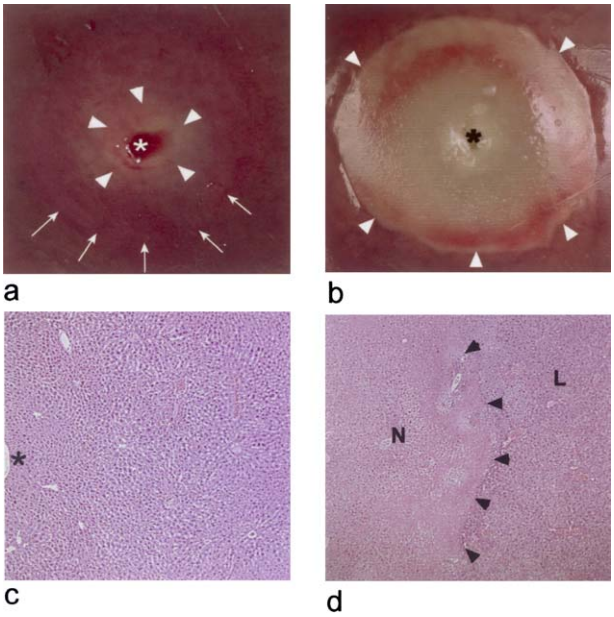

Fig. 1. (**a**) Focal hyperthermia injury to the normal liver immediately after laser application. An area of coagulation (*arrowheads*) surrounds the fiber insertion site (denoted by an *). Liver hyperemia is noted to extend beyond the region of coagulation (*arrows*) (original magnification × 12). (**b**) Extension of tissue is seen 48 hours post laser injury (original magnification × 8). (**c**) Histological evidence of lethal tissue injury on hematoxylin and eosin (H&E) stained sections is poorly defined immediately after post laser application. Vessel congestion is noted with early coagulative changes directly adjacent to the fiber insertion site (denoted by an *) (original magnification × 120). (**d**) At 48 hours after focal hyperthermia injury, a clear line of demarcation (*arrowheads*) develops between necrotic tissue (N) and viable liver (L) (H&E staining) (original magnification × 120).

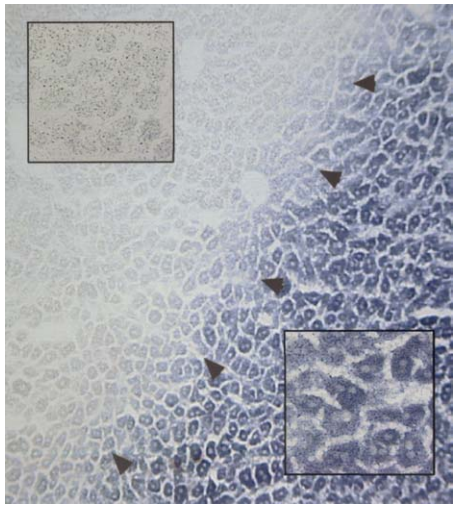

Fig. 2. Nicotinamide adenine dinucleotide (NADH) diaphorase histochemistry in the normal liver demarcating viable from nonviable tissue (*arrows*). The cytoplasm of viable cells are stained blue (lower right insert), whereas nonviable cells stain poorly (upper left insert) (original magnification × 450).

Study 2: Progression of Necrosis in Colorectal Liver Metastases

The area of necrosis immediately after laser application could not be accurately defined macroscopically or on H&E histology (Fig. 4, a). A region of central necrosis was occasionally evident after laser application but was similarly noted in some untreated tumors. Tumor tissue adjacent to the site of laser application was slightly paler than more peripheral regions, but tissue viability could not be ascertained using routine H&E histology. NADH diaphorase staining, however, clearly delineated the extent of heat injury allowing measurement of necrosis. The mean volume of tumor necrosis immediately after laser application was 23.5 (3.4) mm^3.

The volume of tumor necrosis at subsequent time points is illustrated in Fig. 3, c and d. The extent of necrosis was clearly demarcated on routine histology 24 hours after laser application (Fig. 4, b) but was not significantly greater than the initial heat-induced injury. There was, however, a significant increase in the volume of necrosis compared with the initial injury at 48 hours, with a mean volume of necrosis of 36.8 (4.01) mm^3 ($P = 0.009$). The volume of necrosis thereafter was not significantly different compared with the results at 72 hours being 41.6 (3.5) mm^3 ($P = 0.334$) and 5 days being 48.3 (3.8) mm^3) ($P = 0.056$), respectively. A reciprocal quadratic curve correlated best with the data points ($r = 0.6255$) and the volume of necrosis reached a peak of 49.0 (3.5) mm^3 at 4.5 days (Fig. 3, d).

Comparison of Necrosis in the Normal Liver Compared with Tumor Tissue

The mean volume of necrosis caused by direct heat injury immediately after laser application was significantly greater in the tumor tissue (23.5 [3.4] mm^3) than in the normal liver (16.3 [2.6] mm^3) ($P = 0.046$) (Fig. 5). In contrast, the peak volume of necrosis in the normal liver was 137.4 (9.8) mm^3 at 3 days and was significantly greater than the peak volume of necrosis in tumor tissue (49.0 [3.5] mm^3) that occurred at 4.5 days ($P < 0.001$). The increase in volume of necrosis after the initial lethal thermal injury is a ninefold change in the normal liver compared with a twofold increase in the tumor tissue.

Tissue Temperature Measurements

There was no statistically significant differences regarding tissue temperatures in the normal liver

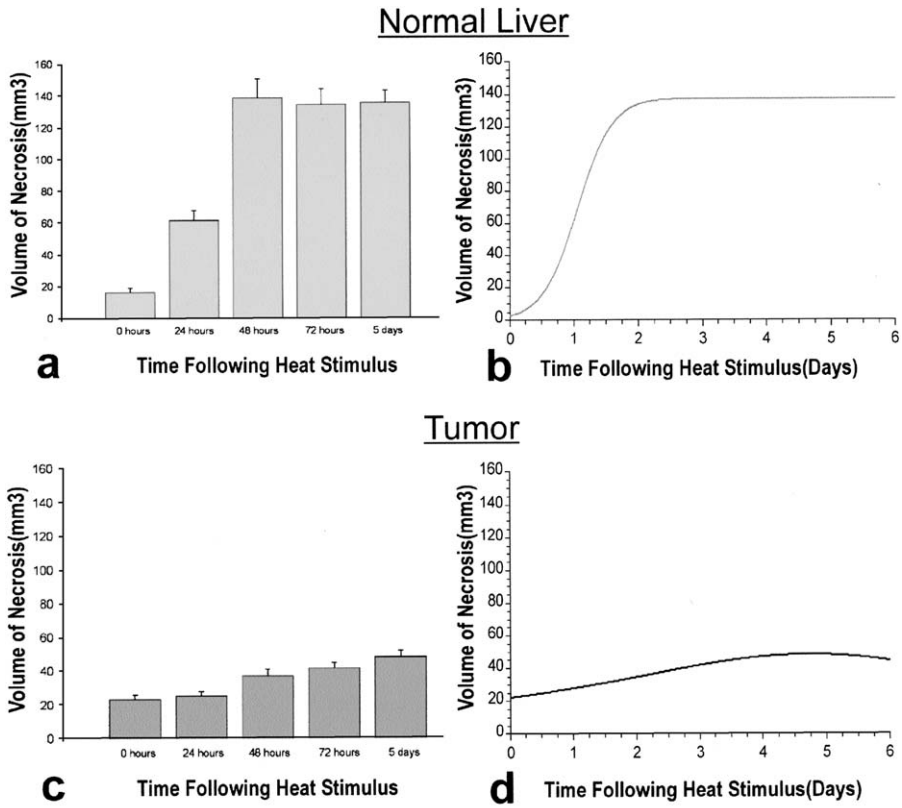

Fig. 3. (**a**) Bar graph indicating volume of necrosis in the normal liver. (**b**) A rational function curve correlates best with the data points (correlation = 0.732, standard deviation = 42.5). The peak volume of necrosis occurred at 3 days. (**c**) Bar graph indicating a more gradual evolution of tissue necrosis in tumor tissue. (**d**) A sinusoidal curve correlates best with the data points (correlation = 0.625, standard deviation = 11.4). The peak volume of necrosis occurred at 4.5 days.

(39.4 [0.9] °C) and the tumors (40.2 [1.1] °C) immediately after focal hyperthermic treatment ($P = 0.64$). Tissue temperatures returned to baseline levels within 2 minutes of therapy in both the normal liver and the tumors.

DISCUSSION

In-situ ablation can be performed using several techniques. In selected patients with colorectal liver metastases, the 5-year survival rate is 5%–30% after therapy.[3,5,6] Focal hyperthermia using laser, radio frequency, and microwave are currently the favored in-situ ablative techniques.[5,6] Despite some potential advantages compared with surgery, the main limitation regarding focal hyperthermia ablation is the inability to achieve complete tumor necrosis, especially of larger tumors.[6] Local recurrence at tumor margins after focal hyperthermia therapy is proportional to the tumor size and range from 1%–10%.[2,3,7] This is generally higher than local recurrences associated with surgical resection.[2,3] The overall recurrence after focal hyperthermia ablation of colorectal liver metastases is even more substantial ranging from 60%–80%.[2,3,7] A greater understanding of the underlying processes involved in focal hyperthermia-induced tissue destruction is essential with regard to devising methods to improve tumor eradication.

Focal hyperthermia seems to achieve its effects in two phases. The first phase is the result of direct thermal effects that produce immediate tissue necrosis. The second phase is an expansion of the area of injury that represents a progression in tissue injury. The nature of this progression in tissue injury and its relation to the initial tissue damage is previously undefined, despite several reports of an expansion of tissue injury after focal hyperthermia.[8–11]

A progression of tissue injury after focal hyperthermia may represent two distinct phenomenons. In the first instance, cells that are lethally damaged

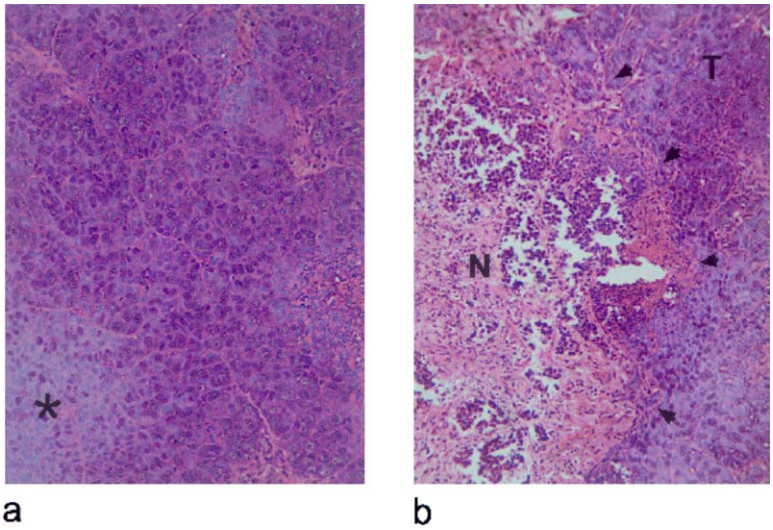

Fig. 4. (**a**) Focal hyperthermia injury in the tumor tissue. Tissue injury immediately after postlaser application is poorly defined. Cells adjacent to the site of laser application (denoted by an *) are slightly paler than the more peripheral areas. The tumor contains regions of necrosis unrelated to heat injury (H&E staining) (original magnification × 130). (**b**) Forty-eight hours after laser application there is a line of demarcation (*arrowheads*) between heat-induced necrotic (N) tumor tissue and viable tumor (T) tissue (H&E staining) (original magnification × 130).

with heat application may initially seem morphologically normal, with the full extent of injury only becoming evident well after the cessation of the initial heat stimulus.[10] The progression in necrosis in such a situation represents an apparent increase in tissue injury. Alternatively, there may be a true increase in tissue injury caused by progressive death of the cells that were viable immediately after the initial heat stimulus. These two processes are only distinguished by sensitive markers of early cell injury that identify lethally injured tissue before identifiable morphological changes.

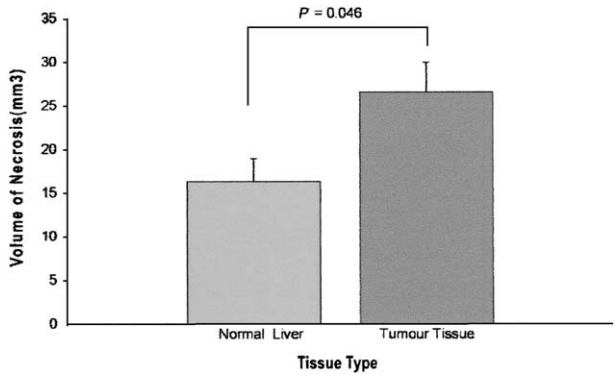

Fig. 5. Comparison of mean volume of immediate injury after application of 100 joules of heat energy to the normal liver and colorectal liver metastases. $P = 0.046$ (Mann–Whitney U test).

There is long-standing belief that focal hyperthermia induces tissue destruction only by direct thermal effects.[8,17–20] In this study, the mean tissue temperatures 3 mm from the fiber insertion site in the normal liver and the tumor tissue immediately upon completion of therapy were 39.4 and 40.2 C, respectively. These temperatures returned to baseline levels within 2 minutes after the completion of therapy. The normal liver and the tumor tissue in this region were exposed to theoretically sublethal temperatures. The indication of tissue injury extending into this area over time suggests that the observed tissue damage was unlikely caused entirely by direct thermal effects. Tissue temperature recordings, however, serve as an indirect method for assessing the extent of immediate heat-induced cell injury, because not all cells respond to temperature changes in the same manner.

The earliest signs of heat injury occur at a subcellular level.[15,16,21] Routine histology and imaging are unable to clearly identify these early changes and, subsequently, underestimate the extent of injury. A cessation of mitochondrial activity precedes any structural change that occurs within these damaged cells.[15,16] One method for assessing mitochondrial function is by histochemical detection of an essential mitochondrial enzyme, NADH diaphorase. The activity of this enzyme subsides immediately after lethal heat injury and was used in this study to clearly demarcate the extent of direct lethal injury.

The initial direct injury regarding tumor tissue in this study was greater than the normal liver based on NADH diaphorase staining, despite equivalent tissue temperature profiles. In-vitro studies have demonstrated that malignant cells are generally more sensitive to heat than normal cells, which is explained by differences in cellular size, distribution of intermediate filaments, and expression of adhesion molecules.[22] In-vivo analyses are not as consistent and may relate to differences in the tumor microenvironment.[23,24] These tissue-specific features may explain the indication of a greater volume of initial necrosis in the tumor tissue compared with the normal liver.

A progression in necrosis occurred in both the tumor tissue and the normal liver after the application of the heat stimulus. The increase in the extent of necrosis beyond the NADH diaphorase defined initial injury represents a true progression with regard to tissue damage unrelated to direct lethal thermal effects. The rate and extent of this increase was significantly greater in the normal liver compared with the tumor tissue. Tissue necrosis peaked at 3 days in the normal liver compared with 4.5 days in the liver metastases based on logistic regression analysis. The overall increase in the volume of necrosis after application of focal hyperthermia to the normal liver was ninefold compared with twofold in the tumor tissue. Progressive tissue injury clearly contributed considerably to the final volume of tissue necrosis, particularly in the normal liver. The exact mechanisms involved in this progressive tissue necrosis are speculative and may include various processes including Kupffer-cell activation, cytokine release, altered apoptosis, thermotolerance, and ischemia reperfusion injury.[8,21,25–27]

In conclusion, this study has revealed that there are two distinct phases of focal hyperthermic tissue destruction. The first phase involves direct thermal injury that is greater in the tumor tissue than in the normal liver. This is followed by a progression of injury unrelated to the direct thermal effects that is greater in the normal liver than in the tumor tissue. The knowledge that focal hyperthermia-induced tissue injury increases after the initial thermal damage leads to the possibility of further manipulation of the processes involved. Increasing this progression of focal hyperthermia injury may be particularly relevant for the complete destruction of tumor margins and adjacent normal liver.

REFERENCES

1. Allen PJ, Jarnagin WR. Current status of hepatic resection. Adv Surg 2003;37:29–49.
2. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239:818–825; discussion 825–817.
3. Curley SA, Cusack JC Jr, Tanabe KK, et al. Advances in the treatment of liver tumors. Curr Probl Surg 2002;39:449–571.
4. Shetty SK, Rosen MP, Raptopoulos V, et al. Cost-effectiveness of percutaneous radiofrequency ablation for malignant hepatic neoplasms. J Vasc Interv Radiol 2001;12:823–833.
5. Nikfarjam M, Christophi C. Interstitial laser thermotherapy for liver tumours. Br J Surg 2003;90:1033–1047.
6. Erce C, Parks RW. Interstitial ablative techniques for hepatic tumours. Br J Surg 2003;90:272–289.
7. Vogl TJ, Straub R, Eichler K, et al. Colorectal carcinoma metastases in liver: Laser-induced interstitial thermotherapy—Local tumor control rate and survival data. Radiology 2004;230:450–458.
8. Matthewson K, Coleridge-Smith P, O'Sullivan JP, et al. Biological effects of intrahepatic neodymium:yttrium-aluminum-garnet laser photocoagulation in rats. Gastroenterology 1987; 93:550–557.
9. Matsumoto R, Selig AM, Colucci VM, et al. Interstitial Nd:YAG laser ablation in normal rabbit liver: Trial to maximize the size of laser-induced lesions. Lasers Surg Med 1992; 12:650–658.
10. Sweetland HM, Wyman A, Rogers K. Evaluation of the effect on the normal liver of interstitial laser hyperthermia using artificial sapphire probes. Lasers Med Sci 1993;8:99–105.
11. Wiersinga WJ, Jansen MC, Straatsburg IH, et al. Lesion progression with time and the effect of vascular occlusion following radiofrequency ablation of the liver. Br J Surg 2003; 90:306–312.
12. Kuruppu D, Christophi C, Bertram JF, et al. Characterization of an animal model of hepatic metastasis. J Gastroenterol Hepatol 1996;11:26–32.
13. Kuruppu D, Christophi C, O'Brien PE. Microvascular architecture of hepatic metastases in a mouse model. Hepato Pancreato Biliary Surg 1997;10:149–157; discussion 158.
14. Nikfarjam M, Muralidharan V, Malcontenti-Wilson C, et al. Scanning electron microscopy study of the blood supply of human colorectal liver metastases. Eur J Surg Oncol 2003; 29:856–861.
15. Neumann RA, Knobler RM, Leonhartsberger H, et al. Histochemical evaluation of the coagulation depth after argon laser impact on a port-wine stain. Lasers Surg Med 1991; 11:606–615.
16. Heisterkamp J, van Hillegersberg R, Zondervan PE, et al. Metabolic activity and DNA integrity in human hepatic metastases after interstitial laser coagulation (ILC). Lasers Surg Med 2001;28:80–86.
17. Welch AJ, Motamedi M, Rastegar S, et al. Laser thermal ablation. Photochem Photobiol 1991;53:815–823.
18. Thomsen S. Pathologic analysis of photothermal and photomechanical effects of laser-tissue interactions. Photochem Photobiol 1991;53:825–835.
19. Overgaard J, Suit HD. Time-temperature relationship in hyperthermic treatment of malignant and normal tissue in vivo. Cancer Res 1979;39:3248–3253.
20. van Hillegersberg R, de Witte MT, Kort WJ, et al. Water-jet-cooled Nd:YAG laser coagulation of experimental liver metastases: Correlation between ultrasonography and histology. Lasers Surg Med 1993;13:332–343.
21. Decker T, Lohmann-Matthes ML, Karck U, et al. Comparative study of cytotoxicity, tumor necrosis factor, and prostaglandin release after stimulation of rat Kupffer cells, murine

Kupffer cells, and murine inflammatory liver macrophages. J Leukoc Biol 1989;45:139–146.
22. Dickson JA, Calderwood SK. Temperature range and selective sensitivity of tumors to hyperthermia: A critical review. Ann NY Acad Sci 1980;335:180–205.
23. Castren-Persons M, Schroder T, Lehtonen E. Sensitivity to Nd:YAG induced laserthermia is a cell-type-specific feature not directly related to tumorigenic potential or proliferation rate. Lasers Surg Med 1996;18:420–428.
24. Song CW. Effect of local hyperthermia on blood flow and microenvironment: A review. Cancer Res 1984;44:4721s–4730s.
25. Decker K. Biologically active products of stimulated liver macrophages (Kupffer cells). Eur J Biochem 1990;192:245–261.
26. Kelleher DK, Engel T, Vaupel PW. Changes in microregional perfusion, oxygenation, ATP and lactate distribution in subcutaneous rat tumours upon water-filtered IR-A hyperthermia. Int J Hyperthermia 1995;11:241–255.
27. Germer CT, Albrecht D, Roggan A, et al. Experimental study of laparoscopic laser-induced thermotherapy for liver tumours. Br J Surg 1997;84:317–320.

Analysis of Prognostic and Immunohistochemical Factors in Gastrointestinal Stromal Tumors With Malignant Potential

Halil Özgüç, M.D., Tuncay Yilmazlar, M.D., Ömer Yerci, M.D., Rusen Soylu, M.D., Volkan Tümay, M.D., Gülaydan Filiz, M.D., Abdullah Zorluoglu, M.D.

The aim of this study was to analyze 37 patients with malignant primary gastrointestinal stromal tumors and to compare the findings and their therapeutic implications with those previously reported. The medical records of 37 patients who were diagnosed and operated on between January 1996 and December 2002 were retrospectively reviewed. The patients' age, tumor size, type of surgery, histologic type, mitotic counts, presence of necrosis, Ki-67 proliferative index, National Institutes of Health 2001 consensus classification, immunohistochemical staining, and recurrence were examined to analyze factors affecting survival. Overall actuarial survival for all patients was 46%. When analyzed by type of resection, the complete resection group (R0 resection) had a mean overall survival of 48.2 ± 6.18 months compared with the patients with incomplete resection (R1–R2) who survived a mean of 10.8 ± 3.2 months ($P = 0.00$). Univariate analysis showed development of recurrence ($P = 0.00$), tumor size of 8 cm or greater ($P = 0.05$), Ki-67 proliferative index greater than 0.82 ($P = 0.0448$), desmin staining ($P = 0.0076$), age younger than 49 years ($P = 0.0009$), and incomplete resection ($P = 0.00$) to be significantly correlated with a poor survival. In multivariate analysis, desmin staining ($P = 0.031$), tumor size ($P = 0.033$), age ($P = 0.01$), recurrence ($P = 0.038$), and R0 resection ($P = 0.02$) were significant independent prognostic factors. We recommend that more careful preoperative and more frequent postoperative follow-up examinations be performed for patients with large tumors, age of younger than 49 years, and Ki-67 proliferative index greater than 0.82. (J GASTROINTEST SURG 2005;9:418–429)

KEY WORDS: Gastrointestinal stromal tumors, prognostic factors, survival analysis, recurrence, surgery

Gastrointestinal (GI) stromal tumors (GISTs) are relatively rare tumors of the GI tract. GISTs constitute 1–2% of all GI malignancies and are considered to originate from neoplastic transformation of intestinal pacemaker cells (Cajal cells). Until recently, mesenchymal tumors of the GI tract were termed smooth muscle tumors (leiomyomas, leiomyoblastomas, and leiomyosarcomas) or schwannomas. Recently, GISTs have been defined as mesenchymal tumors of the GI that express c-*kit* proto-oncogene product (CD-117), a transmembraneous tyrosine kinase receptor molecule. Immunohistochemical findings have made it clear that GISTs may have smooth muscle differentiation, neural differentiation, dual smooth muscle and neural differentiation, or no obvious differentiation. They are nearly uniformly c-kit-positive and frequently express the myeloid stem cell antigen CD34. A significant subset of GISTs also express some other cell-type markers like SMA, desmin, vimentin, and S100, among others.[1–3]

GISTs have a wide clinical spectrum from benign to frankly malignant, and clinical behavior is difficult to predict in an individual patient. Among the various prognostic factors studied, mitotic index and tumor size are considered to provide the most useful prognostic information. Data from literature suggest that any GIST greater than 5 cm in diameter and greater than five mitoses per 50 high-power fields (HPFs) should be considered as the strongest pathologic predictors of malignant behavior. GISTs larger than

From the Departments of Surgery (H.Ö., T.Y., R.S., V.T., A.Z.) and Pathology (Ö.Y., G.F.), Uludag University Medical School, Bursa, Turkey. Reprint requests: Halil Özgüç, M.D., Department of Surgery, Uludag University Medical School, 16059 Bursa, Turkey. e-mail: ozguch@uludag.edu.tr

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.07.003

10 cm in diameter have a high risk of aggressive behavior regardless of the mitotic count, and GISTs of any size with a high mitotic count are also deemed to be high-risk tumors.[4–7] Although many studies have tried to identify prognostic factors, an accurate method to determine the patients at risk for survival has not been generally accepted.

Different studies have shown controversial results probably related to the different criteria used for selection of cases, different methods used, few number of patients contained, long time periods, and benign tumors. Studies about GISTs are increasing in journals. However, a few of these include almost all clinicopathologic findings, including immunohistochemical markers, to evaluate indicators of survival. Data from the studies of different centers that aimed to evaluate prognostic factors may be beneficial for solution of this confusion. This study was designed to analyze clinical presentation and histopathologic examination, to evaluate prognostic factors that affect survival after surgery in our series of 37 GIST patients with malignant potential, and to compare the findings and their therapeutic implications with those previously reported.

METHODS

Patients

The medical records of 37 patients who were diagnosed and operated on for malignant GISTs between January 1996 and December 2002 at the Department of Surgery, Uludag University Medical School, were retrospectively reviewed. Pathologic investigations of all patients were performed at the Department of Pathology in our medical school. Systemic chemotherapy and radiation therapy were excluded from the analyses in this report because they were used in sporadic fashion. Microscopically, tumors with a mitotic count greater than 5, which were determined by counting the mitotic cells seen in 50 consecutive HPFs of the most active areas of tumor, and/or tumor size larger than 5 cm and/or hypercellularity and/or presence of invasion to adjacent tissue metastases was accepted criteria for malignancy.

Clinical and Surgical Findings

Patient charts, operative reports, and histopathologic slides were reviewed to determine clinical presentation, demographic data, histologic type and immunohistochemical features, tumor size, location, type of surgical resection, operative morbidity and mortality, pattern of recurrence, and survival. Follow-up was obtained by chart review and via telephone.

Resections are classified as follows:

1. Incomplete resection (R1–R2) if tumor is nonresectable at exploration or if gross residual disease is present after resection.
2. Complete resection (R0) if excision of all gross disease with negative histopathologic margins is performed. Complete resection is subdivided into two groups: radical resection and limited resection. The limited resection group includes subtotal or wedge gastric resection and segmental bowel resection. The radical resection group includes resection of stomach or bowel with wide margin and removal of contiguous organ involvement.

Pathologic and Immunohistochemical Findings

Mitotic counts were obtained from the areas where mitotic activity was maximum in hematoxylin and eosin–stained preparations. The following variables were examined to analyze factors affecting survival: age, tumor size, type of surgery, histologic type, mitotic counts determined by counting 50 HPFs covering the most active areas, presence of necrosis, Ki-67 proliferative index, National Institutes of Health (NIH) 2001 consensus classification, immunohistochemical staining, and recurrence.

In each case, one representative block was chosen for immunohistochemical staining using the streptavidin-biotin technique. Paraffin sections, 4 μm thick, were deparaffinized with xylene (20 minutes) and then rehydrated through serial baths of ethanol solution to water. Endogenous peroxidase activity was blocked by incubation for 20 minutes with 3% hydrogen peroxide in methanol. The selected sections were autoclaved for 15 minutes in 500 ml of 0.01 mol/L sodium citrate buffer, pH 6.0. They were washed with phosphate-buffered saline solution (pH 7.4) before immunohistochemical staining. The sections were incubated with monoclonal antibodies at room temperature for 20 minutes. The antibody-treated slides were rinsed in phosphate-buffered saline solution and incubated with a biotinylated secondary antibody (Labvision Co., Fremont, CA). The slides were washed in phosphate-buffered saline and then incubated with an avidin-biotin-peroxidase complex (Ultra-streptavidin/Anti-Polyvalent, Labvision Co.) for 30 minutes. As chromogen, 3,3′-diaminobenzene tetrahydrochloride was used with hydrogen peroxide. The sections were counterstained with hematoxylin.

The antigens visualized with antibodies were c-kit protein (clone 117 CO5, ready for use; Neo

Markers, Westinghouse, Fremont, CA), endothelial cell marker CD34 (clone QBEnd/10, 1:75; Neo Markers), smooth muscle markers smooth muscle actin (SMA; clone 1A4, 1:100 dilution; Neo Markers), and desmin (clone D33, 1:150; Neo Markers). Schwann cell–related markers S-100 protein (clone 4C4.9, 1:100 dilution; Neo Markers) and mesenchymal intermediate-filament vimentin (clone V9, 1:100; Neo Markers), and Ki-67 (clone MIB-1, 1:25 dilution; Dako, Glostrup, Denmark). The *Ki-67 proliferative index* (the number of MIB-1–positive cells determined by counting 1,000 cells in most active areas at magnification of ×400) was examined by histopathology. The tumor cells were considered to be positive for Ki-67 when distinct nuclear staining was identified. *Necrosis* was defined as sheets of cell ghosts or areas of cell debris. The risk of aggressive behavior of the tumors was calculated according to the NIH consensus statement of 2001 as follows: a) a tumor size less than 2 cm and mitotic count less than 5:50 HPFs was graded as *very low risk*, b) a tumor size between 2 and 5 cm and a mitotic count less than 5:50 HPFs was graded as *low risk*, c) a tumor size less than 5 cm and a mitotic count between 5:50 and 10:50 HPFs or a tumor between 5 and 10 cm and a mitotic count less than 5:50 HPFs was graded as *intermediate risk*, and d) a tumor size greater than 10 cm or a mitotic count greater than 10:50 HPFs or a tumor size greater than 5 cm and a mitotic count greater than 5:50 HPFs was graded as *high risk*.[8] We had three groups according to the NIH consensus statements because there were no patients in very low risk group.

Immunohistochemical stainings were used in an attempt to assess survival. The GISTs were divided into four groups (smooth muscular, neural, combined smooth muscular–neural, and uncommitted types) according to their immunoreactivity. The tumor was defined as a smooth muscular type when it showed a positive reaction for smooth muscle markers SMA and/or desmin, as a neural type when it showed positive reaction for the neural marker S-100 protein, as a combined smooth muscular–neural type when it showed a positive reaction for both SMA and/or desmin and S-100 protein, and as an uncommitted type when no positive reaction for any of these markers was obtained.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 10 (SPSS, Chicago, IL) was used for all calculations. Fisher's exact and Mann-Whitney *U* tests were used for statistical comparisons of contingency tables and nonparametric values. Descriptive data were expressed as mean ± SD. Pearson's correlation analysis was performed to describe the linear association between age, Ki-67 proliferative index, mitoses, tumor size, necrosis, recurrence, survival time, and NIH consensus classification. Cut points were determined to classify Ki-67 staining, mitoses, age, and size into two groups by the use of receiver-operating characteristic (ROC) curves. An ROC curve is simply a graph of sensitivity versus (1 – specificity) for different values (which also change the sensitivity and specificity). The best value for balancing the sensitivity and specificity of the variable is represented by the point on the curve closest to the upper left-hand corner accepted cutoff point. The investigated factors that affected recurrence were age, mitotic count, tumor size, and Ki-67 proliferative index. Survival curves were constructed with the Kaplan-Meier method. The significance of all investigated prognostic factors for postoperative survival was examined by log-rank test. In multivariate analysis of survival, Cox regression model was used to compare for all prognostic factors found to be significant in univariate analysis in order to identify independent predictors of survival. A value of $P < 0.05$ was considered significant.

RESULTS

Clinical and Operative Findings

The mean age of the patients was 50.6 ± 13.7 years (range, 16–74 years), and there were 21 males and 16 females. The most common anatomic sites of tumor origin were stomach (n = 14), small intestine (n = 14), and mesentery (n = 7). In two patients, tumors were located in the colon; the esophagus was not the origin of tumor in any of the patients in our series (Fig. 1, *A*). The most common presenting complaints were abdominal discomfort and pain (n = 20). Twelve patients had palpable abdominal mass, and 11 patients had GI bleeding. Other presenting complaints were loss of weight (n = 6), acute abdomen (n = 2), and obstruction (n = 2) (Fig. 1, *B*).

All patients underwent surgical resection. Radical resection for locally advanced disease was performed in 25 patients. Limited resection of all gross disease with negative margins was accomplished in 6 patients. Incomplete resections (margin-positive resections or exploratory procedures with biopsy only) were performed in 6 patients. No patient died due to postoperative complications.

Pathologic Findings

The mean tumor size was 9.94 ± 6.9 cm (range, 1–28 cm). A diameter of 8 cm was determined as a

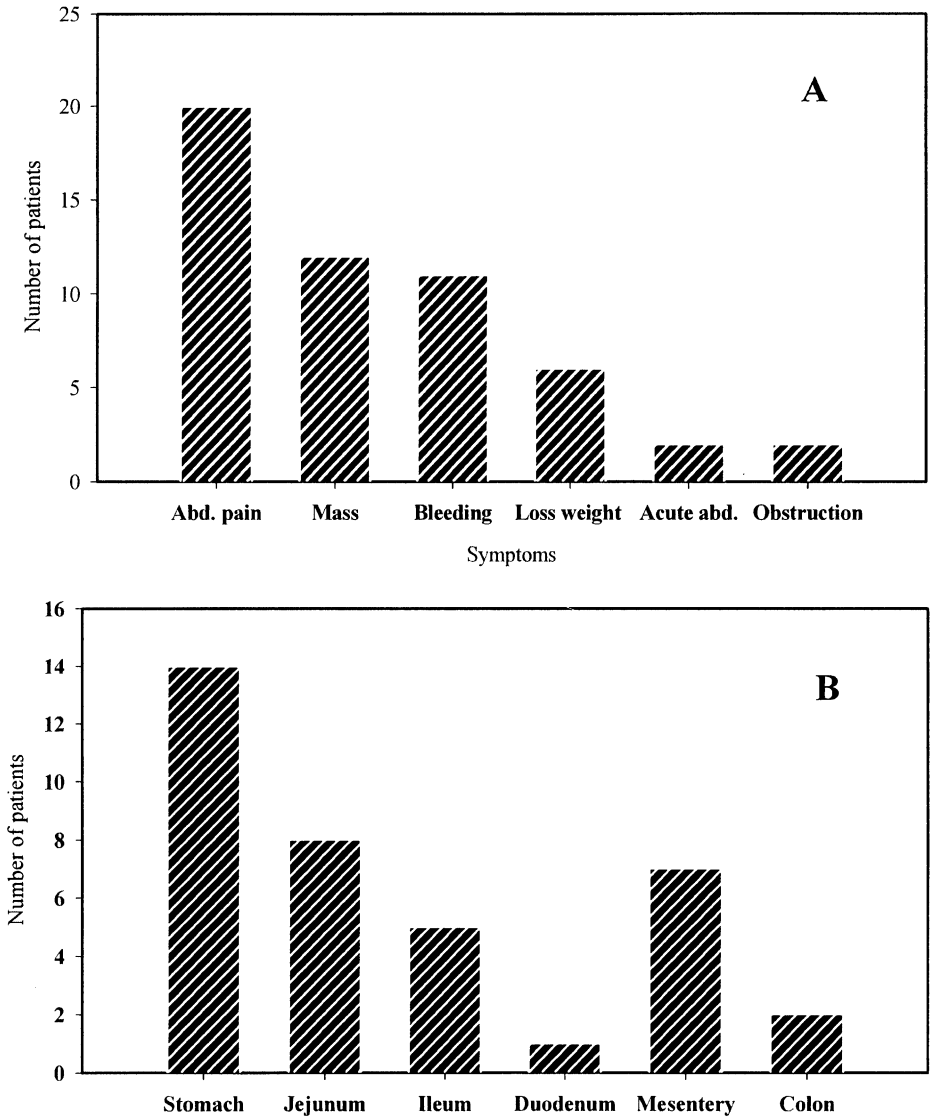

Fig. 1. The most common presenting complaints were abdominal (Abd.) pain (n = 20) and abdominal mass (n = 12) (**A**). The most common locations were stomach (n = 14) and small intestine (n = 14) (**B**).

cutoff point through the use of ROC curve for size. After stratification according to this cutoff point, 22 tumors were smaller than 8 cm in diameter and 15 tumors were 8 cm or larger in diameter. On histologic examination, 15 tumors were of the smooth muscle type, 8 were neural, and 3 were combined smooth muscle–neural type. The remaining 11 tumors could not be differentiated. All tumors had two or more malignant characteristics.

Necrosis were found in 21 tumors. Mitotic count ranged from 1 to 209 per HPF (mean, 21.4 ± 35.5 per HPF). The cutoff point as decision threshold of mitotic count was determined from ROC curve; this value was eight mitoses per 50 HPFs. Seventeen tumors contained fewer than eight mitoses and 20 tumors contained eight or more mitosis per 50 HPFs. Mean Ki-67 proliferative index was 89.3 ± 93 (range, 0–366). The cutoff points were determined as 82 from ROC curve for Ki-67 and 49 years for age. ROC curves for age, size, mitoses, Ki-67 proliferative index, and size are presented in Fig. 2.

Immunohistochemical Results

Thirty-five tumor (94.5%) samples revealed strong diffuse reactivity for c-*kit*. CD34 expressions were observed in 28 (75.6%) of tumor samples. A positive reaction for SMA was obtained in 14 (37.8%),

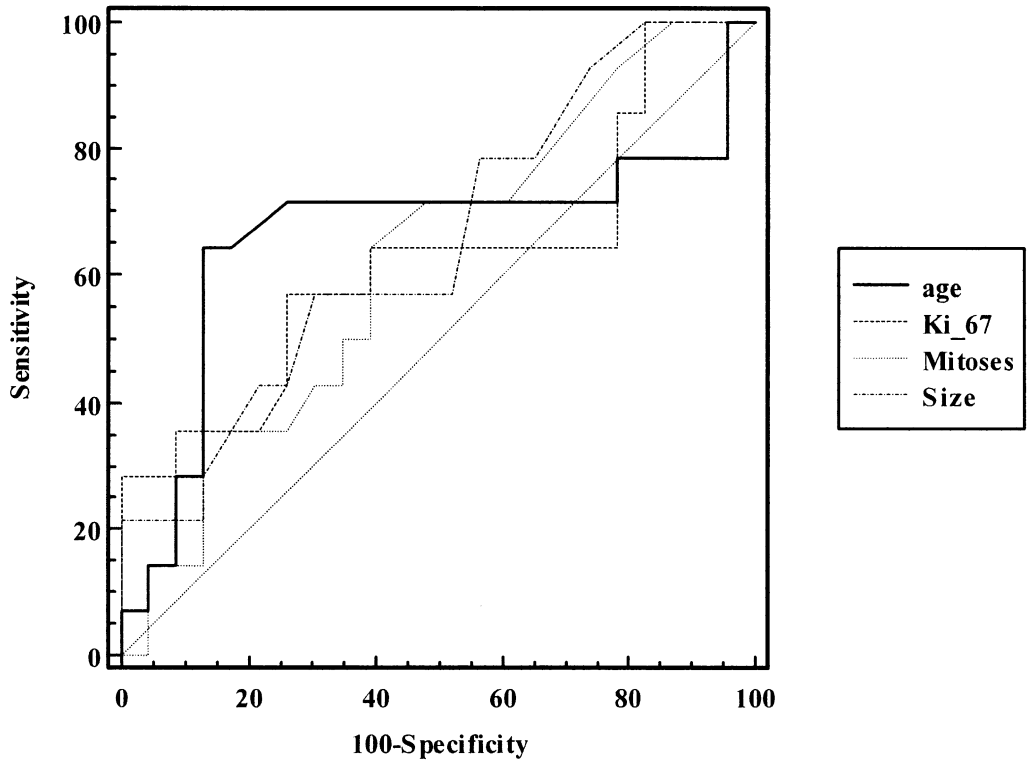

Fig. 2. The Receiver operating characteristic (ROC) curves for age, Ki-67 proliferative index, mitotic count, and size are presented. An ROC curve is simply a graph of sensitivity versus (1 – specificity) for different values. The most accurate ROC curve is one that arches up to the upper right-hand corner of the graph. The best value for balancing the sensitivity and specificity of the variable is represented by the point on the curve closest to the upper left-hand corner accepted cutoff point. Cutoff points were 8.2 for Ki-67 (sensitivity = 57.1%, specificity = 73.9%), 8:50s HPF for mitotic count (sensitivity = 71.4%, specificity = 56.4%), 8 cm for size (specificity = 57.1%, specificity = 69.6%), and 46 years for age (sensitivity = 64.3%, specificity = 87%).

desmin in 3 (8.1%), vimentin in 32 (86.4%), and S-100 protein in 13 (35%) specimens. There was a significant difference between stomach and small intestine in CD34 expression ($P = 0.032$). We did not find any statistical differences among other locations in immunohistochemical staining. In survival analysis, the only significant difference was seen between tumors staining positive and negative for desmin. Patients whose tumors were stained by desmin (n = 3) had 11.3 ± 3.08 months mean survival, but patients whose tumors were desmin negative (n = 34) had 45.8 ± 4.34 months mean survival ($P = 0.0076$). We did not find any relation between other immunohistochemical staining and survival. Immunohistochemical results according to location are presented in Table 1.

Analysis of Prognostic Factors and Survival

Follow-up data were available for all patients. Overall actuarial survival for all patients was 46% (Fig. 3). The mean overall survival was 45.28 ± 4.16 months. When analyzed by type of resection, the complete resection group (R0 resection) had a mean overall survival of 48.2 ± 6.18 months compared with the patients with incomplete resection (R1–R2), who survived a mean of 10.8 ± 3.2 months. This difference was statistically significant ($P = 0.00$).

The relationships between the clinicopathologic findings and survival, as evaluated by Univariate analysis, are shown in Table 2. Univariate analysis showed development of recurrence ($P = 0.00$), tumor size greater than 8 cm ($P = 0.05$), Ki-67 proliferative index greater than (0.82) 82:1,000 cells ($P = 0.0448$), desmin staining ($P = 0.0076$), age younger than 49 years ($P = 0.0009$), and incomplete resection ($P = 0.00$) to be significantly correlated with a poor survival. In multivariate analysis, desmin staining ($P = 0.031$), tumor size ($P = 0.033$), age ($P = 0.01$), recurrence ($P = 0.038$), and R0 resection ($P = 0.02$)

Table 1. Results of univariate analysis

Factor	No. of patients	5-year survival (%)	Mean survival (mo)	*P* value
Size (cm)				
<8	21	58.5	46.2 ± 4.08	0.05
⩾8	14	28.5	36.7 ± 6.35	
Ki-67 (%)				
⩽0.82	15	72	53 ± 6.55	0.042
>0.82	20	17	31.5 ± 5.36	
Location				
Stomach	14	40	39 ± 6.47	0.45
Small intestine	14	61	42.4 ± 5.3	
Mesentery	7	19	34.5 ± 7.68	
Colon	2	100	45.5	
Mitotic rate				
<8	17	70	46.2 ± 5.04	0.282
⩾8	20	34	41.4 ± 5.32	
Necrosis				
Positive	21	39	39.9 ± 4.29	0.74
Negative	14	63	48.2 ± 7.27	
Age (yr)				
⩽49	12	0	27.3 ± 5.05	0.0009
>49	25	70	54.8 ± 4.36	
Histologic type				
Myogenic	15	28	34.3 ± 6.3	0.081
Neurogenic	8	44	39.6 ± 11.3	
Mix	3	0	16 ± 4	
Nondifferantiation	11	9	41.9 ± 6.7	
Operation type				
Radical complete resection	25	47	47.9 ± 5.21	0.00
Limited complete resection	6	52	49.5 ± 13.7	
Nonresection	6	0	10.8 ± 3.12	
Recurrence				
No	20	92	63.3 ± 2.55	0.00
Yes	11	14	35 ± 4.27	
Nonresection	6	0	10.8 ± 3.12	
Classification				
Low to intermediate risk	10	57	41.1 ± 7.66	0.97
High risk	27	40	43.77 ± 4.84	
Immunostaining				
Desmin(+)	3	33	11.3 ± 3	0.0076
Desmin(−)	34	45	45.8 ± 4.34	
Total	37	46	45.2 ± 4.16	

were significant independent prognostic factors (Table 3).

Postoperative Morbidity and Mortality

There were no postoperative deaths in our patients. Postoperatively, major complications developed in two patients (evisceration and gastric bleeding).

Recurrence

Of the 31 patients who performed complete R0 resection, 11 recurred at a mean of 14 months (range, 2–36 months). Recurrences were in peritoneum and liver, and the overall recurrence rate was 35.4%. Five of these underwent operation for repeat resection. Complete R0 resection was achieved in two patients. Debulking (R1 resection) was performed in one patient. Two underwent only biopsy because of diffuse peritoneal disease. One of the two patients who underwent complete repeat resection for recurrences had peritoneal implants and liver metastases at 30 months after repeat resection. Mean survival was 26.6 months (range, 10–46 months). Six of these 11 patients died at a mean of 11.3 months (range,

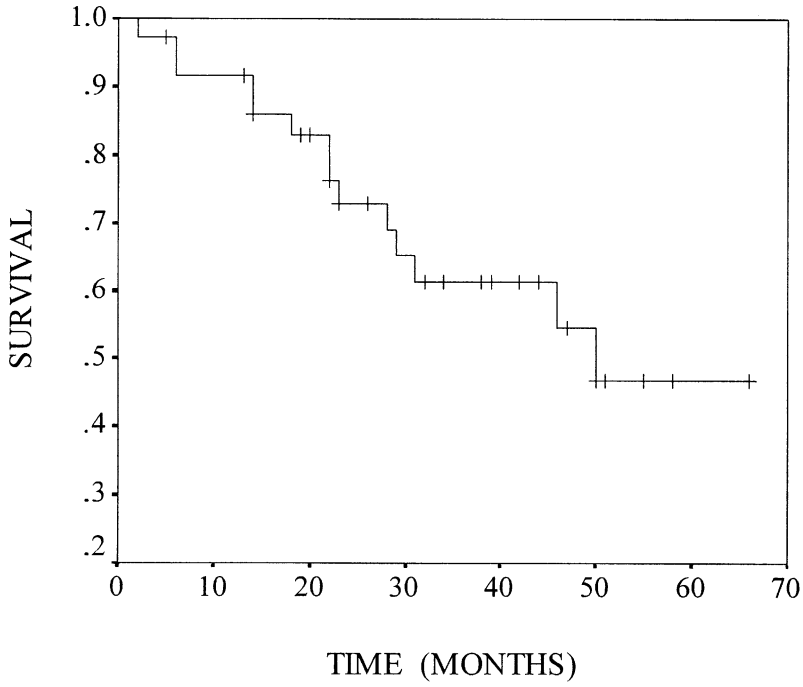

Fig. 3. Kaplan-Meier survival curve for all patients. The 5-year survival rate was 46%, and mean survival time was 45.2 months.

4–26 months). Five patients were alive at last follow-up, at a mean of 15 months (range, 5–31 months).

In correlation analysis among Ki-67 proliferative index, tumor size, age, mitotic count, and NIH consensus classification with recurrence, there was a positive proportional correlation. The patients with recurrence have higher levels of Ki-67 proliferative index (r = 0.463, $P = 0.004$) (Table 4). There were correlations between Ki-67 proliferative index and NIH consensus classification (r = 0.337, $P = 0.041$), necrosis and mitotic count (r = 0.383, $P = 0.037$), and NIH consensus classification and recurrences (r = 0.446, $P = 0.001$). The relationships among investigated parameters in correlation analysis are presented in Table 5.

DISCUSSION

In the literature, there have been many studies that investigated various prognostic factors affecting survival for GISTs. These studies have reported that mitotic count, tumor cellularity, size, presence of necrosis, hemorrhage, ulceration, nuclear atypia, tumor invasion, male sex, age, exogastric growth pattern, pyloid status, positive S-100 protein immunoreactivity, and Ki-67 proliferative index are statistically significant factors of poor prognosis without any consensus being established.[4,5,7,9,10] Sometimes, the results of these studies conflict with each other. Because these tumors are uncommon, most series are composed of cases accumulated over long periods. Furthermore, many of the case series in the literature contain both benign and malignant tumors. Our study evaluated almost all clinicopathologic prognostic factors, including immunohistochemical cell markers, regarding malignant GISTs with complete follow-up in all cases in a relatively short time, from a tertiary care center in Turkey. We believe that our results contribute to the resolution of many conflicting points.

Table 2. Results of multivariate analysis

Factor	Odds ratio	*P* value
Desmin staining	4.66	0.031
Size >8 cm	4.54	0.033
Age >49 yr	6.72	0.010
Recurrence	4.32	0.038
Complete resection	0.124	0.020

Prognostic Factors

In our present study of Turkish cases, age younger than 49 years, Ki-67 proliferative index greater than 0.82, tumor size greater than 8 cm, desmin staining, recurrence, and incomplete resection were found to be helpful in predicting poor survival of patients with malignant GISTs. We did not find any relation

Table 3. Results of Spearman's correlation analysis

	Age	Necrosis	Ki-67	Mitotic count	Size	Recurrence	Classification*
Age	—	−0.047	−0.254	−0.043	−0.118	−0.070	−0.163
		0.804	0.140	0.822	0.534	0.715	0.407
Necrosis		—	0.236	0.383	0.020	0.144	0.251
			0.172	0.037	0.918	0.447	0.197
Ki-67			—	0.167	0.164	0.451	0.343
				0.339	0.348	0.007	0.038
Mitotic count				—	0.253	0.345	0.355
					0.178	0.062	0.031
Size					—	0.324	0.521
						0.067	0.001
Recurrence						—	0.446
							0.006

Values are given as *r* value and *P* value.
*The risk of aggressive behavior of the tumors was classified according to the National Institutes of Health consensus.[8]

among mitotic count, necrosis, and tumor behavior (according to NIH consensus classification) and survival.

Mitotic activity has been regarded as indicating malignant potential by many previous investigators, who considered GISTs malignant when they showed a mitotic count of vie or more per 50 HPFs. Mitotic count is one of the more reliable factors in differentiating between GISTs of varying malignancy, and it also correlates directly with survival, but no gold standard for mitoses has been universally accepted. Akwari et al.[11] reported that mitotic count of five per 50 HPFs should constitute evidence of malignancy. Appelman and Helwig[12] suggested that the mitotic count per HPF is the most important indicator in GISTs. However, Kimura et al.[13] found that neither mitotic index nor cellularity is significantly correlated with survival. There is general agreement on the classification of GISTs with a mitotic rate greater than 10:50 HPFs as high-grade malignant tumors with aggressive behavior. On the other hand, tumors with a mitotic count of more than 1–2 per 50 HPFs are classified by some as low-grade malignant and those with 5–10 mitoses per 50 HPFs are considered malignant. Although a low mitotic rate, less than 0–1:50 HPFs, usually indicates benign behavior, tumors with apparent mitotic activity occasionally metastasize. Evans[14] reported that low-grade GISTs with 1–5 mitoses/50 HPFs have a median survival of 98 months, whereas high-grade tumors with more than 10 mitoses/10 HPFs have a median survival of 25 months. Similar results were reported by Dougherty et al.,[15] in which patients with low-grade lesions (<10 mitoses/50 HPFs) had 80% disease-free survival rate at 8 years, compared with a mean disease-free interval of only 18 months for high-grade lesions (>10 mitoses/50 HPFs). In this study, tumor grade was the most important prognostic factor in resectable disease.

Tumor size is directly linked with the biological behavior of GISTs. However, even smaller neoplasms

Table 4. Results of age, mitotic count, size, and Ki-67 proliferative index in patients without recurrence, with recurrence, and with incomplete resection

Variable	Without recurrence (n = 20)	With recurrence (n = 11)	R1-R2 resection group (n = 6)
Age (yr)	53.7 ± 9.8*†	51.5 ± 11.2	41.3 ± 17
Mitotic count	20.8 ± 46*†	23 ± 18.5†	19.6 ± 20
Size (cm)	8.3 ± 6*	9.5 ± 3.7	8.8 ± 3.2
Ki-67	58.1 ± 60*†	97 ± 77.9†	183.8 ± 147.2

Values given as mean ± SD.
*$P < 0.05$ versus recurrence.
†$P < 0.05$ versus R1-R2 resection group.

Table 5. Distribution of immunohistochemical positivity of 37 patients with gastrointestinal stromal tumors in different locations

Location	CD117	CD34	SMA	Desmin	S100	Vimentin	Total
Stomach	14 (100)	13 (92.8)*	7 (50)	2 (14.3)	4 (28.5)	13 (92.8)	14
Small intestine	13 (92.8)	7 (50)	6 (42.8)	1 (7.1)	5 (35.7)	13 (92.8)	14
Large intestine	1 (50)	1 (50)	2 (100)	0 (0)	0 (0)	2 (50)	2
Mesentery-omentum	7 (100)	7 (100)	2 (28.5)	0 (0)	4 (57.1)	5 (71.4)	7
Total	35 (94.5)	28 (75.6)	14 (37.8)	3 (8.1)	13 (35.1)	32 (86.4)	37

Values given as n (%).
*$P = 0.032$ stomach versus small intestine.

have metastatic potential. Studies indicate that a tumor size of greater than 5 cm correlates with poor survival, whereas this value is greater than 8 cm in our study. Tumor size of 5 cm or less and mitotic activity of five mitoses or fewer per 50 HPFs were prognostically favorable factors in univariate analysis.[16,17] Kontagianni et al.[18] found tumor size greater than 8 cm, presence of necrosis, number of mitoses greater than 5:10 HPFs, metastasis, and proliferative activity index to be independent poor prognostic factors. Our results, especially those regarding tumor size and metastasis, are in harmony with their results. To overcome this prognostic dilemma, a new approach was suggested to define the risk of aggressive behavior in GISTs at the NIH consensus conference in 2001, as presented in the Material and Methods section.[8] According to the data from this conference, we accepted tumor size of 5 cm or greater and/or mitoses of two or more per 50 HPFs as malignancy criteria, and we classified as low, intermediate, and high risk. Because we had planned to examine not the differentiation of malignant and benign tumors but factors affecting survival in only GISTs with malignancy potential, we did not include patients with very low risk tumors. In our patients, mitotic count did not tend to predict survival in univariate analysis, but size was an independent prognostic factor in univariate and multivariate analyses. We believe that the most possible explanation for this difference from many other studies is that most of our patients had a mitotic count higher than 10:50 HPFs. Seventy-three percent of our patients were in the highly aggressive group. Our study results show that there is a positive correlation between recurrence and NIH consensus classification.

The Ki-67 proliferative index has recently been used as an excellent index of cell growth; the index is calculated by, immunohistochemically, evaluating the cell growth–related antigen Ki-67, using the monoclonal antibody MIB-1. Different studies reported that Ki-67 proliferative index of greater than 0.10 was an indicator of poor prognosis, together with tumor size and mitotic activity. Shimoda et al.[16] found that the Ki-67 proliferative index was greater than 0.10 in all of the patients with a mitotic index of more than 10:200 HPFs. Nagasaki et al.[19] reported that the maximum diameter, mitotic index, and Ki-67 proliferative index were useful as an index of malignancy for gastric stromal tumor. Wang et al.[20] found that the overall 5-year survival rate for patients with Ki-67 proliferative index of less than 0.10 was higher than that for patients with Ki-67 proliferative index of greater than 0.10 (0.812 versus 0.437). Toquet et al.[21] reported that Ki-67 proliferative index above 0.10 is an indicator of poor prognosis, especially in gastric GISTs. In our study, 0.82 (82:1,000 cells) was estimated to be the cutoff value for the relation of Ki-67 proliferative index to survival by using ROC curve. A Ki-67 proliferative index of greater than 0.82 was a significant predictor of worse survival than other patients. There was a positive correlation between recurrence and Ki-67 proliferative index. Our study showed that values lower than 0.10 of Ki-67 proliferative index might be suitable in analysis of survival. This result is in conflict with the results of many studies from literature. New prospective studies, especially those focused on this subject by using ROC analysis, may be the answer for this question.

Immunohistochemical Staining and Histology

The typical GISTs express CD117 and CD34 and rarely SMA. Vimentin expression seems to be a constant feature. CD117 expression in the absence of desmin seems to differentiate GISTs from smooth muscle tumors, which are typically desmin and SMA positive and CD34 and CD117 negative. Positive reaction have been reported in 27–74% for SMA, 3–53% for desmin, 92–100% for vimentin, 1–28% for S-100, 56–82% for CD-34, and 72–100% for c-*kit* reactivity in different studies.[22–25] In the present

study, a positive reaction for c-*kit* was demonstrated in 94% of samples, whereas 75% were CD-34 positive. A positive reaction for SMA was obtained in 37%, for desmin in 8%, for vimentin in 86%, and for S-100 protein in 35%. The incidences of immunopositivity for various markers in our present study were somewhat similar to those in previous studies, which included only malignant GISTs. In comparing immunohistochemical staining of different sites, we found that there was a statistical difference in CD34 staining between stomach and intestine (92% versus 50%, $P = 0.032$). In the study of Miettinen et al.,[26] which investigated the immunohistochemical spectrum of GISTs at different localizations, results were similar to those of study. The CD34 positivity of GISTs varied from 88% in malignant tumors of the stomach to 47% in malignant tumors of the small bowel. The effect of immunohistochemical staining on survival has been an undetermined subject; there are an insufficient number of studies in literature. The relation to the aggressiveness of the GISTs was analyzed by Tazawa et al.[22] They found that the malignancy potential correlated with the intestinal location, large tumor size, high cellularity, necrosis, solid pattern of growth, negativity of c-*kit* protein and CD34, high mitotic count, and MIB-1 prognostic index. Fujimoto et al.[9] reported that negative caldesmon immunoreactivity and positive S-100 protein immunoreactivity were also statistically significant indicators of a poor prognosis in univariate analysis. However, cell differentiation markers were not statistically significant predictors of a poor prognosis in the multivariate analysis. Cell differentiation markers, except desmin, were not statistically significantly correlated with survival in our study. Desmin positivity is rare in GISTs. In our series, only three tumors had desmin positivity, and it was a poor prognostic factor in univariate and multivariate analysis. Because all patients with desmin staining underwent R1–R2 resection and because there was an inadequate number of patients, we did not comment on this difference in survival. The question of whether the differences in the immunopositivity rates for markers might reflect differences in the nature of the tumors remains debatable.

The GISTs could be divided into four groups (smooth muscle, neural, combined smooth muscle–neural, and uncommitted) according to immunoreactivity. Hurlimann and Gardiol[27] reported smooth muscle differentiation in 30% of the cases, neural differentiation in 10%, combined smooth muscle–neural differentiation in 3%, and no obvious differentiation in 40%. The majority of the tumors in a series reported by Saul et al.,[28] however, showed smooth muscle differentiation. Seventy percent of malignant gastric tumors and 10% of malignant small-bowel tumors showed smooth muscle differentiation. In our patients, smooth muscle differentiation (40%) is the most frequent subtype of GIST. Distribution of subtype in our patients is similar to that of other studies. Our data suggest that the differentiation into subtypes based on immunohistochemical parameters has no impact on survival. However, the possible significance of immunohistochemical reactivity and subtypes of GISTs on survival should be evaluated in new studies that include a higher number of patients than we have.

Location

Several authors suggested that gastric GISTs have most favorable long-term survival and that small-intestine tumors have the worst. The overall 5-year survival rates reported for gastric GISTs are 19–56% and 40–50% for small and large intestines after complete resection.[1,4,29] Emory et al.[30] suggested that anatomic location was a prognostic factor independent of tumor size, mitotic rate, and patient age, with a trend for small-bowel tumors to have the worst prognosis and esophageal tumors to have the best, but the basis for these differences remains uncertain. Our data suggest that location of tumor is not a reliable predictor of survival.

Survival and Recurrence

Different studies reported that overall survival was 48–65% in patients who underwent complete resection.[19,31–34] Our survival rate in patients who underwent complete resection is similar to that of the majority of studies. Complete primary resection of the tumor with limited or radical resection was achieved in 31 of 37 patients.

Of these patients, 11 had recurrence, and of these, 6 died. In our series, the recurrence rate was 35.4%. Mean survival was 48 months in patients who underwent R0 resection; patients who underwent incomplete resection or only biopsy had a mean of 10 months' survival. All patients who received incomplete resection or biopsy were dead at the last follow-up. Our results confirmed that complete resection of tumor is one of the most important factors affecting survival. We did not find statistical relationship between the extent of surgical resection (limited and radical) and survival. If no metastases are diagnosed preoperatively or encountered during operation, partial resection with margin-negative resection is the suitable surgical therapy. In patients with GISTs, because of the rarity of lymph node metastases, elective dissection of lymph node areas is not indicated.

As the overall risk for recurrence in GISTs is high, even for low-risk and R0 resected tumors, there is a need to develop adjuvant therapies. Nonresectable or metastatic GISTs are associated with short survival and resist conventional chemotherapy or radiotherapy. Imatinib (Gleevec in the United States; Glivec in Europe) is a selective inhibitor of certain protein kinases, including KIT. Results of phase I and II studies indicate that imatinib is the first effective systemic therapy for metastatic and locally inoperable GISTs. Two phase III studies for metastatic GISTs in Europe and the United States are under way.[4,5] Although early results are encouraging, because of the lack of long-term data, widespread use of imatinib outside of approved indications or controlled trials must be avoided. Imatinib must be investigated in the adjuvant setting to evaluate its potential role in prolonging survival. Prospective clinical trials of neoadjuvant and adjuvant use of imatinib will be performed in the near future. Unfortunately, during this study, we did not have the option of using it in our patients with nonresectable or metastatic GISTs due to commercial and financial difficulties.

CONCLUSION

The most powerful unfavorable prognostic factors for malignant GISTs are age of younger than 49 years, Ki-67 proliferative index greater than 0.82, recurrence, and incomplete surgery. An initial surgical approach—resection with a negative margin—remains the best primary treatment for these lesions. The surgeon should make every effort to achieve complete resection of the whole gross disease process, which may necessitate the removal of adjacent organs. However, the extent of resection has no effect on survival as long as the resection is complete. Based on our results, we recommend that a more careful preoperative and more frequent postoperative follow-up examination be performed for the patient with large tumors, of age younger than 49 years, and with Ki-67 prognostic index greater than 0.82. We believe that these criteria related to a poor prognosis may be helpful in the detection of patients who will receive neoadjuvant or adjuvant imatinib therapy. This issue should be addressed through multicenter, cooperative clinical trials.

REFERENCES

1. Rosai J. GISTS: An update. Int J Surg Pathol 2003;11:177–186.
2. Sturgeon C, Chejfec G, Espat NJ. Gastrointestinal stromal tumors: A spectrum of disease. Surg Oncol 2003;12:21–26.
3. Hirota S. Gastrointestinal stromal tumors: Their origin and cause. Int J Clin Oncol 2001;6:1–5.
4. Connoly EM, Gaffney E, Reynolds JV. Gastrointestinal stromal tumors. Br J Surg 2003;90:1178–1186.
5. Joensuu H, Fletcher C, Dimitrijevic S, et al. Management of malignant gastrointestinal stromal tumors. Lancet Oncol 2002;3:655–663.
6. Rudolph P, Chiaravalli AM, Pauser U, et al. Gastrointestinal mesenchymal tumors—Immunophenotypic classification and survival analysis. Virchows Arch 2002;441:238–248.
7. Langer C, Gunawan B, Schüler P, et al. Prognostic factors influencing surgical management and outcome of gastrointestinal stromal tumors. Br J Surg 2003;90:332–339.
8. Fletcher CDM, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Int J Surg Pathol 2002;10:81–89.
9. Fujimoto Y, Nakanishi Y, Yoshimura K, Shimoda T. Clinicopathologic study of primary malignant gastrointestinal stromal tumor of the stomach, with special reference to prognostic factors: Analysis of results in 140 surgically resected patients. Gastric Cancer 2003;6:39–48.
10. Lev D, Kariv Y, Issakov J, et al. Gastrointestinal stromal sarcomas. Br J Surg 1999;86:545–549.
11. Akwari OE, Dozois RR, Weiland LH, Beahrs OH. Leiomyosarcoma of the small and large bowel. Cancer 1978;42: 1375, 1384.
12. Appelman HD, Hekwig EB. Sarcomas of stomach. Am J Clin Pathol 1977;67:2–10.
13. Kimura H, Yonemura Y, Kadoya N, et al. Prognostic factors in primary gastrointestinal leiomyosarcoma: A retrospective study. World J Surg 1991;15:771–776.
14. Evans HL. Smooth muscle tumors of the gastrointestinal tract: A study of 56 cases followed for a minimum of 10 years. Cancer 1985;56:2242–2249.
15. Dougherty MJ, Compton C, Talbert CD, Wood WC. Sarcomas of the gastrointestinal tract: Separation into favorable and unfavorable prognostic groups by mitotic count. Ann Surg 1991;214:569–574.
16. Shimoda T, Fujimoto Y, Hasegawa T, Nakanishi K. A concept and issue of GISTs (gastrointestinal stromal tumor). Pathol Clin Med 2002;20:134–140.
17. Kwoon SJ. Members of the Koreans Gastric Cancer Study Group. Surgery and prognostic factors for gastric stromal tumor. World J Surg 2001;25:290–295.
18. Kontagianni K, Demonakou M, Kavantzas N, et al. Prognostic predictors of gastrointestinal stromal tumors: A multiinstitutional analysis of 102 patients with definition of a prognostic index. EJSO 2003;29:548–556.
19. Nagasaki Y, Misawa K, Kohashi S, et al. Evaluation of malignantancy using Ki-67 prognostic index for gastric stromal tumor. Gastric Cancer 2003;6:168–172.
20. Wang X, Mori I, Tang W, et al. Gastrointestinal stromal tumors: Clinicopathological study of Chinese cases. Pathol Int 2001;51:701–706.
21. Toquet C, Le Neel JC, Guillou L, et al. Elevated (>10%) MIB-1 proliferative index correlates with poor outcome in gastric stromal tumor patients. A study of 35 cases. Dig Dis Sci 2002;47:2247–2253.
22. Tazawa K, Tsukada K, Makuuchi H, Tsutsumi Y. An immunohistochemical study of gastrointestinal stromal tumors. Pathol Int 1999;49:786–798.
23. Strickland L, Letson D, Muro-Cacho CA. Gastrointestinal stromal tumors. Cancer Control 2001;8:252–260.
24. Miettinen M, Majidi M, Lasota J. Pathology and diagnostic criteria of gastrointestinal stromal tumors (GISTs): A review. Eur J Cancer 2002;38(suppl 5):39–51.
25. Miettinen M, Lasota J. Gastrointestinal stromal tumors (GISTs): Definition, occurence, pathology, differential diagnosis and molecular genetics. Pol J Pathol 2003;54:3–24.

26. Miettinen M, Sobin LH, Sarloma-Rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). Mod Pathol 2000;13:1134–1142.
27. Hurlimann J, Gardiol D. Gastrointestinal stromal tumors: An immunohistochemical study of 165 cases. Histopathology 1991;19:311–320.
28. Saul SH, Rast ML, Brooks JJ. The immunohistochemistry of gastrointestinal stromal tumors: Evidence supporting an origin from smooth muscle. Am J Surg Pathol 1987;11: 464–473.
29. Crosby JA, Catton CN, Davis A, et al. Malignant gastrointestinal stromal tumors of the small intestine: A review of 50 cases from a prospective database. Ann Surg Oncol 2001;8: 50–59.
30. Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth muscle (stromal) tumors. Dependence on anatomic site. Am J Surg Pathol 1999;23:82–87.
31. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors. Recurrence patterns and prognostic factors for survival. Ann Surg 2000;232:51–58.
32. Yao KA, Talomonti MS, Langella RL, et al. Primary gastrointestinal sarcomas: Analysis of prognostic factors and results of surgical management. Surgery 2000;128:604–610.
33. Kim CJ, Day S, Yeh KA. Gastrointestinal stromal tumors: Analysis of clinical and pathologic factors. Am Surg 2001;67: 135–137.
34. Sanders L, Silverman M, Rossi R, Braasch J. Gastric smooth muscle tumors: Diagnostic dilemmas and factors affecting outcome. World J Surg 1996;20:992–995.

Perforation Through Small Bowel Malignant Tumors

Tzu-Chieh Chao, M.D., Ph.D., Hsiao-Hsiang Chao, M.D., Yi-Yin Jan, M.D., Miin-Fu Chen, M.D.

Data on 19 patients (6 women and 13 men) with malignancy perforation through small bowel tissue were retrospectively reviewed. The median patient age was 57 years (range, 41–81 years). The histopathology included lymphoma (seven patients), leiomyosarcoma (two patients), gastrointestinal stromal tumor (one patient), adenocarcinoma (one patient), metastatic carcinomas with unknown primary tumor (four patients), metastatic adenocarcinoma from the lung (one patient), and metastatic carcinomas from the hypopharynx (one patient), cervix (one patient), and lung (one patient). Resection of a segment of perforated bowel with primary anastomosis was performed in 16 patients, wedge resection of perforated lesion with plication in two patients, and loop ileostomy in one patient. Postoperative deaths occurred in 10 (52.6%) patients, owing to sepsis and organ functional failure. Seven patients died from the primary malignancy at a median follow-up of 6.5 months (range, 5 months to 1 year 9 months) after surgery. Moreover, two patients with small bowel lymphoma were alive with disease at 4 years 8 months and 7 years 1 month after surgery. In conclusion, perforation through small bowel malignant tumors had a high postoperative mortality rate. High index of suspicion of the disease with early surgical treatment may improve treatment outcomes. (J GASTROINTEST SURG 2005;9:430–435)

KEY WORDS: Chemotherapy, mortality, metastasis, perforation, small bowel

Malignancies of the small bowel can be either primary or metastatic. Primary small bowel malignant tumors are rare, comprising less than 2% of all gastrointestinal malignancies.[1,2] On the other hand, metastatic cancers of the small bowel are more frequent than primary small bowel cancers. Histopathologic subtypes of primary small bowel cancers include adenocarcinoma, sarcoma, lymphoma, and carcinoid.[3–5] Metastatic malignant tumors from the colon, ovary, uterus, and stomach generally invade the small bowel via direct invasion or intraperitoneal spread. Meanwhile, breast cancer, lung cancer, and melanoma metastasize to the small bowel hematogenously.[6,7]

The clinical manifestations of small bowel malignant tumors include abdominal pain, palpable abdominal mass, vomiting, weight loss, and occult gastrointestinal bleeding.[4,5] These symptoms are nonspecific. Accordingly, the diagnosis of small bowel malignant tumors is often delayed and may be made only after complications have occurred.[3,8] Complications of small bowel malignancies include hemorrhage, obstruction, and perforation.[3,9–11] The relative rarity of perforating small bowel malignant tumors means that no single institute has adequate experience of treating the disease. To better characterize this disease, we retrospectively reviewed the data of 19 patients with perforation arising from small bowel malignant tumors.

MATERIAL AND METHODS

During the 16-year period of 1987 through 2002, 375 consecutive patients with either primary or metastatic small bowel cancers, excluding cases of periampullary carcinomas, were surgically treated at our hospital. Of these patients, 21 (5.1%) displayed perforation through small bowel malignant tumors. Two patients with incomplete records were excluded from the study. Data from the remaining 19 patients (6 women and 13 men; median age, 57 years; age range, 51–81 years) were collected from patient charts

From the Division of General Surgery, Department of Surgery, Chang Gung University College of Medicine and Chang Gung Memorial Hospital, Taoyuan, Taiwan.
Supported by Chang Gung Memorial Hospital, Taiwan, under contract No. BMRP072.
Reprint requests: Tzu-Chieh Chao, M.D., Ph.D., Department of Surgery, Chang Gung Memorial Hospital, 5 Fuhsing Street, Kweishan, Taoyuan, Taiwan. e-mail: tcchao@adm.cgmh.org.tw

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.09.022

for each patient on age, gender, clinical manifestations, laboratory data, histopathology, the type of operation performed, operative complications, and survival.

RESULTS

Table 1 provides the clinicopathologic characteristics of 19 patients with perforation through small bowel malignant tumors. There were 11 (57.9%) primary and 8 (42.1%) metastatic small bowel cancers (Fig. 1). Three patients presented with peritonitis and metastatic cancers of the small bowel were not discovered until laparotomy. Moreover, one patient presented initially with right lung metastatic cancer and perforation through a primary small bowel leiomyosarcoma was recognized at operation. Additionally, eight (47.1%) patients presented with concurrent distant or intraperitoneal metastases at the time of perforation, including intraperitoneal carcinomatosis (one case, 5.3%) and metastases to the mesenteric lymph nodes (seven cases, 36.8%), lung (three cases, 15.8%), liver (two cases, 10.5%), and neck lymph node (one case, 5.3%).

All patients displayed abdominal pain; other symptoms included anorexia, nausea and vomiting, malaise, and fever. Three (15.8%) patients exhibited preoperative shock. Moreover, one (5.3%) patient presented with sepsis and acute renal failure before surgery. The median time from the onset of symptoms to surgery was 48 hours (range, 4 hours to 20 days). The median time from the onset of symptoms to surgery in the patients with perforation through primary small bowel tumors did not differ from that in the patients with perforation through metastatic small bowel tumors (48 versus 60 hours; Mann-Whitney U test, $P = 0.5089$). Furthermore, the median time from the onset of symptoms to surgery was not different between those with and without hospital mortality (48 versus 48 hours; Mann-Whitney U test, $P = 0.7751$). Pneumoperitoneum was noted on plain chest films in seven (36.8%) patients. Four patients underwent abdominal computed tomography; only two scans revealed pneumoperitoneum (Fig. 2). Eleven (57.9%) patients presented with anemia, nine (47.4%) with leukocytosis, and three (15.8%) with leukopenia. Albumin serum level was measured in six patients and was below 3.0 g/dl in five (83.3%) of these patients. One patient with squamous cell carcinoma of the hypopharynx underwent dexamethasone 9 days before perforation of the metastatic small bowel tumor. Another patient with squamous cell carcinoma of the uterine cervix underwent chemotherapy (cisplatin, vinblastin, and bleomycin) and radiotherapy to the pelvis at 7 months and 1 year 2 months before perforation of the metastatic small bowel tumor. Additionally, one patient with adenocarcinoma of the lung underwent chemotherapy at another hospital 3 weeks before perforation of metastatic small bowel tumor. Furthermore, one patient with squamous cell carcinoma of the lung and metastases to the liver and adrenal glands completed six courses of gemcitabin and cisplatin 32 days before perforation of the metastatic small bowel tumor. This patient was given one course of docetaxel (75 mg) with steroid, and perforation occurred 4 days later. Four (21.1%) patients had been taking acetaminophen and sulindac (a nonsteroidal anti-inflammatory drug) for at least 1 week before the development of symptoms.

In no patient was the cause of perforation accurately diagnosed before laparotomy. Preoperative diagnoses included intra-abdominal abscess (1 case, 5.3%), intestinal obstruction (1 case, 5.3%), peritonitis (13 cases, 68.4%), perforated peptic ulcer (3 cases, 15.8%), and ruptured appendicitis (1 case, 5.3%). The patients with preoperative diagnosis of intra-abdominal abscess or intestinal obstruction had perforations walled off by the adjacent intestinal loops, and the remaining 17 patients had free perforation. Surgical methods included segmental resection of the perforated bowel with primary anastomosis (16 patients, 84.2%), wedge resection of perforated lesion with plication (2 patients, 10.5%), and loop ileostomy (1 patient, 5.3%). Perforation occurred in the jejunum in 14 patients (73.7%), the ileum in 4 patients (23.5%), and both the jejunum and ileum in 1 patient (5.9%). Culture of ascitic fluid relieved at operation was performed on 10 patients, all of whom had polymicroorganisms. The microorganisms recovered from the ascitic fluid included *Escherichia coli* (six cases), *Enterococcus* (six cases), *Proteus vulgaris* (three cases), *Proteus mirabilis* (three cases), *Klebsiella pneumoniae* (three cases), *Bacteroides fragilis* (two cases), *Enterobacter cloacae* (two cases), *Klebsiella oxytoca* (one case), *Streptococcus viridans* (one case), *Aerobacter aerogenes* (one case), *Citrobacter freundii* (one case), *Citrobacter amalonaticus* (one case), and *Morgarella morganii* (one case).

Ten (52.6%) patients died at 5–60 days (median, 23 days) after surgery, never having left the hospital (Table 1). The hospital mortality rate did not correlate with that of perforations through primary or metastatic tumors (Fisher's exact test, $P = 0.1698$). Walled-off perforation of malignant tumors did not affect hospital mortality (Fisher's exact test, $P = 0.2105$). These patients died of sepsis with simultaneous single or multiple organ failure, including respiratory failure (five cases), renal failure (four cases), pleural effusions (three cases), upper gastrointestinal

Table 1. Clinicopathologic characteristics

Patient	Histopathology	Primary site	Preoperative chemotherapy/steroids	Perioperative complications	Hospital mortality
1	Burkitt's lymphoma	Ileum	Dexamethasone	No	No
2	Diffuse large cell lymphoma	Ileum	No	No	No
3	Diffuse large cell lymphoma	Jejunum	No	Pelvic abscess, wound infection	Yes
4	Diffuse large cell lymphoma	Jejunum	No	Wound infection, renal failure, pleural effusion, pneumonia	Yes
5	Mixed small and large cell lymphoma	Jejunum	No	No	Yes
6	Mixed small and large cell lymphoma	Jejunum	No	Upper gastrointestinal bleeding, respiratory failure	Yes
7	Diffuse large cell lymphoma	Jejunum	Prednisolone	No	No
8	Gastrointestinal stromal tumor	Jejunum	No	No	No
9	Leiomyosarcoma	Jejunum	No	Hypovolemic shock	No
10	Leiomyosarcoma	Jejunum	No	No	No
11	Poorly differentiated adenocarcinoma	Jejunum	No	No	No
12	Metastatic moderately differentiated adenocarcinoma	Lung	Unknown regimen at other hospital	Renal failure	Yes
13	Metastatic moderately differentiated carcinoma	Lung	1. Gemcitabin and cisplatin 2. Dexamethasone and docetaxel	Respiratory failure, renal failure, disseminated intravascular coagulopathy wound dehiscence	Yes
14	Metastatic poorly differentiated carcinoma	Hypopharynx	Cisplatin and 5-fluorouracil	No	No
15	Metastatic squamous cell carcinoma	Cervix	Cisplastin, vinblastin, bleomycin	Pleural effusion, respiratory failure, wound infection	Yes
16	Metastatic squamous cell carcinoma	Unknown	No	No	No
17	Poorly differentiated adenocarcinoma	Unknown	No	Respiratory failure	Yes
18	Metastatic poorly differentiated carcinoma	Unknown	No	Renal failure	Yes
19	Metastatic poorly differentiated carcinoma	Unknown	No	Upper gastrointestinal bleeding, pleural effusion, respiratory failure	Yes

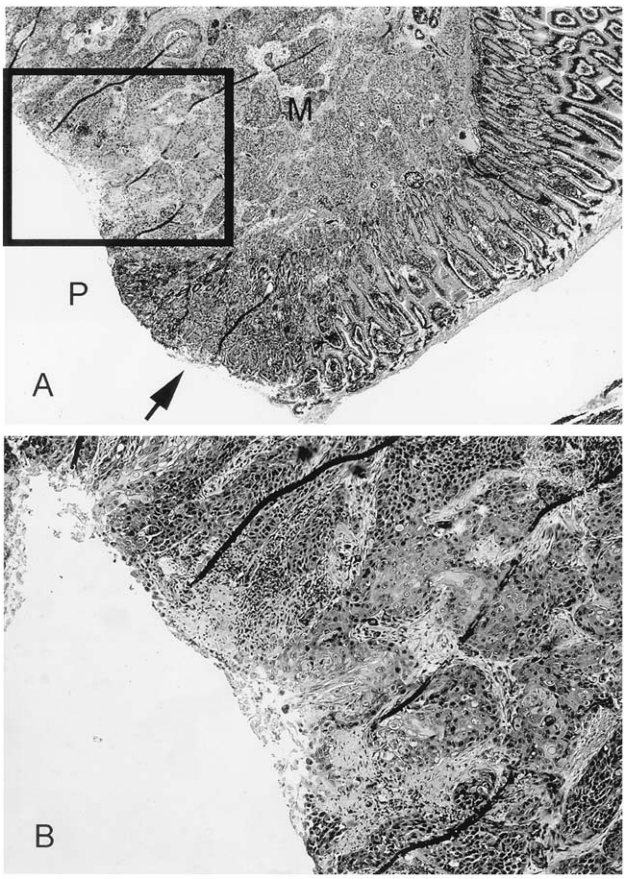

Fig. 1. (**A**) Histologic appearance of a perforated metastatic squamous cell carcinoma at the submucosa (*arrow*) and muscular layer (M) of the jejunum. P indicates the perforation site (hematoxylin and eosin; original magnification, ×40). (**B**) Higher magnification (hematoxylin and eosin; original magnification, ×100) of the square area in **A**.

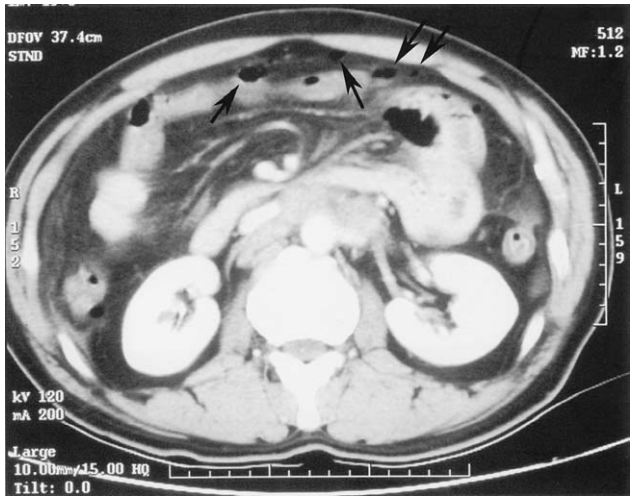

Fig. 2. Abdominal computed tomography scan of a 44-year-old male patient revealed free air (*arrows*) in the peritoneal cavity. Perforation through a metastatic squamous carcinoma of unknown origin at the jejunum was found at surgery.

bleeding (two cases), hypovolemic shock (one case), and disseminated intravascular coagulopathy (one case). Surgery-associated complications included superficial wound infection (three cases), intra-abdominal abscess (one case), wound dehiscence (one case), and pneumonia (one case). Seven (31.6%) patients who survived small bowel perforation eventually died from the primary malignant disease at a median follow-up period of 6.5 months (range, 5 months to 1 year 9 months). One of these seven patients died from recurrent small bowel leiomyosarcoma that ruptured again with massive bleeding (2,500 ml of blood in the peritoneal cavity) and hypovolemic shock 5.5 months after surgery. Two patients with small bowel lymphoma remained alive at 4 years 8 months and 7 years 1 month after segmental resection of the perforated small bowel.

DISCUSSION

The pathogenesis of perforation through small bowel malignant tumors is unclear. The possible perforation mechanisms include replacement of the bowel wall by tumor cells followed by necrosis, ischemia of the intestine because of tumor embolization, increased intraluminal pressure caused by obstruction, and tumor necrosis owing to chemotherapy.[10,12,13] Also, systemic chemotherapy and steroids may induce tumor necrosis and perforation in the intestine.[14–16]

Treatment outcomes of malignancy perforation of small bowel are poor. Most of the patients sampled here who recovered from the surgery eventually died of the malignancy after a median postoperative period of 8 months. Operative mortality was 52.6% in the present patients. Orringer et al.[17] described six patients with perforation through small bowel malignant tumors. Three of these six patients did not undergo surgery because of extremely poor general condition. Moreover, two of the remaining three patients died shortly after surgery. Torosian and Turnbull[18] reported an operative mortality rate of 53% in cancer patients receiving corticosteroids and chemotherapy with perforation of the small bowel and colon. Torosian and Turnbull found that perforation location, perforation through benign or malignant tissue, symptom duration, history of radiation therapy, gender, and age were not related to mortality. High mortality also occurs in cancer patients who undergo chemotherapy and have gastroduodenal perforations.[19,20] Patients exhibiting perforation through small bowel malignant tumors generally have advanced disease,[3,21] frequently associated with nutritional, endocrine, hematologic, immune, and other system disorders.[22] Moreover, patients with advanced

or metastatic malignancy thus are classified as critically ill patients under surgical conditions. Additionally, chemotherapy and corticosteroids, which cause myelosuppression and immunosuppression, further erode the ability of cancer patients to respond to stress.[22]

Because patients with perforation through small bowel malignant tumors have high operative mortality, nonsurgical management has been considered as an alternative to surgery for treating these patients. Nonsurgical treatment has yielded good outcomes in perforated peptic ulcers when water-soluble contrast medium upper gastrointestinal study shows self-sealing.[23] However, perforated small bowel tumors are rarely spontaneously sealed by the omentum or adjacent organs. High levels of toxins in the ascites produced by polymicrobial infection in perforated small bowel tumors become life threatening. Source control by resection of the perforated segment or by repair or decompression may reduce morbidity and death from perforated small bowel tumors.[24] Some authors recommend extensive intraoperative lavage to supplement surgical treatment for reducing toxin levels in infected ascites.[25]

Time of initial operation influences survival in secondary peritonitis. A shorter time between the onset of disease or perforation and surgery implies there is less time for infection and sepsis to develop, cumulating in multiple organ failure. Timely intervention positively influenced treatment outcomes in the perforation of small bowel tumors.[25] In the sample patients, the median interval from the onset of symptoms to surgery was 48 hours, and the cause of perforation was not accurately diagnosed before laparotomy in any of the sample patients. Malignant tumors of the small bowel are frequently discovered at a late stage and in some cases are not discovered until perforation occurs.[3,8] Delayed diagnosis results from the clinical manifestations of small bowel tumors generally being nonspecific and inconsistent.[4,5] Although pneumoperitoneum is a common sign of perforation of stomach and colon, it is not a constant finding in small bowel perforation.[26,27] Additionally, manifestations of inflammation or peritonitis are frequently muted by the anti-inflammatory effects of corticosteroids if cancer patients are treated with corticosteroids.[14,18]

Perforation through small bowel malignant tumors has a high postoperative mortality rate and a fatal prognosis. When patients with primary or metastatic small bowel tumors exhibit acute abdominal symptoms, perforation should be considered in the differential diagnosis. A high index of suspicion of the disease with early surgical treatment may improve treatment outcomes in patients with perforation of small bowel tumors.

REFERENCES

1. Barelay TH, Schapira DV. Malignant tumors of the small intestine. Cancer 1983;51:878–881.
2. Ojha A, Zacherl J, Scheuba C, Jakesz R, Wenzl E. Primary small bowel malignancies: Single center results of three decades. J Clin Gastroenterol 2000;30:289–293.
3. Brophy C, Cahow CE. Primary small bowel malignant tumors: Unrecognized until emergent laparotomy. Am Surg 1989;55:408–412.
4. Talamonti M, Goetz L, Rao S, Joehl R. Primary cancers of the small bowel: Analysis of prognostic factors and results of surgical management. Arch Surg 2002;137:564–571.
5. Gill SS, Heuman DM, Mihas AA. Small intestinal neoplasms. J Clin Gastroenterol 2001;33:267–282.
6. Patel JK, Didolkar MS, Pickren JW, Moore RH. Metastatic pattern of malignant melanoma: A study of 216 autopsy cases. Am J Surg 1978;135:807–810.
7. Berger A, Cellier C, Daniel C, et al. Small bowel metastasis from primary carcinoma of the lung: Clinical findings and outcome. Am J Gastroenterol 1999;94:1884–1887.
8. Chaikof EL. Nontraumatic perforation of the small bowel. Am J Surg 1987;153:355–358.
9. Miles RM, Crawford D, Duras S. The small bowel tumor problem: An assessment based on a 20 year experience with 116 cases. Ann Surg 1979;189:732–740.
10. Leidich RB, Rudolf LE. Small bowel perforation secondary to metastatic lung carcinoma. Ann Surg 1981;193:67–69.
11. Gitt SM, Flint P, Fredell CH, Schmitz GL. Bowel perforation due to metastatic lung cancer. J Surg Oncol 1992;51:287–291.
12. Ise N, Kotanagi H, Morri M, et al. Small bowel perforation caused by metastasis from an extra-abdominal malignancy: Report of three cases. Surg Today 2001;31:358–362.
13. Kessler WF, Shires GT, Fahey TJ. Surgical complications of nonsteroidal antiinflammatory drug-induced small bowel ulceration. J Am Coll Surg 1997;185:250–254.
14. ReMine SG, McIlrath DC. Bowel perforation in steroid-treated patients. Ann Surg 1980;192:581–586.
15. Hande KR, Fisher RI, DeVita VT, Chabner BA, Young RC. Diffuse histiocytic lymphoma involving the gastrointestinal tract. Cancer 1978;41:1984–1989.
16. Wada M, Onda M, Tokunaga A, et al. Spontaneous gastrointestinal perforation in patients with lymphoma receiving chemotherapy and steroids: Report of three cases. Nippon Ika Daigaku Zasshi 1999;66:37–40.
17. Orringer RD, Coller JA, Veidenheimer MC. Spontaneous free perforation of the small intestine. Dis Colon Rectum 1983;26:323–326.
18. Torosian MH, Turnbull ADM. Emergency laparotomy for spontaneous intestinal and colonic perforations in cancer patients receiving corticosteroids and chemotherapy. J Clin Oncol 1988;6:291–296.
19. Chao T-C, Jeng L-B, Jan Y-Y, Wang C-H, Chen M-F. Spontaneous gastroduodenal perforation in cancer patients receiving chemotherapy. Hepatogastroenterology 1998;45:2157–2160.
20. Ricci JL, Turnbull ADM. Spontaneous gastroduodenal perforation in cancer patients receiving cytotoxic therapy. J Surg Oncol 1989;41:219–221.
21. Ferrara JJ, Martin EW Jr, Carey LC. Morbidity of emergency operations in patients with metastatic cancer receiving chemotherapy. Surgery 1982;92:605–609.
22. Fox KR. Surgery in the patient with cancer. In Goldmann DR, Brown FH, Guarnieri DM, eds. Perioperative Medicine. New York: McGraw-Hill, 1994, pp 283–293.

23. Berne TV, Donovan AJ. Nonoperative treatment of perforated duodenal ulcer. Arch Surg 1989;124:830–832.
24. Wittmann DH, Schein M, Condon R. Management of secondary peritonitis. Ann Surg 1996;224:10–18.
25. Seiler CA, Brugger L, Forssmann U, Baer HU, Buchler MW. Conservative surgical treatment of diffuse peritonitis. Surgery 2000;127:178–184.
26. Grassi R, Pinto A, Rossi G, Rotondo A. Conventional plain-film radiology, ultrasonography and CT in jejuno-ileal perforation. Acta Radiol 1998;39:52–56.
27. Mischinger HJ, Berger A, Kronberger L, Fellbaum C. Spontaneous small bowel perforation: A rare cause of acute abdomen. Acta Chir Scand 1989;155:593–599.

Pancreatic Necrosectomy: Definitions and Technique

L. William Traverso, M.D., Richard A. Kozarek, M.D.

Pancreatic necrosis implies a permanent condition in which a portion of the pancreas loses its blood supply. This condition is irreversible, yet many cases of "necrosis" will, after recovery, culminate in a patient with a normal pancreas by computed tomography or endoscopic retrograde cholangiopancreatography. The problem is in our definitions. An understanding of this disease through its related definitions is required before judgment deems "necrosectomy to be appropriate." These definitions are of pancreatic ductal disruption, peripancreatic fluid collections, pseudocyst, pancreatic abscess, and pancreatic necrosis. The technique of necrosectomy removes mature "necrosum" and is described in this article. Once necrosectomy is completed, the surgeon still depends on the continued support of interventional radiology through regular exchange of large-bore pancreatic drains. In our institution, many of these drain sites are placed at some time before necrosectomy. Once the team method has been implemented, the following improved outcomes will result—lowered need for necrosectomy and single digit mortality. (J GASTROINTEST SURG 2005;9:436–439)

Before describing the technique of pancreatic necrosectomy, a list of definitions is discussed. Pancreatic necrosis implies a permanent condition in which a portion of the pancreas loses its blood supply. It is irreversible, yet many cases of "necrosis" will, after recovery, culminate in a patient with a normal pancreas on computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP). The problem is in our definitions.

Depending on the extent of necrosis, mild to severe complications of necrosis ensue. Almost every case of severe pancreas inflammation is associated with a pancreatic duct disruption with or without necrosis. Unclear is which of the events occurred first—necrosis or ductal disruption. We believe that almost every case of severe pancreatitis is made worse by a "plumbing" problem in the form of a leak. Our studies have shown us that the presence of a ductal disruption is significantly associated with the presence of necrosis, mortality, and the length of hospital stay.[1] Pancreatic necrosis and pancreatic ductal disruptions are integrally entwined. Taken further, the amount of pancreatic necrosis directly affects the outcomes of mortality and length of stay.[2,3] The amount of necrosis determines the computer tomography severity index (CTSI).[2]

Necrosis evolves into five potential findings on subsequent imaging. The outcomes depend on the extent of necrosis and the severity of the ductal disruption. These five outcomes are resolution, peripancreatic fluid collections with or without pancreatic enzymes, formation of a pseudocyst, infected pseudocyst, or infected necrosis. The terms *pancreatic necrosis*, *peripancreatic fluid collections*, *pseudocyst*, and *pancreatic abscess* need to be defined here.

DEFINITIONS

Pancreatic necrosis is devitalized tissue that can be either pancreatic parenchyma or peripancreatic tissue. In our experience, the majority of the "necrosum" is peripancreatic. If a segment of the gland is missing (usually the body of the gland), then, after resolution of the cavity (usually with percutaneous drainage), the images show a "disconnected" gland.

From the Departments of General Surgery (L.W.T.) and Gastroenterology (R.A.K.), Virginia Mason Medical Center, Seattle, Washington. Reprint requests: L. William Traverso, M.D., Virginia Mason Medical Center, Section of General, Thoracic, and Vascular Surgery, 1100 Ninth Avenue, Seattle, WA 98111. e-mail: gtslwt@vmmc.org

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.05.013

This syndrome of persistent pancreatic fistula drainage is due to an end pancreatic fistula from the separated upstream pancreatic remnant.

Peripancreatic Fluid Collections, Pseudocyst, and Pancreatic Abscess

To reemphasize the role of ductal disruption and to determine how peripancreatic necrosis may occur, one must understand the mechanism of ductal disruption. For many reasons, one of the small side branches of the pancreatic ductal system begins to leak, resulting in a pancreatic fistula that, if contained within the capsule, is self-limited and self-healing. The leak may occur from focal necrosis (alcohol etiology) or downstream ductal obstruction with side branch blowout (passage of a gallstone). Regardless of the reason, if the rupture breaks through the capsule, the peripancreatic enzyme-rich fluid bathes the pancreas and peripancreatic tissues, depending on where the ductal disruption is located. In more than two thirds of the cases, the disruption is to the left of the portal vein and a peripancreatic fluid collection occurs in the lesser sac. If the source of fluid ceases as the ductal disruption seals, then the fluid will be reabsorbed or walled-off to form a *pseudocyst*. If this fluid is infected or becomes infected, the result is a *pancreatic abscess*, which usually occurs 3 to 4 weeks after the initial bout. We rarely see a pancreatic abscess (pus in an infected peripancreatic fluid collection or pseudocyst), because with new technology, at least in our institution, all of these symptomatic peripancreatic fluid collections are percutaneously drained. A pseudocyst is uncommonly seen for the same reason—unless the patient is transferred with untreated disease.

Because pancreatic necrosis is devitalized tissue found at surgery, one must remember that when the radiologist says "pancreatic necrosis" is present, this could just be nonenhancement of the pancreatic tissue and does not necessarily represent irreversible pancreatic necrosis. Unfortunately, the "nonenhancement" seen on imaging is used interchangeably with pancreatic necrosis. This can lead to unnecessary procedures.

One of the best ways to improve surgical judgment with pancreatic necrosis is to always read the CT scan. Over the years of doing this, we have observed the following patterns. When present, the peripancreatic fluid collections make visualization of the pancreatic parenchyma impossible, and these cases are overcalled as "necrosis." After the fluid has been drained or reabsorbed, there is no lack of parenchymal enhancement. If peripancreatic fluid collections are not interfering with observation of the parenchyma during a contrast-enhanced CT scan and if the parenchyma shows nonenhancement, then these patients should be assumed to have parenchymal pancreatic nonenhancement and not necrosis.

The term "necrosis" unfortunately instills the knee-jerk response to perform necrosectomy. Over time, the necrosis will dissolve ("necrolyse") or become infected. Infected pancreatic necrosis is an indication for operative debridement in most medical centers throughout the world. However, in our institution we begin with percutaneous drainage and have drastically lowered the need for pancreatic necrosectomy to less than 10% of severe pancreatitis cases while keeping the mortality rate in single digits. In 73 patients with necrosis, we were able to lower the necrosectomy rate to 21% while observing a mortality rate of 11%.[2]

We have found that the presence of a persistent ductal disruption will increase the likelihood for pancreatic necrosectomy.[1] The definition of *ductal disruption* was an enzyme-rich fluid that comes from a percutaneous drain or a disruption demonstrated on ERCP. Ductal disruption is an important item to seek, because control of the leak at its source prevents uncontrolled spread of enzyme-rich juice, digestive necrosis, and ultimate infection in this dead space. Draining the leak at the source of ductal disruption and minimizing the resulting peripancreatic necrosis may be all that is necessary to allow the process to improve. One caveat here: to prevent abscess formation in a sterile fluid collection, any observed ductal disruption on ERCP must be drained within 24 hours. Infection of a sterile environment with ERCP has led to others to not use this valuable technique. Because the presence and location of the disruption are so important for truncation of the disease, it is also important to not provide an iatrogenic abscess. We use endoscopically placed main pancreatic duct stents through the papilla and/or percutaneous drains to decompress the potentially infected area. This requires a hospital team of interventional radiologists, therapeutic endoscopists, and surgeons practicing the principles of surgical drainage.

Pancreatic necrosectomy is the last option in patients who are symptomatic, and it is used when all of the other options have failed. These options include (1) percutaneous drainage with large-bore catheters that are frequently changed under fluoroscopic control every 3 days regardless of clinical condition and (2) trans-drain tract endoscopic debridement that will admit a 10-mm working laparoscope.

TECHNIQUE OF PANCREATIC NECROSECTOMY

1. Use an upper midline incision above the umbilicus to minimize the risk of incisional hernia.

This approach preserves the rectus abdominus muscles and allows great exposure to the areas of interest. This incision also avoids the already placed percutaneous drains. The drain tracts should be preserved and are rarely placed in the midline. The angle to approach the lesser sac from the left and the inferior pancreatic head from the right is superb if the drains are directed over either pararenal space. These drains are easily placed by interventional radiology and are usually in place before surgery.

2. Wide mobilization of the omentum through the avascular plane between the omentum and the entire transverse colon. The transverse mesocolon is preserved to remain a barrier and protect the inferior abdominal contents from contamination. For this reason, we do not recommend debridement through the mesocolon.
3. Blunt dissection of omentum and stomach up and off the transverse colon and its mesocolon and then off the pancreatic body and tail (Fig. 1).
4. Use just two instruments to avoid bleeding—the finger and a ring forcep. Finger dissection begins at the top of the necrosum and begins to break up the necrosum. A ring forcep can be used to help peel the densely adherent "peanut butter" substance gently off surrounding organs and major vessels. Experience operating in this area is a great help to the surgeon in staying out of major organs and vessels. Follow the planes that have already been outlined by the necrosum. Most commonly, the normal pancreas will be encountered. The viable pancreas gland should not be debrided even if particles of necrosum remain. Finding a normal gland explains the observation of a normal ERCP months after the surgeon "removed" the entire pancreas during necrosectomy and supports the concept that the majority of "necrosis" during necrosectomy is peripancreatic tissue.
5. Use the CT scan as a map. The surgeon should read all of the CT scans before necrosectomy using the computer monitor. Scrolling through the areas of necrosis makes the guided operation more efficient and shortens operating time.
6. Lesser sac necrosis. Follow the necrosum inferiorly over and under the superior mesenteric vein down the root of the small bowel mesentery into the retroperitoneum (Fig. 1). Using interventional techniques ahead of time has lowered the expansion of necrosum, and the operations do not have to be as extensive. The areas with the decreased extension are down the left anterior renal, right perirenal, and right gutter. The cavity uncommonly extends into either perirenal space, but if it does, by CT or at exploration, then blunt retrieval of the necrosum is important. The necrosum at this stage is "mature" because by this time in the course of the disease, after all of the other

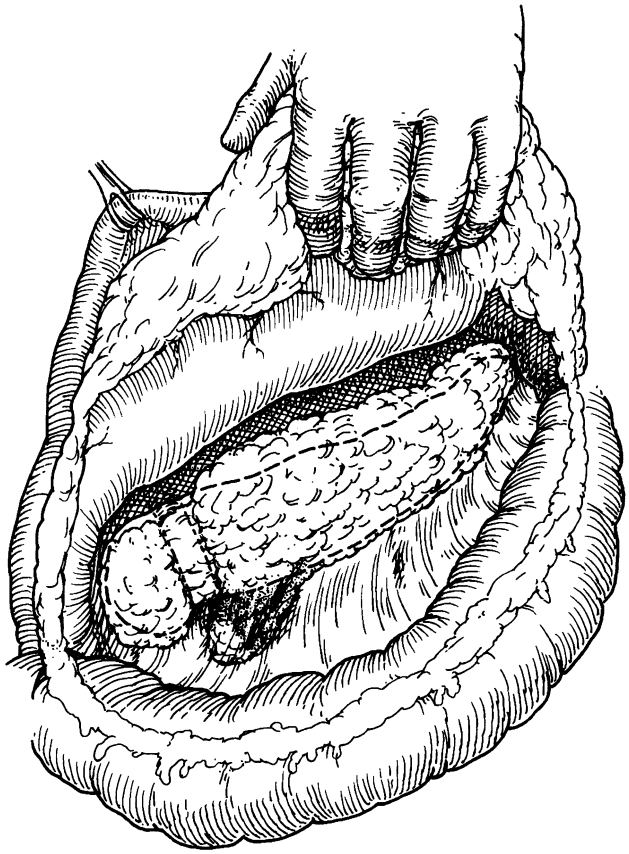

Fig. 1. The operating hand is holding the greater omentum and stomach upward off the pancreas as the transverse colon and intact transverse mesocolon remain below. The dotted lines show the deep outline of the pancreas. Covering the pancreas is a diffuse peripancreatic necrosis that extends cephalad off the body and tail over the splenic artery area. The necrosum is also extending caudad and dorsal under the superior mesenteric vein (SMV, also depicted in dashed lines) from the left. This extending necrosis is frequently associated with other necrosis coming from the right side under the SMV. The latter is hard to depict in the illustration but originates from under the pancreatic head over the ventral surface of the right kidney and under the duodenum. The dorsal SMV area is an important area to empty of necrosum and leave well drained. Other areas of extension not depicted are down from under the pancreatic tail over the ventral surface of the left kidney and superiorly over and then under the left side of the portal vein from the pancreatic body. Use the computed tomography scan to guide to a pocket of necrosis and follow the necrosum with aid of tactile sensation of the surgeon's finger. Do not debride normal tissue.

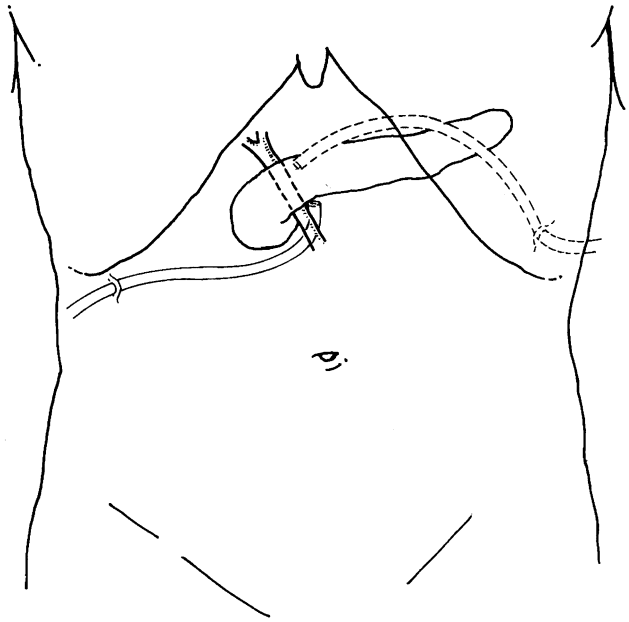

Fig. 2. The final position of large-bore drainage catheters after necrosectomy is depicted. Ideally, these catheters should meet in the midline. The picture shows the right catheter entering a surgically placed drain in the right subcostal area that goes under the duodenum to lie under the superior mesenteric vein. The left catheter penetrated the dorsal flank and was originally placed by interventional radiology only to be exchanged at the time of necrosectomy for a larger catheter (28 F). The route of this catheter is best acquired by interventional technique as it courses over the left kidney and under the splenic flexure and spleen to enter the lesser sac. This dorsal flank entrance site is surprisingly better tolerated than a subcostal site.

previously tried minimally invasive techniques have failed, the extending peripancreatic necrosis has been truncated primarily by decompressing the ductal disruption. The mature necrosum is fairly easy to remove with the dissecting finger and a ring forcep. Weigh the necrosum as at least 25 g should be removed.[3] Weights of greater than 50 g have been reported to connote a significant mortality rate. These high mortality rates are not being seen in our institution. Arrest of the dynamic spreading necrosis with ductal decompression and early percutaneous drainage has significantly reduced mortality.

7. At the time of surgery, if new drain sites are needed, then place large-bore (28 F) closed-suction catheters into all major cavities. These should be obtained from the interventional radiology department, which will ensure subsequent ease of catheter exchange over guidewires. This maneuver usually requires just two catheters crossing from both sides of the abdomen (Fig. 2). The repetitive exchanges of these catheters by interventional radiology in the postoperative period are mandatory. These exchanges have to be done even after discharge from the hospital. The catheters are exchanged at 3-day intervals after surgery along with sinogram tube checks. CT scans are also done at each of these times to ensure the cavities are closing. After several weeks, the tubes can be "downsized" as the cavity decreases in size.
8. Remove the gallbladder whether or not gallstones are noted. With the prolonged disuse of the gastrointestinal tract, it is surprising how frequent smoldering cholecystitis from cystic duct occlusion is observed. The gallbladder itself may be the cause of sepsis, which is surprisingly not due to underlying pancreatic necrosis. Obtain an intraoperative cholangiogram, as 31% of patients will have reflux into the main pancreatic duct, thus providing valuable "plumbing" information.[4]
9. Close the midline abdominal fascia with interrupted wide figure-eight nonabsorbable monofilament sutures. This is a contaminated wound and the skin will have to close via secondary intention.

REFERENCES

1. Lau ST, Simchuk EJ, Kozarek RA, Traverso LW. A pancreatic duct leak should be sought to direct treatment in patients with acute pancreatitis. Am J Surg 2001;181:411–415.
2. Simchuk EJ, Traverso LW, Nukui Y, Kozarek RA. Computed tomography severity index is a predictor of outcomes for severe pancreatitis. Am J Surg 2000;179:352–355.
3. Beger H, Rau B, Mayer J, et al. Natural course of acute pancreatitis. World J Surg 1997;21:130–135.
4. Traverso LW, Hauptmann EM, Lynge DC. Routine intraoperative cholangiography and its contribution to the selective cholangiographer. Am J Surg 1994;167:464–468.

Review Article

Current Management of Acute Pancreatitis

Thomas E. Clancy, M.D., Eric P. Benoit, M.D., Stanley W. Ashley, M.D.

Acute pancreatitis may vary in severity, from mild, self-limiting pancreatic inflammation to pancreatic necrosis with life-threatening sequelae. In the majority of the more than 185,000 patients who develop acute pancreatitis each year in the United States, the process is limited to mild parenchymal edema without distant organ dysfunction and an uneventful recovery.[1] Although the overall mortality rate with acute pancreatitis is 2–10%, this is primarily related to patients with more severe disease. Approximately 10–30% of patients develop severe illness with pancreatic inflammation progressing to pancreatic and peripancreatic necrosis. The severity of the local response can lead to development of the systemic inflammatory response syndrome (SIRS) and multiorgan failure, with considerable morbidity and mortality.[2,3]

The management of patients with mild acute pancreatitis is generally standardized and is primarily limited to identification and management of etiologic factors, resuscitation, and supportive care. Patients with severe and necrotizing pancreatitis require more intensive therapy, possibly including aggressive surgical management for debridement of infected pancreatic necrosis or to address other local complications of the disease. The precise indications for surgery in these patients have been controversial, although in recent years many investigators have adopted a more conservative stance toward early intervention.[4,5] This review provides current diagnostic and therapeutic strategies in acute pancreatitis, with particular attention to recent developments in our understanding of severity assessment, nutrition, prophylactic antibiotics, indications for and timing of surgery, and the role of minimally invasive techniques.

DIAGNOSIS, STAGING, AND SEVERITY

Despite advances in the understanding of the pathophysiology of pancreatitis and improvements in imaging technology, diagnostic modalities for acute pancreatitis have not changed drastically in recent years. Clinical signs and symptoms, such as upper abdominal pain, back pain, vomiting, fever, tachycardia, and leukocytosis, are relatively nonspecific. The periumbilical and flank bruising seen with hemorrhagic pancreatitis (Cullen and Grey-Turner signs) are uncommon and nonspecific for any particular etiology. Diagnosis therefore typically depends on a high level of clinical suspicion and the demonstration of elevated plasma concentrations of pancreatic enzymes. Levels of both amylase and lipase peak within the first 24 hours of symptoms, and amylase has a slightly shorter half-life in plasma. As a result, lipase levels may have a slightly greater sensitivity than amylase levels, particularly when measured late (>24 hours) after initial presentation.[6] Moreover, hyperamylasemia is neither specific for pancreatitis[7] nor perfectly sensitive, as normoamylasemia has been described in acute pancreatitis.[8] Other pancreatic enzymes have not been shown to have any advantage over amylase and lipase for diagnostic purposes. Of note, plasma levels of pancreatic enzymes serve a purely diagnostic and not a prognostic role; absolute levels have no direct correlation with disease severity.

An early goal in management is to identify patients with severe pancreatitis to institute directed therapy early in the course of the disease. Although progress has been made in this area, an objective and reproducible measure of disease severity has not been universally accepted.[9] Clinical evaluation at presentation is not always straightforward. Initial signs and symptoms of necrotizing pancreatitis are only different in degree from edematous pancreatitis; likewise, severe and mild forms of disease share the same etiologies.[10] Despite considerable experimental effort to identify differences in the pathogenesis of edematous and necrotizing pancreatitis,[11] this has not resulted in a successful model of predicting which patients, at initial presentation, will progress to severe disease.

From the Department of Surgery, Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts.
Reprint requests: Stanley W. Ashley, M.D., Department of Surgery, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. e-mail: SAshley@Partners.org

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.09.027

Clinical scoring systems specific for pancreatitis, such as the Ranson[12] and Glasgow[13] systems, have been shown to predict outcomes in groups of patients with acute pancreatitis but require 48 hours from admission for full assessment. Furthermore, although higher scores suggest poorer outcomes, these scoring systems have not been adequately reassessed to reflect the substantial improvements in critical care since their introduction more than two decades ago.[14] The Acute Physiology And Chronic Health Evaluation (APACHE II) score, although not specific for pancreatitis and somewhat more cumbersome, is as accurate at 24 hours as are other systems at 48 hours and therefore is thought to be the optimal scoring system to assess disease severity.[9] Unlike other systems, the APACHE II score may be continuously recalculated through the course of the disease. APACHE II scores have also been identified as an independent predictor of outcome after pancreatic debridement.[15] The newer APACHE III system uses an additional five physiologic variables to improve accuracy, although the newer system may be less useful than the APACHE II score in distinguishing mild from severe pancreatitis.[16] A recent modification of the APACHE II system, which includes a clinical assessment of obesity (APACHE-O score), has been suggested to further improve predictive accuracy, with a positive predictive value of 74%.[17]

In addition to multiple-factor scoring systems, several isolated indicators of prognosis have been suggested. Brown et al.[18] and Lankisch et al.[19] have shown that hemoconcentration predicts necrotizing pancreatitis and organ failure. A number of biological markers have been studied as prognostic markers in both laboratory and clinical settings; none have yet gained widespread clinical applicability. C-reactive protein (CRP) is readily available and rises with disease severity; however, it is useful to identify severe disease only 48 hours after the onset of symptoms.[20] Inflammatory mediators such as interleukin (IL)-8 and IL-6 show promise as early indicators of severe disease but await general availability and further clinical validation.[21] Assays for other markers of inflammation, including tumor necrosis factor–soluble receptors and polymorphonuclear elastase, await clinical validation and the availability of reproducible assays before their use as prognostic markers in acute pancreatitis. Several other markers of inflammation have been investigated in this regard, including serum procalcitonin, soluble IL-2 receptors, and soluble E-selectin,[22] although clinical usefulness of these markers awaits further investigation.

A growing body of literature suggests that assays for trypsinogen activation peptide (TAP) may be a useful marker of disease severity. TAP, released with activation of trypsinogen to trypsin, is known to correlate with severity of pancreatitis. However, the molecule is present in low concentrations in urine and is cleared rapidly from plasma. Recent reports of high sensitivity and specificity of elevated urinary TAP in severe pancreatitis[23,24] are promising; similarly, a recent report of plasma TAP levels suggested that severe acute pancreatitis could be recognized with sensitivity and specificity of 70% and 78%, respectively, using a plasma assay.[25] Reliable TAP assays may prove to be clinically useful as an indicator of disease severity.

The computed tomography (CT) scan is an important adjunct in determining disease severity in acute pancreatitis.[26] CT findings in pancreatitis include enlargement of the pancreas with loss of peripancreatic fat planes, areas of decreased density, and occasionally the presence of fluid collections (Fig. 1). The presence of pancreatic inflammation and peripancreatic fluid collections has been incorporated into grading systems such as the Balthazar system, and CT findings have thereby been correlated with morbidity and mortality.[27,28] The use of dynamic contrast-enhanced CT is perhaps most useful in its ability to demonstrate pancreatic necrosis. Nonenhanced pancreas will show CT attenuation numbers of 30–50 Hounsfield units (HU) that increase by more

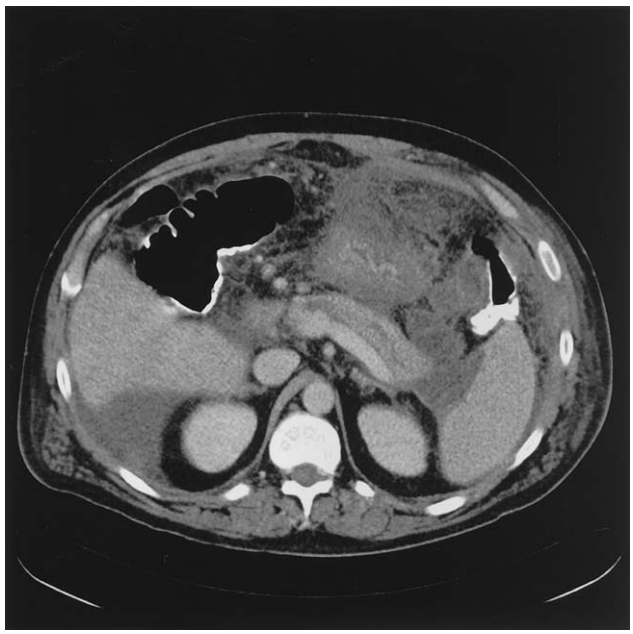

Fig. 1. Contrast-enhanced abdominal computed tomography scan in a 47-year-old man with acute pancreatitis. Relevant findings include significant fat stranding of the peripancreatic tissue, with a fluid collection at the tail of the pancreas measuring approximately 4 cm × 4 cm. Pancreatic parenchyma enhances with intravenous contrast, with no evidence of pancreatic necrosis.

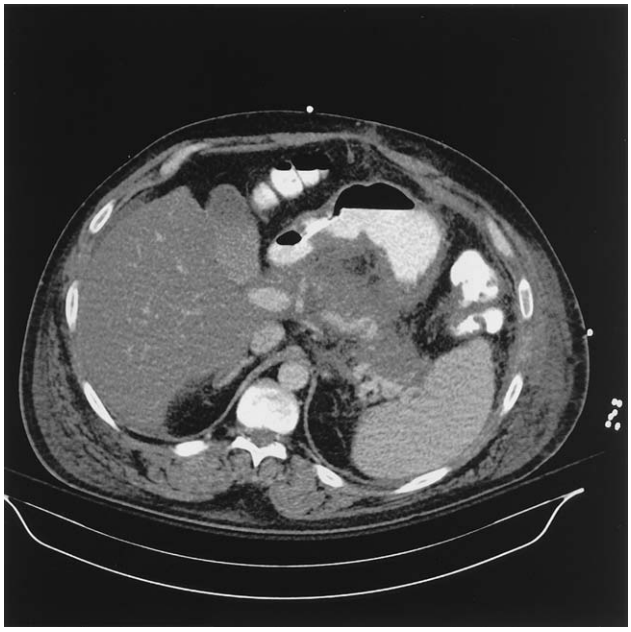

Fig. 2. Contrast-enhanced abdominal computed tomography scan in the 47-year-old man shown in Fig. 1 with a second episode of acute pancreatitis. Scan shows stranding of peripancreatic fat, consistent with acute pancreatitis. Most notable is the near-complete absence of pancreatic enhancement, diagnostic of pancreatic necrosis.

than 50 HU with intravenous contrast, but a decrease in or lack of enhancement of pancreatic parenchyma correlates with necrosis (Fig. 2). Recognized criteria to diagnose necrosis include nonenhancement of more than 30% of the pancreatic parenchyma or an area of greater than 3 cm without enhancement.[29] Sensitivity and specificity increase with degree of nonenhancement, and degree of complications has been shown to correlate with degree of nonenhancement.[28] Contrast-enhanced CT scan may be contraindicated in the presence of renal impairment or a history of allergic reaction to intravenous contrast; although nonenhanced CT provides important information, recent data support the use of magnetic resonance imaging (MRI) as an alternative. MRI and CT have been shown to have comparable sensitivity and specificity for severe acute pancreatitis[30]; whether MRI is practical for most critically ill patients remains to be determined.

The timing of imaging studies remains an issue of some discussion. Early scans may not identify developing necrosis until such areas are better demarcated, often 2–3 days after the initial clinical onset. No data support the use of CT to diagnose necrosis or to predict severity within the first 24 hours of illness. Limited and contradictory experimental evidence has suggested that intravenous contrast might exacerbate early pancreatic necrosis,[31] although clinical evidence to support this phenomenon in humans is lacking. Sensitivity for the diagnosis of pancreatic necrosis approaches 100% after 4 days from diagnosis.[9] In general, patients with clinical and biochemical features of acute pancreatitis who do not improve with conservative management should undergo an abdominal CT scan with oral and intravenous contrast. Follow-up scans may be obtained with any signs of clinical deterioration.

Although clinicians in recent years have adopted increasingly conservative trends in the management of sterile pancreatic necrosis, infection remains an absolute indication for intervention.[1] The early and accurate diagnosis of infected pancreatic necrosis is therefore desirable. Clinical and laboratory features of infected pancreatic necrosis, such as significant leukocytosis and fever, are also seen in severe sterile necrosis. Radiographic evidence of infection, or emphysematous pancreatitis, is uncommon. The ability to use image-guided percutaneous aspiration to diagnose infection in patients with pancreatic necrosis who are not improving clinically has therefore been a major advance (Fig. 3). The sensitivity and specificity for detection of infection are reported as 96.2% and 99.4%, respectively, with a positive predictive

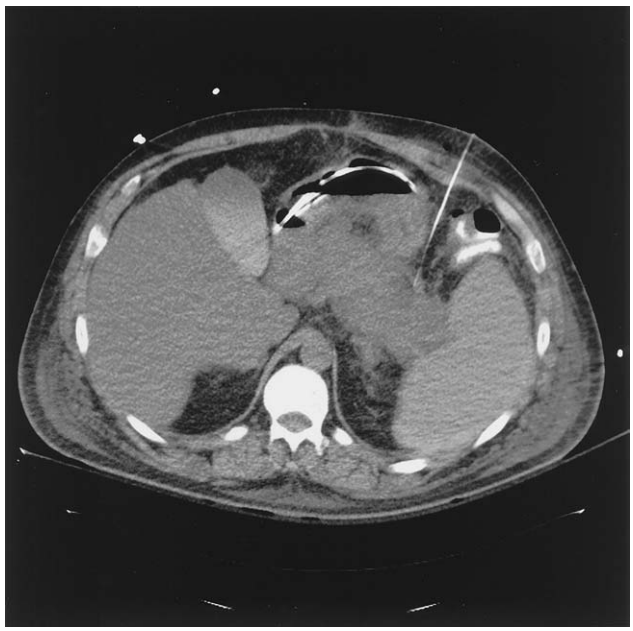

Fig. 3. Computed tomography (CT)-guided percutaneous fine needle aspiration of the pancreatic tail. The aspiration area had previously been identified as necrotic in the contrast-enhanced CT scan shown in Fig. 2. Gram stain and cultures were negative for organisms, consistent with sterile pancreatic necrosis.

value of 99.5% and negative predictive value of 95.3%.[32] Samples are sent for aerobic, anaerobic, and fungal culture, although Gram stain of the aspirate is positive in the majority of cases with infection. The interval from initial presentation to infection is variable, and pancreatic necrosis is variable, and increases up to 3 weeks. For this reason, repeat CT-guided aspirations are often necessary. In a series at our institution with fine needle aspirations (FNAs) demonstrating infection, the first aspirate was positive in 17 of 30 patients (57%); 7 patients (23%) required two procedures and 6 patients (20%) required three or more aspirations to demonstrate infection.[33]

PRINCIPLES OF MANAGEMENT

Resuscitation and Monitoring

Medical therapy for acute pancreatitis has become increasingly standardized in recent years.[3,34–36] An algorithm for the diagnosis and management of acute pancreatitis is suggested in Fig. 4. A cornerstone of initial management is aggressive fluid resuscitation to replenish the often massive third-space losses. Intravenous fluids at rates of greater than 200 ml/hr are necessary to restore and maintain intravascular volume, and close monitoring of respiratory, cardiovascular, and renal function is required to detect and treat complications from hypovolemia. Inadequate fluid resuscitation not only predisposes to systemic complications, particularly acute renal insufficiency, but also has recently been shown to pose a significant risk for further pancreatic injury. Brown et al.[37] have shown that although aggressive fluid resuscitation does not necessarily prevent the progression to pancreatic necrosis, patients with inadequate resuscitation have an increased risk of developing necrosis. Monitoring is tailored to disease severity. All patients require close assessment of fluid balance including the use of a Foley catheter. Close monitoring for respiratory compromise and electrolyte imbalance is important in all, and any patient with severe disease should be admitted to an intensive care unit with the capacity for continuous blood pressure and oxygen saturation monitoring. Intravenous narcotics are often essential for pain control in these patients. No data support the use of nasogastric drainage to reduce the severity of pancreatitis, although it may be useful in treating ileus and preventing aspiration pneumonia.

Nutritional Support

Classic teaching in the management in pancreatitis has included the limitation of enteral feeding, theoretically to avoid stimulation of pancreatic exocrine function and thereby avoid further pancreatic injury from release of proteolytic enzymes. Brief periods without oral intake may be expected in very mild cases of pancreatitis, and a full diet is often possible in several days with the resolution of pain. Severe cases may have a prolonged course, hypercatabolic state, and ileus, which has led to a general use of parenteral nutrition in these patients.[38] In recent years, increasing evidence has accumulated to suggest that enteral nutrition may be feasible and safe even for cases of severe pancreatitis[39] (Table 1). In addition to avoiding the cost of and catheter-related complications associated with total parenteral nutrition (TPN), enteral nutrition may avoid the alterations to intestinal barrier function and altered intestinal permeability seen with TPN.[40] For instance, a small trial from 1997 randomized 38 patients with severe pancreatitis to TPN versus nasojejunal feeding.[41] In this cohort, enterally fed patients had significantly fewer septic and total complications. McClave et al.[42] randomized 30 patients in a similar fashion and demonstrated only a trend toward fewer complications in the enterally fed group. The one significant advantage of enteral nutrition was cost, which was four times greater in the TPN group. Windsor et al.[43] demonstrated that pancreatitis patients randomized to enteral nutrition had significant improvement in CRP and APACHE II scores. Recently, a larger study from China[44] randomized 96 patients with severe pancreatitis to TPN versus nasojejunal feeding. Measures of inflammation including CRP and IL-6 decreased earlier with enteral nutrition, as did APACHE II scores. Furthermore, mucosal permeability was improved, as inferred by urine endotoxin levels. Others have suggested that the addition of *Lactobacillus* preparations to enteral nutrition formulas may have a role in decreasing infectious complications in pancreatitis.[45] The abovementioned studies all involve nasojejunal feeding, although others have investigated the counterintuitive use of nasogastric feeding in pancreatitis. Investigators from Glasgow[46] have recently shown in a nonrandomized cohort with severe pancreatitis that nasogastric feeding is well tolerated in most patients. Whether this method is feasible and provides sufficient caloric support deserves further investigation.

Although a recent systematic review of the literature has not concluded that there are sufficient data to definitively recommend enteral nutrition in acute pancreatitis,[47] studies continue to accumulate demonstrating its safety and feasibility. TPN will continue to have an important role in severe pancreatitis, particularly in cases with prolonged ileus. However, early enteral nutrition should be considered for patients who will not resume oral intake early in the course of their disease.

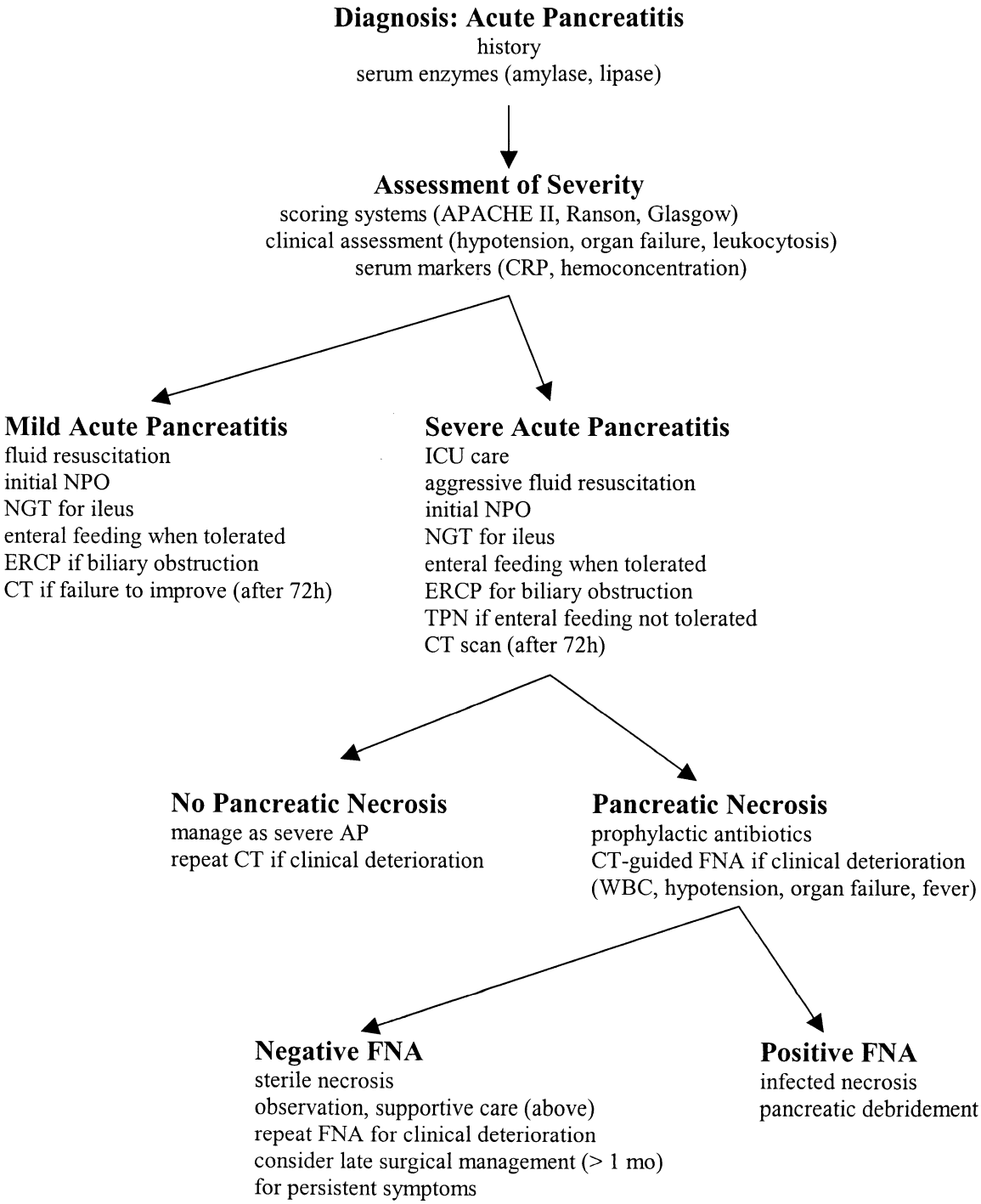

Fig. 4. Management algorithm for acute pancreatitis. APACHE II = Acute Physiology And Chronic Health Evaluation, CRP = C-reactive protein, ICU = intensive care unit, NPO = nothing by mouth, NGT = nasogastric tube, ERCP = endoscopic retrograde cholangiopancreatography, CT = computed tomography, TPN = total parenteral nutrition, AP = acute pancreatitis, FNA = fine needle aspiration, WBC = white blood cells.

The Role of Endoscopic Retrograde Cholangiopancreatography

Gallstones are increasingly recognized as the primary cause of most cases of acute pancreatitis.[48] The role of endoscopic retrograde cholangiopancreatography (ERCP) as a diagnostic and potentially therapeutic modality in acute pancreatitis has been the subject of some debate. Although early ERCP is not used in mild cases, its role in acute biliary pancreatitis

Table 1. Controlled trials of nutritional support in patients with acute pancreatitis

Author	Inclusion Criteria	N	Design	Outcome	Findings
Sax et al.[92] (1987)	Acute pancreatitis	54	Early total parenteral nutrition versus no nutritional support	Days to oral diet, length of stay (LOS), complications	No advantage to TPN
McClave et al.[42] (1997)	Acute pancreatitis	32	Enteral versus parenteral nutrition	Days to oral diet, LOS, infection rate, mortality, cost	Better outcome with enteral group; cost is only significant difference (less with enteral)
Kalfarentzos et al.[41] (1997)	Glasgow Coma Scale score ≥ 3, APACHE II score >8, C-reactive protein (CRP), >120 mg/L, or grade D/E Balthazar score	38	Enteral versus parenteral nutrition	Complications, LOS, cost	Fewer septic and total complications with enteral nutrition, cost significantly less with enteral nutrition
Windsor et al.[43] (1998)	Serum amylase >1000 U/L	34	Enteral versus parenteral nutrition	APACHE II score, CRP, sepsis, organ dysfunction, LOS, mortality	Significant decrease in APACHE II score and CRP in enteral group only at 7 days; sepsis, organ dysfunction, LOS, mortality with nonsignificant trend to improvement with enteral nutrition
de Beaux et al.[93] (1998)	Glasgow Coma Scale score ≥ 3	14	Parenteral nutrition—conventional versus glutamine enhanced	Change in inflammatory mediators	Nonsignificant trend to improved lymphocyte proliferation and interleukin 8 release in glutamine group

Modified from Lobo et al.[39]

with biliary obstruction or cholangitis is not disputed. More controversial is the utilization of early ERCP and papillotomy in acute biliary pancreatitis without obstruction. Both Neoptolemos et al.[49] and Fan et al.[50] demonstrated a significant reduction in morbidity with nonsignificant trends to improved mortality when patients with acute pancreatitis are randomized to early ERCP. These studies were criticized for the inclusion of patients with obstruction and cholangitis in the cohort, possibly accounting for the observed benefit from intervention. A more recent multicenter randomized study by Folsch et al.,[51] which excluded patients with known biliary sepsis or obstruction, demonstrated increased complications and mortality in the ERCP group. It was therefore suggested that early ERCP might be harmful in the absence of ongoing obstruction. Although these findings have been subsequently called into question given the small number of patients per center,[52] it is generally thought that there is insufficient evidence to recommend ERCP in acute biliary pancreatitis in the absence of biliary obstruction or infection. Recent advances in diagnostic radiology have provided clinicians with magnetic resonance cholangiopancreatography (MRCP) as an alternative to ERCP. Although MRCP does not allow therapeutic maneuvers to clear identified stones, it may play an important diagnostic role when ERCP cannot be performed.[53] As mentioned previously, the use of MRI techniques poses unique challenges in the critically ill patient, including the need for prolonged scan times and compatible nonmetallic equipment for ventilators and intravenous fluid administration. As technology evolves, it is expected that MRI and MRCP will play an increased role in the diagnosis of pancreatitis and ductal obstruction.

Antibiotics

The vast majority of deaths from pancreatitis occur from local and systemic infectious complications. Local infection occurs more commonly in patients with increasing amounts of pancreatic necrosis and is more often seen late in the course of the disease. In one study, 24% of patients operated on for pancreatic necrosis had infection at 1 week, whereas 71% of patients were infected when exploration was performed at 3 weeks.[54] Infection of necrotic pancreatic tissue usually involves aerobic and anaerobic gastrointestinal flora, and infections may be monomicrobial or polymicrobial. In a collected series of more than 1,100 cases, the organisms involved were *Escherichia coli* (35%), *Klebsiella pneumoniae* (24%), *Enterococcus* (24%), *Staphylococcus* (14%), and *Pseudomonas* (11%).[55]

Exposure to broad-spectrum antibiotics is demonstrated to alter the bacterial flora of pancreatic infections, with a tendency to develop antibiotic-resistant bacterial infections and fungal infections.[56,57] Still, the clear association of pancreatic infection with mortality has driven the widespread use of prophylactic systemic antibiotics for pancreatic necrosis. The use of antibiotics to prevent or forestall pancreatic infection has been widely investigated.[58,59]

Numerous animal studies have shown a benefit from early antibiotic administration with pancreatitis,[58] but this benefit has not been as consistently demonstrated in humans. Early clinical studies of prophylactic antibiotics in pancreatitis did not show a benefit, possibly due to inclusion of patients at low risk for infection or for the use of antibiotics with poor pancreatic penetration. A significant investigative effort has been put forth to characterize the penetration of various antibiotics into the pancreatic parenchyma.[60] Still, the precise relation between antibiotic levels in pancreatic tissue and efficacy in preventing or treating infection in necrotic pancreatic tissue is unclear.

Several recent studies have addressed the use of systemic antibiotic prophylaxis in severe pancreatitis, with somewhat conflicting results (Table 2). Pederzoli et al.[61] randomized 74 patients with necrotizing pancreatitis to systemic imipenem or no antibiotics. While pancreatic infection was decreased with imipenem (12% versus 30%), there was no difference in the rate of multiorgan system failure, need for surgery, or overall mortality. Of note, antibiotic therapy was particularly useful with mild necrosis; no patient with less than 50% necrosis developed septic complications with imipenem compared with 29% in the control group.

In contrast, Saino et al.[62] showed a decrease in infectious complications, operations, and mortality with the use of cefuroxime in a randomized fashion in patients with necrotizing alcoholic pancreatitis. However, the apparent mortality benefit was not associated with any difference in local pancreatic infection. Further criticisms include a high incidence of antibiotic use at some point in therapy in the control arm of the study. Another small randomized study[63] with 26 patients showed a nonsignificant trend to improved mortality with intravenous ofloxacin and metronidazole for CT-confirmed pancreatic necrosis. Still others[64] suggested no difference in mortality or the development of infected pancreatic necrosis with the use of ciprofloxacin and metronidazole, although this study was not limited to patients with CT-confirmed pancreatic necrosis.

The inconsistencies among these small trials may result from the relatively small number of patients per study and the limited statistical power to detect such differences. In addition, there is considerable heterogeneity in patient selection (use of CT criteria for necrosis, etiology of pancreatitis) and antimicrobials used. Other differences exist among the studies in the nonantibiotic management of patients, particularly with fluid resuscitation, enteral nutrition, timing of surgery, and other factors. Meta-analyses have been performed to address this question. In one, [65] early antibiotic use was associated with decreased mortality from pancreatitis for patients with severe pancreatitis receiving broad-spectrum antibiotics. A second meta-analysis looked at randomized, controlled, nonblinded studies of prophylactic antibiotics in necrotizing pancreatitis. A nonsignificant trend toward decreased local infection was suggested with the use of imipenem, cefuroxime, or ofloxacin. Sepsis and overall mortality were significantly lower with antibiotic use, and the authors therefore supported the use of prophylactic antibiotics for all patients with acute necrotizing pancreatitis.[66]

Despite variations in institutional practices, a consensus is emerging that broad-spectrum antibiotics should be initiated early in patients with necrotizing pancreatitis, particularly with signs of organ failure or systemic sepsis.[67] The risks of superinfection with fungal or antibiotic-resistant organisms is well-recognized,[68] and length of treatment is therefore typically limited. Although the optimal duration of antimicrobial therapy has not been defined, the incidence of pancreatic infection increases for approximately the first 3 weeks after diagnosis.[69] A treatment course of 1–4 weeks is therefore generally pursued, with many authors limiting treatment to 14 days.[5] The role of prophylactic antifungal therapy is also undefined, although mortality is high when fungal infection complicates the use of prophylactic antibiotics. Some groups have therefore recommended fluconazole for all patients receiving antibiotic therapy for necrotizing pancreatitis.[57] A recent randomized trial of antifungal therapy in severe acute pancreatitis showed a definite reduction in the incidence of fungal infection with the prophylactic use of the antifungal garlicin or fluconazole.[70] Given a relatively low incidence of side effects from fluconazole, this approach may be an appropriate adjunct to the prophylactic regimen.

Given the gastrointestinal origin of bacteria in infected pancreatic necrosis, pancreatic infection might theoretically be reduced through the reduction of intestinal bacteria. Early laboratory evidence suggested that gut decontamination might decrease mortality in experimental pancreatitis, lending support to the role of intestinal bacteria in pancreatic infection.[71] Selective gut decontamination has been reported in only one clinical study. Luiten et al.[72] randomized

Table 2. Controlled trials of antibiotic use in acute pancreatitis

Author	Inclusion Criteria	N	Antibiotic regimen	Mortality rate (%)		Comments
				Controls	Antibiotic Group	
Pederzoli et al.[61] (1993)	Acute pancreatitis, necrosis on computed tomography (CT) scan	74	Imipenem for 14 days	12	7	Significant decrease in pancreatic infection, not mortality
Sainio et al.[62] (1995)	CRP >120 mg/L, decreased pancreatic enhancement on CT	60	Cefuroxime for 14 days or until CRP normalized	23	3	Significant decrease in mortality and overall infections, not in pancreatic infections
Luiten et al.[72] (1995)	Imrie score ⩾3, Balthazar CT grade D or E	102	Oral colistin, amphotericin, and norfloxacin until clinical recovery, plus intravenous (IV) cefotaxime until gram-negative bacteria eliminated from oral cavity	35	22	Not all patients with necrosis; decreased late (>2 wk) mortality with four antibiotics and selective gut decontamination
Delcenserie et al.[94] (1996)	Acute pancreatitis, >2 fluid collections on CT	23	Ceftazidime, amikacin, and metronidazole for 10 days	25	9	Not all patients with pancreatic necrosis
Schwarz et al.[63] (1997)	Acute pancreatitis with pancreatic necrosis on CT	26	Ofloxacin and metronidazole for 10 days	15	0	Improved outcome in treatment group; no change in pancreatic infections
Isenmann et al.[64] (2004)	Acute pancreatitis, CRP, >150 mg/L or necrosis on CT	114	IV ciprofloxacin and metronidazole for 14 days if clinical improvement, or 21 days	5	7	No differences in rate of infected pancreatic necrosis, systemic complications, or mortality

Modified from Golub et al.[65]

patients with severe acute pancreatitis to oral and rectal administration of nonabsorbable antibiotics. Mortality was decreased in the treatment group, predominantly via a reduction in late mortality and decrease in gram-negative pancreatic infection. However, the short use of intravenous antibiotics in the study may confound the results, and the effect of gut decontamination alone is unclear. Definitive recommendations regarding the use of gut decontamination awaits further studies.

Surgical Management

In the majority of patients with acute pancreatitis, the process is limited to parenchymal edema without necrosis. In these patients, surgical therapy is largely limited to the delayed treatment of local complications, such as pseudocysts, and to the use of cholecystectomy to prevent further illness. Between 10% and 30% of patients develop severe illness, with pancreatic and peripancreatic necrosis, as well as the systemic inflammatory response syndrome and considerable morbidity and mortality.[2] This latter group of patients may require debridement or other aggressive intervention during the acute phase of the disease. Although an increasingly conservative surgical approach has been adopted in recent years, the timing of debridement and the indications for debridement in patients with sterile necrosis remain controversial.

Patients with infected pancreatic necrosis account for the majority of the deaths from acute pancreatitis, and the absolute need for debridement is generally accepted. The mortality rate from necrotizing pancreatitis has historically been reported to range from 20% to 40%, although recent reports suggest this may be reduced to less than 15% with appropriate monitoring and intervention.[4,33,73,74] Mortality in infected pancreatic necrosis is virtually 100% without debridement. Radiographic signs of pancreatic infection such as emphysematous pancreatitis are seen in only a minority of cases; CT-guided FNA is therefore typically required to diagnose infection.

Historically, the presence of pancreatic necrosis was considered sufficient justification for surgical debridement. Bradley and Allen[54] questioned this practice in 1991 with the publication of a small series of 11 patients with sterile pancreatic necrosis managed nonoperatively. Indications for surgery in patients with sterile necrosis have continued to be refined since that time. Some authors have argued that patients with severe disease benefit from debridement regardless of the status of infection.[75] Considerable effort has been made to identify criteria for debridement other than infection.[76,77] Unfortunately, none have shown to be specific enough to use as a basis of decision-making.[78] Series using aggressive surgery regardless of pancreatic infection continue to be reported,[73,74] although most centers have increasingly managed sterile necrosis in a conservative manner. A prospective study from Bern[4] followed 86 patients with necrotizing pancreatitis prospectively with a conservative protocol, reporting a mortality rate of 10% and the need for operation in the absence of documented infection in only one patient. A retrospective review of conservative management of sterile necrosis was recently reported from Brigham and Women's Hospital.[33] Of note, 59 patients did not develop infection and were managed conservatively with a mortality of 11%. Thirty-four patients developed infected necrosis requiring debridement or drainage, and mortality in this group was 12%. Of note, when analyzing the patients who died, the authors were not able to find clinical or laboratory characteristics that would help prospectively identify patients who might benefit from more aggressive management. Overall, the results suggest that conservative strategies can be used in most patients with sterile necrosis with reasonable outcomes (Fig. 5).

Despite a general acceptance among most authors of initial nonoperative management for sterile pancreatic necrosis, some have emphasized the eventual need to operate on patients who do not clinically improve. Warshaw[79] described a group of patients with sterile necrosis who have "persistent unwellness," with continuing pain, malaise, and inability to eat. Isenmann et al.[80] described other patients with sterile necrosis but persistent organ failure for whom conservative treatment failed due to the severity of their systemic illness. Unfortunately, the precise indications for and timing of surgery for this group of patients have not been precisely defined. Small nonrandomized series suggest better outcomes with delayed versus early debridement.[73,81] The pathologic correlate of the pancreas later in the course of the disease is what Baron et al.[82] describe as "organized pancreatic necrosis": a process of maturation of the inflammatory tissue with improved demarcation from healthy pancreatic and peripancreatic tissue. In the above-mentioned series of 99 patients with pancreatic necrosis at the Brigham and Women's Hospital, 5 patients underwent an operation for this indication at a mean of 29 days (23–34) after presentation. This group accounted for approximately one fifth of the patients who had undergone a negative CT-guided FNA.[33] Fernandez-del Castillo and associates[73] suggested that there is no added benefit in these patients in waiting longer than 27 days from the onset of illness. Such delayed procedures are an important part of a conservative management strategy that emphasizes nonoperative management for most cases of sterile necrosis and late operations whenever possible.

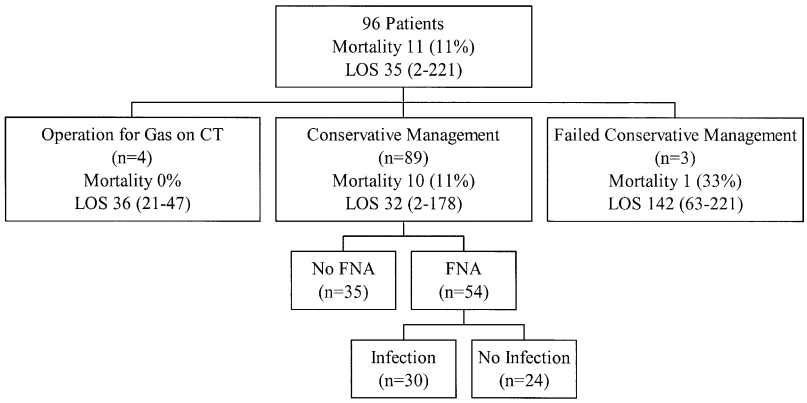

Fig. 5. Management strategy in necrotizing pancreatitis. CT = computed tomography; FNA = fine needle aspiration; LOS = length of stay. Reproduced with permission from Ashley SW, Peres A, Pierce EA, et al. Necrotizing pancreatitis: Contemporary analysis of 99 consecutive cases. Ann Surg 2001;234: 572–580.

A variety of techniques have been described for pancreatic debridement and drainage,[73,74,83,84] all of which involve open debridement followed by external drainage of some sort. Three general approaches include the following: (1) open debridement with abdominal closure and external drainage via closed suction or Penrose drains, (2) debridement with placement of several soft drains in the retroperitoneum for continuous lavage, or (3) aggressive debridement with open packing and planned reexploration. The necrosectomy may be approached via the gastrocolic ligament or through the transverse mesocolon. In general, an approach tailored to the location of necrotic tissue on CT imaging may be most beneficial. Debridement is done primarily with blunt technique, attempting to remove as much necrotic tissue as deemed safe. Formal pancreatic resection is not indicated in this setting.

If debridement is adequate, multiple soft drains are placed and the abdomen closed, with the understanding that reexploration is required in more than one third of patients for ongoing necrosis. If debridement is thought to be inadequate, postoperative closed high-volume lavage via large drains in the lesser sac has been described with some success for residual necrotic tissue.[84,85] In other patients who have only limited debridement due to bleeding or with a clear need for further debridement, open packing is appropriate. This approach is associated with a high incidence of postoperative complications, especially enteric fistulas. In our recent series of 99 patients with pancreatic necrosis,[33] 31 of 36 patients managed surgically were adequately treated with closed drainage. A conservative approach with delayed surgical intervention may in fact facilitate a closed drainage technique.

Minimally Invasive Approaches

Traditional open surgical techniques remain the gold standard of therapy for patients who require debridement. In recent years, however, there has been a proliferation of reports suggesting that minimally invasive approaches may be of benefit in some cases of necrotizing pancreatitis. Percutaneous, endoscopic, and laparoscopic techniques have all been described. Solid pancreatic debris has traditionally been thought to be too thick for adequate evacuation with percutaneous drains; still, at least one study has demonstrated successful percutaneous management in infected pancreatic necrosis. Freeny et al.[86] successfully managed 16 of 34 such patients with percutaneous methods alone; in 9 others, percutaneous intervention was not the sole means of therapy but allowed eventual open surgical intervention to be delayed. The concept that percutaneous drainage of infected necrosis may delay the need for early intervention, permitting surgery once the process has become more organized, is appealing but needs further validation.

Other investigators have suggested endoscopic therapy for pancreatic necrosis and have recently summarized these results.[87] Forty-four patients with pancreatic necrosis were treated for suspected or documented infection or for intractable symptoms from organized necrosis, including nausea, pain, or early satiety. Endoscopic transmural drainage was successful in 31 (72%) of patients with pancreatic necrosis, although 9 (29%) experienced recurrence and 16 (37%) experienced complications. Transmural drainage was more successful with central necrosis than with peripheral necrosis due to close proximity of the necrotic area to the gastric wall. Seifert et al.[88] described

a method of retroperitoneal endoscopy via transgastric fenestration. Direct visual access to retroperitoneal collections is thereby afforded to allow optimal drainage. Few patients have been described using this method, and larger studies are necessary to validate this approach. The above approaches were not always performed for infected pancreatic necrosis. Of concern is the certainty that if sterile collections are accessed via the gastrointestinal tract, these collections soon become contaminated.[89] Inadequate drainage therefore clearly has the ability to complicate a troublesome but not life-threatening collection.

A number of minimal access surgical techniques have been proposed to assist with management of pancreatic necrosis. Gambiez et al.[90] suggest using a retroperitoneal approach via dorsal lumbotomy and a 23-cm endoscope to explore and drain the peripancreatic area; necrotic peripancreatic tissue could be removed by blunt dissection and drains may be left for irrigation. This procedure was repeated at regular 5-day intervals until the resolution of necrotic debris, with a mean of five procedures. Purported advantages include an avoidance of peritoneal contamination, and subsequent laparotomy was required in just two patients for persistent collections. Overall mortality in 20 patients with infected pancreatic necrosis was 10%, which compares favorably with historical controls. Larger studies should help clarify whether direct retroperitoneal endoscopy is feasible in most patients. Laparoscopic techniques have also been described for direct debridement in pancreatic necrosis,[91] although further study is indicated.

Summary

The treatment of mild pancreatitis has changed little in recent years, but advances in the management of severe pancreatitis have been associated with significantly reduced morbidity and mortality. Improvements in the recognition of severe disease with scoring systems and serial CT scanning has allowed early goal-directed therapy in appropriate patients. Early aggressive resuscitation and invasive monitoring are standard, with an increased recognition of the role of prophylactic antibiotics and image-guided FNA to diagnose infection. Although the need for aggressive intervention in infected pancreatic necrosis remains unchanged, initial conservative management of most patients with sterile pancreatic necrosis has gained widespread acceptance. Some patients with sterile necrosis may eventually require delayed debridement either for persistent systemic illness or failure to thrive, although accurate prospective identification of these patients has not been possible. For patients who need debridement, open surgical techniques remain the gold standard of management. Advances in minimally invasive technology hold promise as adjuncts to open procedures in the future, particularly as a means of delaying surgery until the necrosis becomes more organized.

REFERENCES

1. Banks PA. Acute pancreatitis: Medical and surgical management. Am J Gastroenterol 1994;89:S78–S85.
2. Beger HG, Rau B, Mayer J, Pralle U. Natural course of acute pancreatitis. World J Surg 1997;21:130–135.
3. Yousaf M, McCallion K, Diamond T. Management of severe acute pancreatitis. Br J Surg 2003;90:407–420.
4. Buchler MW, Gloor B, Muller CA, Friess H, Seiler CA, Uhl W. Acute necrotizing pancreatitis: Treatment strategy according to the status of infection. Ann Surg 2000;232: 619–626.
5. Clancy TE, Ashley SW. Current management of necrotizing pancreatitis. Adv Surg 2002;36:103–121.
6. Kazmierczak SC, Catrou PG, Van Lente F. Diagnostic accuracy of pancreatic enzymes evaluated by use of multivariate data analysis. Clin Chem 1993;39:1960–1965.
7. Sternby B, O'Brien JF, Zinsmeister AR, DiMagno EP. What is the best biochemical test to diagnose acute pancreatitis? A prospective clinical study. Mayo Clin Proc 1996;71:1138–1144.
8. Clavien PA, Robert J, Meyer P, et al. Acute pancreatitis and normoamylasemia. Not an uncommon combination. Ann Surg 1989;210:614–630.
9. Dervenis C, Johnson CD, Bassi C, et al. Diagnosis, objective assessment of severity, and management of acute pancreatitis. Santorini Consensus Conference. Int J Pancreatol 1999;25: 195–110.
10. Baron TH, Morgan DE. Acute necrotizing pancreatitis. N Engl J Med 1999;340:1412–1417.
11. Lerch MM, Hernandez CA, Adler G. Acute pancreatitis. N Engl J Med 1994;331:948–949.
12. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet 1974;139: 69–81.
13. Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. Gut 1984;25:1340–1346.
14. Eachempati SR, Hydo LJ, Barie PS. Severity scoring for prognostication in patients with severe acute pancreatitis: Comparative analysis of the Ranson score and the APACHE III score. Arch Surg 2002;137:730–736.
15. Connor S, Ghaneh P, Raraty M, et al. Increasing age and APACHE II scores are the main determinants of outcome from pancreatic necrosectomy. Br J Surg 2003;90:1542–1548.
16. Williams M, Simms HH. Prognostic usefulness of scoring systems in critically ill patients with severe acute pancreatitis. Crit Care Med 1999;27:901–907.
17. Triester SL, Kowdley KV. Prognostic factors in acute pancreatitis. J Clin Gastroenterol 2002;34:167–176.
18. Brown A, Orav J, Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. Pancreas 2000;20:367–372.
19. Lankisch PG, Mahlke R, Blum T, et al. Hemoconcentration: an early marker of severe and/or necrotizing pancreatitis? A critical appraisal. Am J Gastroenterol 2001;96:2081–2085.

20. de Beaux AC, Goldie AS, Ross JA, Carter DC, Fearon KC. Serum concentrations of inflammatory mediators related to organ failure in patients with acute pancreatitis. Br J Surg 1996;83:349–353.
21. Pezzilli R, Billi P, Miniero R, et al. Serum interleukin-6, interleukin-8, and beta 2-microglobulin in early assessment of severity of acute pancreatitis. Comparison with serum C-reactive protein. Dig Dis Sci 1995;40:2341–2348.
22. Kylanpaa-Back ML, Takala A, Kemppainen EA, et al. Procalcitonin, soluble interleukin-receptor, and soluble E-selectin in predicting the severity of acute pancreatitis. Crit Care Med 2001;29:63–69.
23. Tenner S, Fernandez-del Castillo C, Warshaw A, et al. Urinary trypsinogen activation peptide (TAP) predicts severity in patients with acute pancreatitis. Int J Pancreatol 1997; 21:105–110.
24. Neoptolemos JP, Kemppainen EA, Mayer JM, et al. Early prediction of severity in acute pancreatitis by urinary trypsinogen activation peptide: A multicentre study. Lancet 2000;355: 1955–1960.
25. Kemppainen E, Mayer J, Puolakkainen P, Raraty M, Slavin J, Neoptolemos JP. Plasma trypsinogen activation peptide in patients with acute pancreatitis. Br J Surg 2001;88:679–680.
26. Balthazar EJ. Staging of acute pancreatitis. Radiol Clin North Am 2002;40:1199–1209.
27. Balthazar EJ, Ranson JH, Naidich DP, Megibow AJ, Caccavale R, Cooper MM. Acute pancreatitis: Prognostic value of CT. Radiology 1985;156:767–772.
28. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: Value of CT in establishing prognosis. Radiology 1990;174:331–336.
29. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg 1993;128:586–590.
30. Arvanitakis M, Delhaye M, De Maertelaere V, et al. Computed tomography and magnetic resonance imaging in the assessment of acute pancreatitis. Gastroenterology 2004; 126:715–713.
31. Schmidt J, Hotz HG, Foitzik T, et al. Intravenous contrast medium aggravates the impairment of pancreatic microcirculation in necrotizing pancreatitis in the rat. Ann Surg 1995; 221:257–264.
32. Banks PA, Gerzof SG, Langevin RE, Silverman SG, Sica GT, Hughes MD. CT-guided aspiration of suspected pancreatic infection: Bacteriology and clinical outcome. Int J Pancreatol 1995;18:265–270.
33. Ashley SW, Perez A, Pierce EA, et al. Necrotizing pancreatitis: Contemporary analysis of 99 consecutive cases. Ann Surg 2001;234:572–579; discussion 579–580.
34. Toouli J, Brooke-Smith M, Bassi C, et al. Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol 2001;17(Suppl):S15–S39.
35. Uhl W, Warshaw A, Imrie C, et al. IAP guidelines for the surgical management of acute pancreatitis. Pancreatology 2002;2:565–573.
36. Tenner S, Banks PA. Acute pancreatitis: Nonsurgical management. World J Surg 1997;21:143–148.
37. Brown A, Baillargeon JD, Hughes MD, Banks PA. Can fluid resuscitation prevent pancreatic necrosis in severe acute pancreatitis? Pancreatology 2002;2:104–107.
38. Goodgame JT, Fischer JE. Parenteral nutrition in the treatment of acute pancreatitis: Effect on complications and mortality. Ann Surg 1977;186:651–658.
39. Lobo DN, Memon MA, Allison SP, Rowlands BJ. Evolution of nutritional support in acute pancreatitis. Br J Surg 2000; 87:695–707.
40. Buchman AL, Moukarzel AA, Bhuta S, et al. Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. J Parenter Enteral Nutr 1995;19:453–460.
41. Kalfarentzos F, Kehagias J, Mead N, Kokkinis K, Gogos CA. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: Results of a randomized prospective trial. Br J Surg 1997;84:1665–1669.
42. McClave SA, Greene LM, Snider HL, et al. Comparison of the safety of early enteral vs parenteral nutrition in mild acute pancreatitis. J Parenter Enteral Nutr 1997;21:14–20.
43. Windsor AC, Kanwar S, Li AG, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. Gut 1998;42:431–435.
44. Zhao G, Wang CY, Wang F, Xiong JX. Clinical study on nutrition support in patients with severe acute pancreatitis. World J Gastroenterol 2003;9:2105–2108.
45. Olah A, Belagyi T, Issekutz A, Gamal ME, Bengmark S. Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. Br J Surg 2002;89:1103–1107.
46. Eatock FC, Brombacher GD, Steven A, Imrie CW, McKay CJ, Carter R. Nasogastric feeding in severe acute pancreatitis may be practical and safe. Int J Pancreatol 2000;28:23–29.
47. Al-Omran M, Groof A, Wilke D. Enteral versus parenteral nutrition for acute pancreatitis. Cochrane Database Syst Rev 2003:CD002837.
48. Mitchell RM, Byrne MF, Baillie J. Pancreatitis. Lancet 2003; 361:1447–1455.
49. Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet 1988;2:979–983.
50. Fan ST, Lai EC, Mok FP, Lo CM, Zheng SS, Wong J. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med 1993;328:228–232.
51. Folsch UR, Nitsche R, Ludtke R, Hilgers RA, Creutzfeldt W. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. N Engl J Med 1997; 336:237–242.
52. Mergener K, Baillie J. Endoscopic treatment for acute biliary pancreatitis. When and in whom? Gastroenterol Clin North Am 1999;28:601–613.
53. Varghese JC, Farrell MA, Courtney G, Osborne H, Murray FE, Lee MJ. Role of MR cholangiopancreatography in patients with failed or inadequate ERCP. Am J Roentgenol 1999;173:1527–1533.
54. Bradley EL 3rd, Allen K. A prospective longitudinal study of observation versus surgical intervention in the management of necrotizing pancreatitis. Am J Surg 1999;161:19–14; discussion 24–25.
55. Lumsden A, Bradley EL 3rd. Secondary pancreatic infections. Surg Gynecol Obstet 1990;170:459–467.
56. Bassi C, Falconi M, Talamini G, et al. Controlled clinical trial of perfloxacin versus imipenem in severe acute pancreatitis. Gastroenterology 1998;115:1513–1517.
57. Grewe M, Tsiotos GG, Luque de-Leon E, Sarr MG. Fungal infection in acute necrotizing pancreatitis. J Am Coll Surg 1999;188:408–414.
58. Ratschko M, Fenner T, Lankisch PG. The role of antibiotic prophylaxis in the treatment of acute pancreatitis. Gastroenterol Clin North Am 1999;28:641–659.
59. Bassi C, Larvin M, Villatoro E. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database Syst Rev 2003:CD002941.

60. Buchler M, Malfertheiner P, Friess H, et al. Human pancreatic tissue concentration of bactericidal antibiotics. Gastroenterology 1992;103:1902–1908.
61. Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet 1993;176:480–483.
62. Saino V, Kemppainen E, Puolakkainen P, et al. Early antibiotic treatment in acute necrotizing pancreatitis. Lancet 1995; 346:663–667.
63. Schwarz M, Isenmann R, Meyer H, Beger HG. Antibiotic use in necrotizing pancreatitis. Results of a controlled study. Dtsch Med Wochenschr 1997;122:356–361.
64. Isenmann R, Runzi M, Kron M, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: A placebo-controlled, double-blind trial. Gastroenterology 2004;126:997–1004.
65. Golub R, Siddiqi F, Pohl D. Role of antibiotics in acute pancreatitis: A meta-analysis. J GASTROINTEST SURG 1998; 2:496–503.
66. Sharma VK, Howden CW. Prophylactic antibiotic administration reduces sepsis and mortality in acute necrotizing pancreatitis: A meta-analysis. Pancreas 2001;22:28–31.
67. Powell JJ, Campbell E, Johnson CD, Siriwardena AK. Survey of antibiotic prophylaxis in acute pancreatitis in the UK and Ireland. Br J Surg 1999;86:320–323.
68. Gloor B, Muller CA, Worni M, et al. Pancreatic infection in severe pancreatitis: The role of fungus and multiresistant organisms. Arch Surg 2001;136:592–596.
69. Rau B, Uhl W, Buchler MW, Beger HG. Surgical treatment of infected necrosis. World J Surg 1997;21:155–161.
70. He YM, Lv XS, Ai ZL, et al. Prevention and therapy of fungal infection in severe acute pancreatitis: A prospective clinical study. World J Gastroenterol 2003;9:2619–2621.
71. Lange JF, van Gool J, Tytgat GN. The protective effect of a reduction in intestinal flora on mortality of acute haemorrhagic pancreatitis in the rat. Hepatogastroenterology 1987; 34:28–30.
72. Luiten EJ, Hop WC, Lange JF, Bruining HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. Ann Surg 1995;222:57–65.
73. Fernandez-del Castillo C, Rattner DW, Makary MA, Mostafavi A, McGrath D, Warshaw AL. Debridement and closed packing for the treatment of necrotizing pancreatitis. Ann Surg 1998;228:676–684.
74. Branum G, Galloway J, Hirchowitz W, Fendley M, Hunter J. Pancreatic necrosis: Results of necrosectomy, packing, and ultimate closure over drains. Ann Surg 1998;227:870–877.
75. Rattner DW, Legermate DA, Lee MJ, Mueller PR, Warshaw AL. Early surgical debridement of symptomatic pancreatic necrosis is beneficial irrespective of infection. Am J Surg 1992;163:105–109; discussion 109–110.
76. McFadden DW, Reber HA. Indications for surgery in severe acute pancreatitis. Int J Pancreatol 1994;15:83–90.
77. Rau B, Pralle U, Uhl W, Schoenberg MH, Beger HG. Management of sterile necrosis in instances of severe acute pancreatitis. J Am Coll Surg 1995;181:279–288.
78. Ashley SW. Sterile pancreatic necrosis: Is operation necessary? J Am Coll Surg 1995;181:363–364.
79. Warshaw AL. Pancreatic necrosis: To debride or not to debride—that is the question. Ann Surg 2000;232:627–629.
80. Isenmann R, Rau B, Zoellner U, Beger HG. Management of patients with extended pancreatic necrosis. Pancreatology 2001;1:63–68.
81. Mier J, Leon EL, Castillo A, Robledo F, Blanco R. Early versus late necrosectomy in severe necrotizing pancreatitis. Am J Surg 1997;173:71–75.
82. Baron TH, Morgan DE, Vickers SM, Lazenby AJ. Organized pancreatic necrosis: Endoscopic, radiologic, and pathologic features of a distinct clinical entity. Pancreas 1999;19:105–108.
83. Sarr MG, Nagorney DM, Mucha P Jr, Farnell MB, Johnson CD. Acute necrotizing pancreatitis: Management by planned, staged pancreatic necrosectomy/debridement and delayed primary wound closure over drains. Br J Surg 1991;78:576–581.
84. Beger HG. Operative management of necrotizing pancreatitis—necrosectomy and continuous closed postoperative lavage of the lesser sac. Hepatogastroenterology 1991;38:129–133.
85. Beger HG, Isenmann R. Surgical management of necrotizing pancreatitis. Surg Clin North Am 1999;79:800, ix.
86. Freeny PC, Hauptmann E, Althaus SJ, Traverso LW, Sinanan M. Percutaneous CT-guided catheter drainage of infected acute necrotizing pancreatitis: Techniques and results. Am J Roentgenol 1998;170:969–975.
87. Baron TH, Harewood GC, Morgan DE, Yates MR. Outcome differences after endoscopic drainage of pancreatic necrosis, acute pancreatic pseudocysts, and chronic pancreatic pseudocysts. Gastrointest Endosc 2002;56:7–17.
88. Seifert H, Wehrmann T, Schmitt T, Zeuzem S, Caspary WF. Retroperitoneal endoscopic debridement for infected peripancreatic necrosis. Lancet 2000;356:653–655.
89. Kozarek RA. Endotherapy for organized pancreatic necrosis: Perspective on skunk-poking. Gastroenterology 1996;111: 820–823.
90. Gambiez LP, Denimal FA, Porte HL, Saudemont A, Chambon JP, Quandalle PA. Retroperitoneal approach and endoscopic management of peripancreatic necrosis collections. Arch Surg 1998;133:66–72.
91. Zhou ZG, Zheng YC, Shu Y, et al. Laparoscopic management of severe acute pancreatitis. Pancreas 2003;27:e46–e50.
92. Sax HC, Warner BW, Talamini MA, et al. Early total parenteral nutrition in acute pancreatitis: Lack of beneficial effects. Am J Surg 1987;153:117–114.
93. de Beaux AC, O'Riordain MG, Ross JA, Jodozi L, Carter DC, Fearon KC. Glutamine-supplemented total parenteral nutrition reduces blood mononuclear cell interleukin-8 release in severe acute pancreatitis. Nutrition 1998;14:261–265.
94. Delcenserie R, Yzet T, Ducroix JP. Prophylactic antibiotics in treatment of severe acute alcoholic pancreatitis. Pancreas 1996;13:198–201.

These Guidelines have been written by the Patient Care Committee of The Society for Surgery of the Alimentary Tract (SSAT). Their goal is to guide physicians to the appropriate utilization of surgical procedures on the alimentary tract or related organs. They are based on a critical review of the literature and expert opinion. Together these sources of information result in a consensus that is recorded in the form of these Guidelines. The consensus addresses the *range* of acceptable clinical practice and should not be construed as a standard of care. These Guidelines will require periodic revision to ensure that clinicians utilize procedures appropriately, but the reader must realize that clinical judgment may justify a course of action outside of the recommendations contained herein. If you would like to ask a medical question, please use the SSAT Directory to find an SSAT physician in your area. (J GASTROINTEST SURG 2005;9:453–454)

Surgical Treatment of Injuries and Diseases of the Spleen

Introduction

Our evolving understanding of the spleen's role in the immune surveillance system has markedly altered the indications for splenectomy. Newer treatment modalities for hematologic neoplasms and benign disorders, innovative techniques for achieving hemostasis and splenic salvage, and the accuracy of intra-abdominal imaging techniques have also had a profound effect. Laparoscopic splenectomy, which is becoming increasingly common, appears to be safe and is associated with less pain, shorter hospital stay, and more rapid convalescence.

Indications for Splenectomy

Trauma. Traumatic injury to the spleen is no longer an immediate or mandatory indication for operation or splenectomy. Computed tomographic (CT) scanning or ultrasound imaging can accurately characterize splenic injury in patients with blunt trauma. Nonoperative support with in-hospital observation for up to 5 days is indicated in children and adults with splenic injury and hemodynamic stability, provided there is no evidence of other intra-abdominal injuries that might require laparotomy. Accepted indications for operation in adults include the following: hemodynamic instability, bleeding of more than 1000 ml, transfusion of more than 2 units of blood, or other evidence of ongoing blood loss. In children under 14 years of age, more aggressive nonoperative support is justified. When operative intervention is necessary, preservation of the spleen should be considered if bleeding can be controlled quickly and when there are no other life-threatening intra-abdominal injuries. Again, in children under 14 years of age, more aggressive attempts at intraoperative splenic salvage are justified. Splenic autotransplantation using portions of the spleen as free grafts for maintenance of specific splenic immunity is of no proven value.

Iatrogenic (Intraoperative) Splenic Injury. The spleen may be injured during the performance of intraperitoneal procedures, especially those involving the distal esophagus, stomach, distal pancreas, or splenic flexure of the colon. These injuries may occur directly from operative retractors or by traction on splenic capsular adhesions leading to persistent bleeding. To avoid splenectomy, hemostasis should be attempted using suture plication, topical hemostatic agents (including absorbable mesh), electrocautery, or argon beam coagulation. However, if secure hemostasis is not possible before blood loss is sufficient to require blood transfusion, the patient is better managed by splenectomy than by repeated attempts at splenic salvage.

Hematologic Diseases. Indications for splenectomy should be determined with the close cooperation of a hematologist/oncologist. Common indications include immune thrombocytopenic purpura (ITP), hereditary spherocytosis, thalassemia major, and certain forms of autoimmune hemolytic anemia unresponsive to medical management. Thrombotic thrombocytopenic purpura (TTP) and hairy-cell leukemia unresponsive to other tratment strategies are occasional indications for splenectomy.

Myeloproliferative disorders may lead to massive splenomegaly. Related symptoms may be best relieved by splenectomy, although it does not usually alter overall survival. This information should be clearly discussed with the patient prior to operation, and patients should be aware of the frequent requirement for blood or blood products when splenectomy

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.05.003

is carried out for very large spleens. Massive splenomegaly may preclude a laparoscopic approach. In these circumstances an open or "hand-assisted" laparoscopic technique may be used. The operative morbidity and mortality rates are higher in these patients because of the hematologic comorbidity.

Other Indications for Splenectomy. Less common indications for splenectomy include splenic abscesses, cysts, sinistral portal hypertension secondary to isolated splenic vein thrombosis or obstruction, or splenic mass presumed to be a neoplasm. Splenectomy is occasionally included in en bloc resection for malignancy in an adjacent organ. Distal pancreatectomy usually includes splenectomy if preservation of the splenic artery and vein is either contraindicated (malignancy) or technically impossible.

Operative and Postoperative Morbidity and Mortality

Operative mortality for elective splenectomy is less than 1%, except in patients with myeloproliferative disorders. These patients are at increased risk for postoperative hemorrhage. In trauma patients, the mortality rate for splenectomy depends on the extent of other injuries. Postoperative complications of open splenectomy include pneumonia, thrombotic complications, wound infection, hernia formation, hemorrhage, subphrenic abscess, pancreatic abscess/fistula, pancreatic pseudocyst, and, rarely, gastric fistula/perforation. These potential complications also exist when the laparoscopic approach is used, although wound complications consist primarily of herniation at trocar sites.

Postsplenectomy Sepsis

Late sequelae related to splenectomy are much more common in children, especially those under 6 years of age. Overwhelming postsplenectomy sepsis is a rare (less than 1%) but potentially fatal complication of splenectomy, because these children have not yet developed extrasplenic specific immunity to encapsulated organisms such as pneumococcus and meningococcus. Adults are susceptible to similar infections following splenectomy, but the incidence is likely much lower than in children.

Most pediatricians believe that children who have undergone splenectomy before the age of 5 years should be treated with a daily dose of penicillin until the age of 10 years. The benefit of prophylactic penicillin is less clear in children over 5 years of age and in adults. All patients who have undergone nonelective splenectomy should be immunized with Pneumovax (a nonviable pneumococcal vaccine). When planning elective splenectomy, patients should be immunized with Pneumovax, and against *H. influenza* and meningococcus, preferably 2 or more weeks before operation.

Qualifications for Performing Surgery on Splenic Disorders

The qualifications of a surgeon to perform any operative procedure should be based on education, training, experience, and outcomes. At a minimum, the surgical treatment of splenic disorders should be carried out by surgeons who are certified or eligible for certification by the American Board of Surgery, the Royal College of Physicians and Surgeons of Canada, or their equivalent.

SUGGESTED READINGS

Glasgow RE, Mulvihill SJ. Laparoscopic splenectomy. World J Surg 1999;23:384–388.

Katkhouda N, Hurwitz MB, Rivera RT, et al. Laparoscopic splenectomy. Outcome and efficacy in 103 consecutive patients. Ann Surg 1998;228:568–578.

Lucas CE. Splenic trauma. Choice of management. Ann Surg 1991;213:98–103.

Munser G, Lazer G, Hocking W, Busuttil W. Splenectomy for hematological disease: The UCLA experience with 306 patients. Ann Surg 1984;200:40–48.

Shackford SR, Molin MR. Management of splenic injuries. Surg Clin North Am 1990;70:595–620.

KEY WORDS: Patient, guideline, hematologic diseases/surgery, spleen, splenectomy, surgical procedures/laparoscopic, trauma, ultrasound, CT scan, iatrogenic, Pneumovax.

Surgical Management of Hemorrhoids

These Guidelines have been written by the Patient Care Committee of The Society for Surgery of the Alimentary Tract (SSAT). Their goal is to guide physicians to the appropriate utilization of surgical procedures on the alimentary tract or related organs. They are based on a critical review of the literature and expert opinion. Together these sources of information result in a consensus that is recorded in the form of these Guidelines. The consensus addresses the *range* of acceptable clinical practice and should not be construed as a standard of care. These Guidelines will require periodic revision to ensure that clinicians use procedures appropriately, but the reader must realize that clinical judgment may justify a course of action outside of the recommendations contained herein. If you would like to ask a medical question, please use the SSAT Directory to find an SSAT physician in your area. (J GASTROINTEST SURG 2005;9:455–456)

Introduction

Every individual is born with hemorrhoids, but they are clinically known as "hemorrhoids" only when they become enlarged and symptomatic. Hemorrhoids are symptomatic in approximately 4% of the general population and in 50% of Americans over the age of 50 years. Predisposing or associated conditions include heredity factors, constipation, and increased intra-abdominal pressure due to pregnancy, ascites, coughing, vomiting, or strenuous work.

Hemorrhoids may present with symptoms typical of most anal conditions, including bleeding, pain, discharge, or a mass. Hemorrhoids are generally categorized as internal (covered with mucosa) and external (covered with squamous epithelium). Internal hemorrhoids bleed and prolapse to give a mass effect, and patients will notice that hemorrhoids may protrude with bowel movements. Internal hemorrhoids are staged according to the degree of prolapse as follows:

Stage I = Bleeding only, no prolapse
Stage II = Prolapse that reduces spontaneously, with or without bleeding
Stage III = Prolapse that requires manual reduction, with or without bleeding
Stage IV = Irreducible prolapsed hemorrhoidal tissue

External hemorrhoids generally do not bleed but can thrombose and cause acute pain. Although external hemorrhoids can become necrotic and drain, most thrombosed hemorrhoids resolve spontaneously. Redundant "skin tags" may remain and may cause pruritus if the area cannot be properly cleansed.

Acute complications can occur with either prolapse of internal hemorrhoids or thrombosis of external hemorrhoids. Acute pain is usually constant and related to a visible mass. Pain occurring after a bowel movement is rarely due to a hemorrhoid complication; it is more likely due to a fissure or an ulcerating anal mass. Chronic anal pain and pruritus are generally not symptoms of hemorrhoids, but rather other diseases including anal fissure, mucosal prolapse, anal mass, or anal fistula, which may be associated with excessive moisture leading to pruritus.

Symptoms and Diagnosis

Symptoms of hemorrhoids include local protrusion and swelling, discomfort related to protruding or swollen masses, and bleeding that may be significant enough to result in anemia. These symptoms are nonspecific, and the presence of hemorrhoids should not be presumed. More severe conditions, such as inflammatory bowel disease and cancer, can mimic hemorrhoidal symptoms. Patients with severe pain or incarcerated protrusions should be seen promptly.

Diagnosis is established with direct visualization by anoscopy or proctoscopy. All patients with rectal bleeding should have their colon examined to rule out proximal sources of bleeding, even in the presence of enlarged hemorrhoids. Because most sources of bright red bleeding are within the reach of a flexible sigmoidoscope, patients should undergo flexible sigmoidoscopy as well as anoscopy to rule out other causes of bleeding. Intermittent protrusion or occasional bleeding does not require urgent consultation. However, patients with acute symptoms of bleeding, pain, or incarcerated protrusions should be seen promptly.

Treatment

Initial therapy for chronic symptoms of hemorrhoidal disease should be conservative, including stool "bulking" and topical therapy with ointments or suppositories. Outpatient surgical treatment is appropriate if conservative treatment fails and the patient

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.05.004

desires relief of symptoms. Operative treatment is reserved for symptomatic patients with stage III or IV hemorrhoids. If the patient has evidence of anemia, full colonic examination is indicated, and more aggressive treatment is necessary.

In patients with stage I, II, or III disease, local treatment is appropriate in the form of infrared coagulation, local injection, or "rubber banding." Stage I and II hemorrhoids are effectively treated by any of these modalities, with resolution of symptoms in at least 90% of patients. Cryotherapy should be avoided because of excessive posttreatment symptoms. Stage III disease is probably best treated by hemorrhoidal banding to remove redundant tissue, but long-term resolution of symptoms is likely in only 70% of these patients. Stage IV disease requires surgical intervention, which is associated with long-term resolution of symptoms in 95% of patients. The term "laser hemorrhoidectomy" refers to excision of hemorrhoidal tissues using a laser rather than standard surgical instruments. Nonetheless, it is a surgical procedure.

Symptoms may also arise from residual hemorrhoidal tissue after an episode of acute thrombosis of external hemorrhoids. These external anal tags may prevent proper cleansing and can be excised during an office procedure if symptoms warrant.

Risks

The risks of hemorrhoidal disease are continued symptoms, anemia-producing bleeding, and thrombosed hemorrhoids that undergo necrosis. Risks of treatment include bleeding and infection. The risk of bleeding after local therapy is approximately 1%. The risk of infection after local treatment is unknown but is certainly less than 1%. Local pain is a common side effect of local treatment. Pain after banding and injection typically lasts 24 to 36 hours, and continued pain requires medical attention. Excessive pain after treatment is due to sphincter spasm and may render urination difficult. Urinary retention is an occasional symptom of occult sepsis.

Bleeding and infection are greater risks after open hemorrhoidectomy, but they occur less than 5% of the time. Pain after open hemorrhoidectomy is significant and generally requires narcotics for relief. The fear of a bowel movement because of pain may lead to fecal impaction in a few patients. Comorbid conditions such as diabetes, human immunodeficiency virus, and heart disease increase the risks of local treatment but do not alter the type of complications. There may be subtle changes in continence of gas or liquid stool following local treatment or surgery, but they are rarely socially significant. Injury to the anal sphincter muscle is a recognized risk, but is extremely rare in experienced hands. Anal incontinence is a rare complication of surgery for hemorrhoidal disease.

Expected Outcomes

Following local treatment, symptoms of local protrusion and bleeding should be eradicated. The risk of recurrent symptoms following local treatment varies with the extent of local disease, with a 10% recurrence rate for stage I and II disease, and a 30% rate for stage III disease. Hemorrhoidectomy carries a 5% risk of recurrent symptoms.

Most hemorrhoidal disease can be treated in the office. Surgical hemorrhoidectomies can generally be carried out under local anesthesia with sedation. A brief stay in the hospital may be necessary for pain control, depending on the patient's pain threshold.

Symptoms following local treatment are minimal after 24 to 48 hours, with patient activity limited only by discomfort. After surgical hemorrhoidectomy, pain may persist for 2 weeks, with activity again permitted by the level of comfort.

Qualifications for Performing Surgery for Hemorrhoids

The qualifications of a surgeon to perform any operative procedure should be based on education, training, experience, and outcomes. At a minimum, the surgical treatment of hemorrhoids should be carried out by surgeons who are certified or eligible for certification by the American Board of Surgery, the American Board of Colon and Rectal Surgery, the Royal College of Physicians and Surgeons of Canada, or their equivalent.

SUGGESTED READINGS

Cheetham MJ, Phillips RK. Evidence-based practice in haemorrhoidectomy. Colorectal Dis 2001;3:126–134.

Smyth EF, Baker RP, Wilken BJ, Hartley JE, White TJ, Monson JR. Stapled versus excision haemorrhoidectomy: Long-term follow up of a randomised controlled trial. Lancet 2003; 361:1437–1438.

Sardinha TC, Corman ML. Hemorrhoids. Surg Clin North Am 2002;82:1153–1167.

Wilson MS, Pope V, Doran HE, Fearn SJ, Brough WA. Objective comparison of stapled anopexy and open hemorrhoidectomy: A randomized, controlled trial. Dis Colon Rectum 2002;45: 1437–1444.

Senagore AJ. Surgical management of hemorrhoids. J Gastrointest Surg 2002;6:295–298.

KEY WORDS: Patient, guideline, hemorrhoids, hemorrhoidectomy, banding, infrared coagulation, anoscopy, colonoscopy, pain, skin tags

Treatment of Perineal Suppurative Processes

These Guidelines have been written by the Patient Care Committee of The Society for Surgery of the Alimentary Tract (SSAT). Their goal is to guide physicians to the appropriate utilization of surgical procedures on the alimentary tract or related organs. They are based on a critical review of the literature and expert opinion. Together these sources of information result in a consensus that is recorded in the form of these Guidelines. The consensus addresses the *range* of acceptable clinical practice and should not be construed as a standard of care. These Guidelines will require periodic revision to ensure that clinicians use procedures appropriately, but the reader must realize that clinical judgment may justify a course of action outside of the recommendations contained herein. If you would like to ask a medical question, please use the SSAT Directory to find an SSAT physician in your area. (J GASTROINTEST SURG 2005;9:457–459)

Introduction

Suppurative processes in the perineum and surrounding areas can be a frightening, if not dangerous, situation for patients and a challenge for their physicians. Abscesses, fistulas, and chronic inflammatory conditions such as pilonidal cysts, hidradenitis suppurativa, and pruritis ani are the most common of these maladies and will be addressed in these guidelines.

Clinical Presentation

Most anorectal infections originate in the cryptoglandular area located in the anal canal at the level of the dentate line. Abscesses within these glands can then penetrate the surrounding anal sphincter and track in a variety of directions. This leads to larger abscesses within the perianal, intersphincteric, ischiorectal, and supralevator spaces. A small number of anorectal abscesses have a noncryptoglandular etiology such as Crohn's disease, atypical infection (e.g., tuberculosis, lymphogranuloma venereum), malignancy, or trauma. Particularly virulent organisms, immunologic deficiency in the patient (e.g., poorly controlled diabetes, human immunodeficiency virus), or localized scarring from previous operations can make the diagnosis more challenging. Fever, rigors, and shock may occur before more subtle localized findings. Pain and swelling are the most frequent complaints. Bleeding and purulent discharge may also be present. A perianal abscess is usually evident at the anal verge. An inflammatory process in the soft tissues of the buttock would more commonly indicate a perirectal abscess. Pelvic pain and dysuria may herald a supralevator abscess.

The majority of patients with a fistula-in-ano have a history of abscess development with persistent drainage, pain, and possibly bleeding. The external opening on the skin is evident, and digital rectal examination, anoscopy, or proctoscopy may reveal an indurated area in the anal canal corresponding to the internal opening. Anal fistulas are categorized according to their relationship with the anal sphincter complex. The majority of these fistulas are intersphincteric and about one fourth are transphincteric. If there is any suspicion of an underlying disease such as Crohn's disease or immune suppression, this should be thoroughly evaluated prior to the formal treatment of the fistula.

Pilonidal cysts initially present as an abscess and/or cellulitis in the sacrococcygeal area. Spontaneous drainage often occurs followed by chronic drainage from secondary sinuses. Some of these may track toward the anus, potentially being confused with a fistula-in-ano or hidradenitis suppurativa. The latter is a chronic suppurative disease of the dermal apocrine sweat glands. Consequently, it can occur in the perineal/perianal region, in the areolar area of the breasts, and quite frequently in the axillae. It is most commonly seen in the second through fourth decades of life and is thought to be hormonally influenced.

In primary pruritis ani, impaired sphincter function predisposes this area to moisture and inflammatory fecal elements from such dietary elements as caffeinated and acidic dietary products. Excessive cleansing or poor hygiene will also initiate an irritative process. Intertrigo, a mixed bacterial infection associated with obesity, may also be involved. Pinworms should be considered in children and exposed adults. Pruritis vulvae, resulting from urinary incontinence or vaginal discharge, may spread to the perianal region, and mycotic infections should also be considered in the differential diagnosis.

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.05.005

Treatment

Anorectal pain that prevents a digital examination necessitates an examination under anesthesia. Needle aspiration can demonstrate a collection of pus that is accessible to percutaneous drainage. As with any abscess, incision and drainage is the definitive form of therapy. Antibiotics should also be considered when there is significant cellulitis surrounding the abscess or when the patient is immunocompromised or has cardiac valvular pathology. Perianal and ischiorectal abscesses can usually be drained using local anesthesia, if they have tracked to the subcutaneous area. A cruciate incision or an elliptical excision of skin overlying the area of fluctuance is recommended to avoid premature closure of the drainage site during the period of resolution. The surgical incision should be as close to the anal verge as possible, so as to minimize the length of a potential fistula. If the abscess cavity is large, and the procedure is being performed under general anesthesia, digital exploration should be performed to break up any loculations. Packing of the wound is only necessary for initial hemostasis. Adequate drainage, followed by frequent sitz/tub baths, especially after bowel movements, will reduce the risk of continued infection and recurrence. If there is palpable crepitus, a Gram stain of the tissue/fluid can be helpful in identifying clostridia.

Established operative goals for an anal fistula are to open the tract and remove the epithelial lining by curettage, electrocautery, or other means. There has been some success with the use of fibrin glue for these fistulas. Several methods of determining the configuration of a fistula are possible. Any resistance to the passage of a probe should be avoided so as to prevent the creation of false passages. If the internal opening is not evident, injection of dilute methylene blue dye, milk, or hydrogen peroxide into the external opening with an angiocatheter may facilitate its visualization. Judicious unroofing of the observable tract may also allow better recognition of the entire tract. Preoperative transanal ultrasound imaging and fistulography are useful diagnostic modalities to be considered. If little or no external sphincter muscle is involved, the external opening and skin overlying the tract may be excised. When more than half of the external sphincter muscle is involved, or in the patient where sphincter integrity is already at risk, a seton can be applied. In this setting, after the skin and involved internal sphincter are opened, a strip of material is inserted around the overlying external sphincter component and tied snugly. Setons can be fashioned from silk sutures, vessel loops, or Penrose drains. During the 1 to 2 months following the operation, the seton will erode into the muscle and cause an inflammatory response, which prevents significant retraction of the sphincter ends. Either the seton will completely erode through, or the remaining smaller amount of external sphincter can then be transected. A newer alternative, after the seton stabilization period, is the installation of fibrin glue into the tract after the internal opening is closed with a suture.

Treatment in the acute phase of a pilonidal cyst/abscess involves simple incision and drainage. Antibiotics are used if there is significant cellulitis. Any septations should also be disrupted. Because hair and particulate matter are often found within the cavity/sinuses, the use of depilatory cream in the sacral area should be considered to lower the risk of recurrence. The development of chronic sinuses will require further operative intervention for removal.

For hidradenitis suppurativa, unless there are abscesses that need operative drainage, local symptomatic therapy and antibiotics for the cellulitis are initially adequate. Unfortunately, chronicity is common, and the drainage and pain can be debilitating. Because the etiology involves the epidermal sweat glands, the only definitive treatment is the excision of involved tissue. Wound healing by secondary intention is frequently chosen, but very large areas may need coverage with tissue transfers from surrounding areas. In order to optimize the healing of complicated wound closures, a temporary diverting colostomy should be considered.

With pruritis ani, patient education, reassurance, and close follow-up are imperative. The goal is to attain clean, dry, intact skin. Overzealous cleansing, scratching, and colored or perfumed toilet papers should be avoided. Secondary pruritis ani can result from anatomic pathology of the anorectum such as fistulas, fissures, and hemorrhoids. Infectious processes, radiation damage, and neoplasms can also be responsible.

Risks

The potential effect on continence is an important consideration in the treatment of any anorectal suppurative condition. Incision and drainage should be completed with as little damage to the sphincter musculature as possible. The risks of fecal incontinence and possible recurrence of the suppurative process should be discussed with the patient before any operative intervention on the anorectum.

Because of the significant risk for chronic morbidity following an anal fistulotomy in patients with Crohn's disease, observation alone should always be considered with asymptomatic fistulas. An interventional alternative is placement of a seton to drain the tract(s) and prevent abscess formation. When treating chronic hidradenits, as with any nonhealing lesion, a malignant process should be ruled out by biopsy.

Topical steroids compromise normal skin resistance to trauma and infection. Although topical anesthetic agents provide temporary comfort, they are often sensitizing and can worsen irritation and inflammation. Pruritis ani is usually symmetrical around the anus. Persistent, unilateral lesions should always be biopsied to rule out a malignant process.

Qualifications for Performing Surgery on Perineal Suppurative Processes

The qualifications of a surgeon to perform any operative procedure should be based on education, training, experience, and outcomes. At a minimum, the surgical treatment of perineal suppurative processes should be carried out by surgeons who are certified or eligible for certification by the American Board of Surgery, the American Board of Colorectal Surgery, the Royal College of Physicians and Surgeons of Canada, or their equivalent.

SUGGESTED READINGS

Vasilevsky C-A. Fistula-in-ano and abscess. In Beck D, Wexner S, eds. Fundamentals of Anorectal Surgery, 2nd ed. Philadelphia: WB Saunders, 1998, pp 153–173.

Karulf R, Perry WB. Pilonidal disease. In Beck D, Wexner S, eds. Fundamentals of Anorectal Surgery, 2nd ed. Philadelphia: WB Saunders, 1998, pp 225–232.

Waters GS, Nelson H. Perianal hidradenitis suppurativa. In Beck D, Wexner S, eds. Fundamentals of Anorectal Surgery, 2nd ed. Philadelphia: WB Saunders, 1998, pp 233–236.

Church JM, Fazio VW, Lavery IC, et al. The differential diagnosis and comorbidity of hidradenitis suppurativa and Crohn's disease. Int J Colorectal Dis 1993;8:117–119.

Corman M. Anorectal abscess and anal fistula. In Corman M, ed. Colon and Rectal Surgery, 4th ed. Philadelphia: Lippincott-Raven, 1998, pp 224–271.

Gordon PH. Anorectal abscesses and fistula-in-ano. In Gordon PH, Nivatvongs S, eds. Principles and Practice of Surgery for the Colon, Rectum, and Anus, 2nd ed. St. Louis: Quality Medical Publishing, 1999, pp 241–286.

Nivatvongs S. Pilonidal disease. In Gordon PH, Nivatvongs S, eds. Principles and Practice of Surgery for the Colon, Rectum, and Anus, 2nd ed. St. Louis: Quality Medical Publishing, 1999, pp 287–301.

Smith LE. Perianal dermatologic disease. In Gordon PH, Nivatvongs S, eds. Principles and Practice of Surgery for the Colon, Rectum, and Anus. St. Louis: Quality Medical Publishing, 1992, pp 281–300.

Friend WG, Pruritus ani. In Fazio V, ed. Current Therapy in Colon and Rectal Surgery. Toronto: BC Decker, 1990 pp 42–45.

KEY WORDS: Perianal abscess, perirectal abscess, fistula-in-ano, Crohn's disease, anorectal abscess, hidradenitis suppurativa