Right Hepatic Artery Injury Associated With Laparoscopic Bile Duct Injury: Incidence, Mechanism, and Consequences

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Because most bile duct injuries involve the common hepatic duct, the right hepatic artery, which is nearby, can also be injured. Reports on the frequency and significance of right hepatic artery injury (RHAI) associated with bile duct injury are sparse but suggest that RHAI increases mortality and decreases the success of the biliary repair. We studied the incidence, mechanism, and consequences of RHAI accompanying major bile duct injury. A total of 261 laparoscopic bile duct injuries were analyzed. Distribution was as follows: class I, 6%; class II, 22%; class III, 61%; and class IV, 11%. RHAI was present in 84 cases (32%): class I, 6%; class II, 17%; class III, 35% ($P < 0.04$ vs. class I/II); and class IV, 64% ($P < 0.007$ vs. class I/II/III). RHAI was more commonly associated with abscess, bleeding, hemobilia, right hepatic lobe ischemia, and subsequent hepatectomy (54% with RHAI vs. 11% without RHAI; $P < 0.0001$). RHAI had no influence on the success of the bile duct injury repair or on the mortality rate. Complications occurred more often with RHAI among cases repaired by the primary surgeon (41% RHAI vs. 2% no RHAI; $P < 0.0001$) but not among repairs by a biliary surgeon (3% RHAI vs. 2% no RHAI, P = NS; $P < 0.0001$ primary vs. biliary surgeon). RHAI increased morbidity, and occurred more often with class III and IV injuries reflecting the mechanisms of these injuries. RHAI did not increase the mortality rate or alter the success of biliary repair. Among biliary injuries repaired by the primary surgeon, RHAI was associated with a higher incidence of postoperative abscess, bleeding, hemobilia, hepatic ischemia, and the need for hepatic resection. A similar increase in the complication rate was not seen in patients treated by a biliary specialist. (J GASTROINTEST SURG 2004;8:523–531)

KEY WORDS: Hepatic arterial injury, bile duct injury, laparoscopic, biliary, cholecystectomy

The incidence of hepatic artery injury in association with bile duct injury is difficult to ascertain. Few reports on biliary injury mention the subject.[1–14] Although there are no data on comparative frequency, we suspect that right hepatic artery injury (RHAI) may be more common with bile duct injury complicating laparoscopic in comparison to open cholecystectomy because mechanisms of laparoscopic bile duct injury may facilitate RHAI. The most common type of bile duct injury involves resection of the central portion of the common duct.[1,2,4] Because the right hepatic artery lies behind the common hepatic duct, the usual level of transection, the right hepatic artery is more vulnerable in such cases. Similar conditions also exist with class IV injuries (isolated injuries to the right hepatic ducts), especially in instances where the right hepatic duct has been mistaken for the cystic duct.

The consequences of RHAI have not been clearly delineated. Several articles, consisting of small series and case reports, suggest that associated arterial injury decreases the success of the bile duct repair and increases the frequency of hepatic abscess formation, the

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need for hepatectomy, and the mortality rate,[7–19] although one larger series[6] mentions the presence of associated RHAI but not any associated consequences. Complications associated with RHAI could occur after the index cholecystectomy or after attempted repair of the bile duct injury. The available reports on this subject do not address the timing of complications or whether the conduct of the operation or level of expertise of the surgeon performing the repair influences the frequency of these complications. We examined the incidence, mechanisms, and consequences of RHAI accompanying major bile duct injury in a large series of laparoscopic bile duct injuries. We also examined the influence of surgeon's expertise on complications after biliary repair among cases of bile duct injury with and without associated RHAI.

METHODS

We analyzed 261 cases of major bile duct injuries referred for evaluation after laparoscopic cholecystectomy with respect to concomitant RHAI. Operative records, clinical notes, radiology reports, operative and postoperative x-ray films, and 22 unedited videotapes of laparoscopic cholecystectomies with bile duct injuries were analyzed. The following criteria were used as evidence of RHAI: right hepatic artery ligation or clipping noted during the initial cholecystectomy or a subsequent operation; identification of right hepatic artery ligation during a biliary repair (Fig. 1) or videotape review; hepatic angiography demonstrating RHAI; or nonenhancement of the right hepatic lobe during the arterial phase of a contrast CT scan. In the absence of one of these findings, the artery was assumed to be intact.

The bile duct injuries were sorted according to the Stewart-Way classification (Fig. 2), which groups the injuries according to anatomic pattern and causation (Table 1). The relationship between RHAI and class was calculated. Comparisons were made between patients with and without RHAI with regard to the following: abscess formation; intra- and postoperative bleeding; hemobilia; right hepatic lobe ischemia; need for hepatectomy; success of bile duct injury repair; and mortality rate. Comparisons were drawn between patients with and without RHAI repaired by the primary surgeon or a specialist biliary surgeon.

The influence of RHAI on injury propagation was also examined. Comparisons were made between the injury level following laparoscopic cholecystectomy (common bile duct/common hepatic duct, bifurcation, hepatic ducts, segmental ducts, or hepatic necrosis) and the level following successful biliary repair. Injuries that advanced to a more proximal level (e.g., from common hepatic duct to bifurcation) during biliary repair(s) were considered to demonstrate injury propagation.

There were 203 women and 58 men, whose average age was 47 years (range 18 to 86 years). The

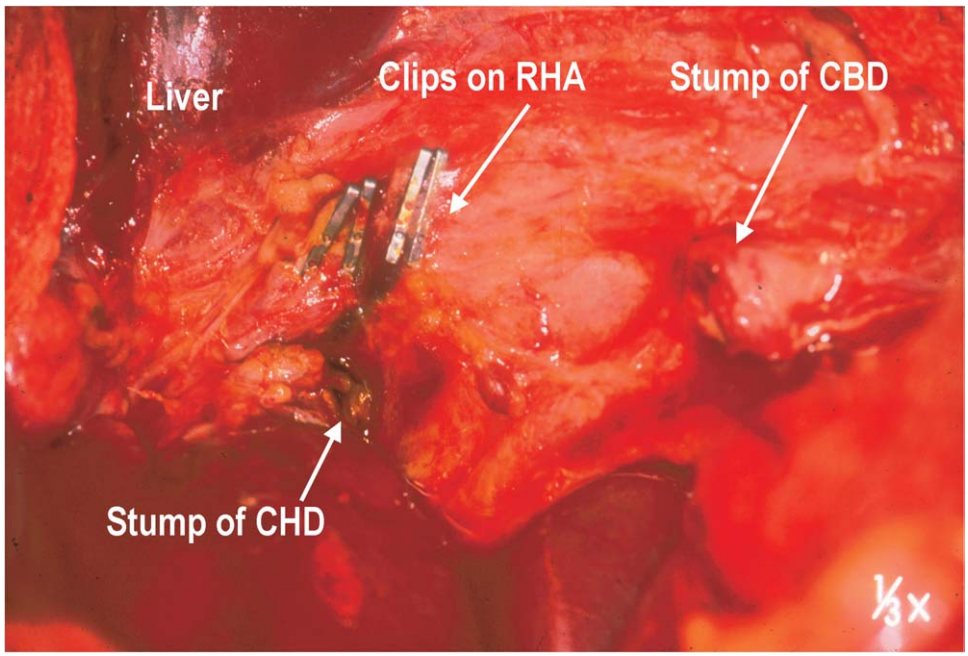

Fig. 1. Operative photograph of a class III bile duct injury demonstrating clips on the right hepatic artery (*RHA*). CHD = common hepatic duct; CBD = common bile duct.

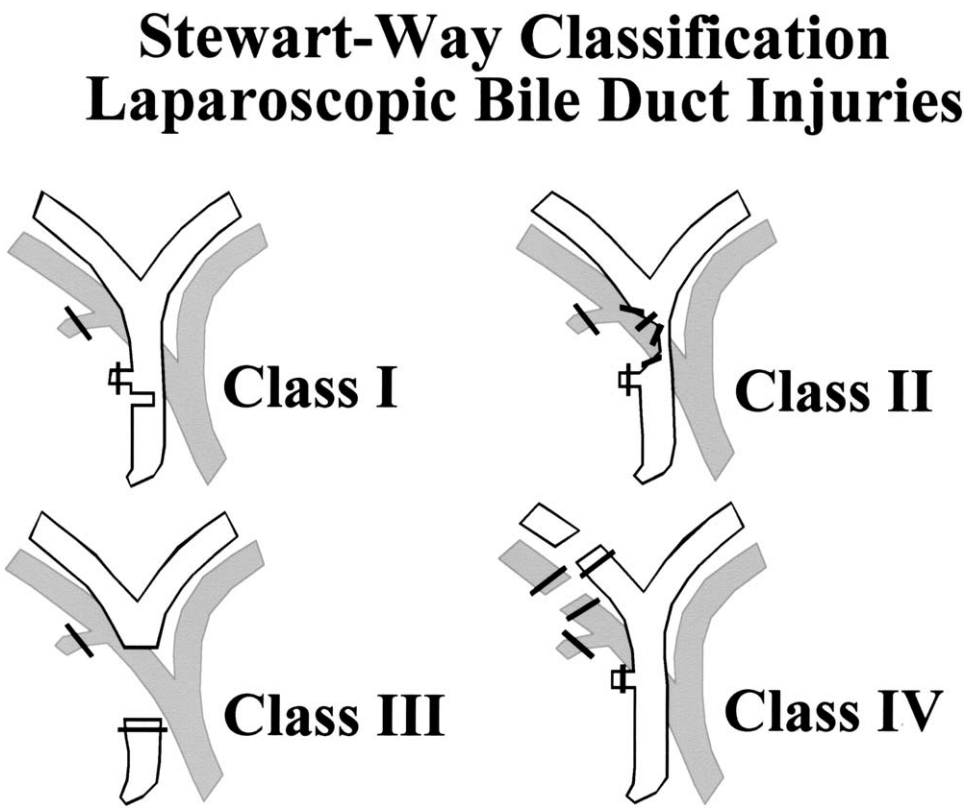

Fig. 2. Stewart-Way classification of laparoscopic bile duct injuries. The mechanisms of injury are listed in Table 1.

preoperative diagnosis was chronic cholecystitis in 176 patients, acute cholecystitis in 78 patients, gallstone pancreatitis in five patients, cholangitis in one patient, and one injury occurred as a complication of a fundoplication for gastroesophageal reflux.

Statistical Analysis

Statistical analysis was performed using the chi-square test or Fisher's exact test for variables on a nominal scale (rates and proportions).

RESULTS

The distribution of injuries was as follows: 17 class I (6%); 58 class II (22%); 158 class III (61%); and 28 class IV (11%). RHAI, which was present in 84 cases (32%), was distributed as follows: class I, 6%; class II, 17%; class III, 35% ($P < 0.04$ vs. class I/II, χ^2); and class IV, 64% ($P < 0.004$ vs. class I, II, or III, χ^2) (Table 2). RHAI occurred during the initial laparoscopic cholecystectomy in 78 patients and during a repair of a bile duct injury in five patients (treated by the primary surgeon). These last five patients presented with hemobilia and are discussed below. RHAI was more common with proximal bile duct injuries (Table 3).

Complications Associated With Right Hepatic Artery Injury

RHAI was more commonly associated with intraoperative bleeding, postoperative bleeding, hemobilia, abdominal and hepatic abscess formation, right

Table 1. Mechanism of laparoscopic bile duct injuries

Stewart-Way class	Mechanism of bile duct injury
I	CBD mistaken for cystic duct, but recognized Cholangiogram incision in cystic duct extended into CBD
II	Lateral damage to the CHD from cautery or clips placed on duct Often associated bleeding, poor visibility
III	CBD mistaken for cystic duct, not recognized CBD, CHD, or right or left hepatic ducts transected and/or resected
IV	RHD mistaken for cystic duct, RHA mistaken for cystic artery RHD and RHA transected Lateral damage to the RHD from cautery or clips placed on duct

CBD = common bile duct; CHD = common hepatic duct; RHD = right hepatic duct; RHA = right hepatic artery.

Table 2. Incidence of right hepatic artery injury by Stewart-Way class of bile duct injury

Class	Bile duct injury	RHAI
I	17 (6%)	1 (6%)
II	58 (22%)	10 (17%)
III	158 (61%)	55 (35%)*
IV	28 (11%)	18 (64%)†
Total	261 (100%)	84 (32%)

RHAI = right hepatic artery injury.
*$P < 0.035$ vs. class I or II (χ^2).
†$P < 0.0001$ vs. class I or II, and $P = 0.006$ vs. class III (X^2).

hepatic lobe ischemia, and subsequent need for hepatectomy. Of the 84 patients with RHAI, 45 (54%) had one or more of these complications compared with 20 (11%) among 177 patients without RHAI ($P < 0.0001$; χ^2) (Table 4). Among the 84 patients with RHAI, these complications occurred after the initial laparoscopic cholecystectomy in 35 patients (42%) and in association with the biliary reconstruction in 25 patients.

Bleeding. Intraoperative bleeding occurred in 35 patients (13%); in 69% of them the bleeding was associated with RHAI. Intraoperative bleeding occurred in 24 (32%) of 84 patients with RHAI and in 11 (7%) of 177 patients without RHAI ($P < 0.0001$ (χ^2). Postoperative bleeding (including hemobilia) occurred in 18 patients (7%); 94% of these 18 patients had RHAI. Postoperative bleeding occurred in 17 (20%) of 84 patients with and in 1 (0.6%) of 177 patients without RHAI ($P < 0.0001$ (χ^2).

Hemobilia. Seven patients, all of whom had RHAI, presented with hemobilia: two following the initial laparoscopic cholecystectomy and five following an attempted repair of the bile duct injury by the primary surgeon. The manifestations were hypotension, gastrointestinal bleeding, and large (4 to 19 units) amounts of blood loss. Five patients had class III and two had class IV injuries. The two who presented after the index cholecystectomy were treated with blood transfusion (average 4 units), and their conditions stabilized. Angiography demonstrated the RHAI. The five patients with hemobilia after biliary repair had massive hemorrhage requiring more aggressive treatment: two died, one before any kind of intervention could be performed and the other after an exploratory laparotomy during which the site of bleeding could not be found. Autopsies in these cases revealed blood in the Roux-en-Y limb. Two patients underwent emergency exploratory operations and ligation of the right hepatic artery. One patient was treated with angiographic embolization. These patients received an average of 13 units of blood (range 5 to 19 units) during resuscitation.

Table 3. Incidence of right hepatic artery injury by level of bile duct injury

Level bile duct injury	Bile duct injury	RHAI
CBD/CHD	161 (61%)	29 (18%)
Bifurcation	39 (15%)	16 (41%)*
Hepatic ducts	25 (10%)	13 (52%)†
Segmental ducts	8 (3%)	8 (100%)‡
Isolated RHD injury	28 (11%)	18 (64%)§
Total	261 (100%)	84 (32%)

CBD = common bile duct; CHD = common hepatic duct; RHD = right hepatic duct; RHAI = right hepatic artery injury.
*$P = 0.004$ vs. CBD/CHD, X^2.
†$P < 0.0001$ vs. CBD/CHD, X^2.
‡$P < 0.04$ vs. hepatic ducts, bifurcation, or CBD/CHD, X^2.
§$P < 0.0001$ vs. CBD/CHD, $P = 0.084$ vs. bifurcation, X^2.

Table 4. Complications and right hepatic artery injury (RHAI)

	RHAI (N = 84)	No RHAI (N = 177)	*P* value (X^2)
Intraoperative bleeding	24 (29%)	11 (6%)	<0.0001
Postoperative bleeding	17 (20%)	1 (0.6%)	<0.0001
Hemobilia	7 (8%)	0	<0.0001
Abscess formation (any)	20 (24%)	6 (3%)	<0.0001
Hepatic abscess	12 (14%)	3 (2%)	<0.0001
Hepatic ischemia	9 (11%)	1 (0.6%)†	<0.0001
Need for hepatectomy	4 (5%)	0	0.005
Mortality rate	2 (2.4%)	1 (0.6%)	0.531
Total*	45 (54%)	20 (11%)	<0.0001

*Some patients had more than one complication.
†Patients with thrombosis of the posterior branch right portal vein following percutaneous transhepatic cholangiography.

Abscess Formation, Right Hepatic Ischemia, and Hepatectomy. Abscesses, which developed in 26 patients (10%), were located as follows: 15 hepatic; 12 abdominal; and one splenic. Seventy-seven percent occurred in conjunction with RHAI. Abscess formation occurred in 20 (24%) of 84 patients with RHAI and in 6 (3%) of 177 patients without RHAI ($P < 0.0001$, χ^2). Among the 15 patients with hepatic abscess, 80% had an occurrence in conjunction with RHAI. Hepatic abscesses formed in 12 (14%) of 84 patients with and in 3 (2%) of 177 patients without RHAI ($P < 0.0001$, χ^2).

Hepatic ischemia was present in 10 patients, nine with RHAI and one with injury to a branch of the portal vein during percutaneous transhepatic cholangiography. Hepatectomy was required in four cases (3 partial lobectomies and 1 right lobectomy); the other six patients (including the one with segmental portal vein injury) had associated hepatic abscesses.

Biliary Reconstruction

A total of 254 patients underwent 354 biliary repairs. Seven were treated nonoperatively. RHAI had no apparent influence on the success of the biliary repair irrespective of the experience of the surgeon performing the operation. One hundred forty-seven bile duct injuries were first repaired by the primary surgeon; 25 of these operations (17%) were successful. Six (15%) of 41 repairs in patients with RHAI were successful, whereas 19 (18%) of 106 repairs without RHAI were successful ($P = 0.817$, χ^2). One hundred eighty-eight biliary injuries were repaired (primarily in 96 cases; secondarily in 92 cases) by a specialist biliary surgeon. A total of 182 (94%) were successful after one operation, whereas six required a second repair. Fifty-eight (95%) of 61 repairs with associated RHAI were successful, whereas 124 (98%) of 127 repairs without associated RHAI were successful ($P = 0.624$, χ^2).

Complications Following Biliary Reconstruction

Among the 147 patients treated by the primary surgeon, 17 (41%) of the 41 patients with RHAI had postoperative complications: bleeding in eight patients, hemobilia in five patients, abdominal abscess in four patients, hepatic abscess in eight patients, and/or hepatic ischemia in four patients. Only 2 (2%) of the 106 patients without RHAI had any such problem ($P < 0.0001$, χ^2).

Complications following biliary reconstruction by a biliary surgeon were infrequent irrespective of right hepatic artery status. Among the 188 patients treated by a biliary surgeon, 2 (3%) of 61 patients with and 1 of 127 patients without RHAI had at least one of these postoperative complications ($P = 0.513$, χ^2). Thus postoperative complications among patients with RHAI were less frequent after repairs by a biliary surgeon (3%) compared with those done by the primary surgeon (41%) ($P < 0.0001$, χ^2) (Table 5).

Table 5. Postoperative complications following biliary reconstruction: Correlation with surgeon and RHAI

	Primary surgeon		Biliary surgeon	
	RHAI (N = 41)	No RHAI (N = 106)	RHAI (N = 61)	No RHAI (N = 127)
Bleeding	8 (20%)	0	2 (3%)	0
Hemobilia	5 (12%)	0	0	0
Abdominal abscess	3 (7%)	1 (1%)	0	0
Hepatic abscess	8 (20%)	1 (1%)	0	1 (2%)*
Hepatic ischemia	4 (10%)	0	0	1 (2%)*
Mortality	2 (5%)	0	0	1 (0.8%)
Total	17 (41%)†‡	2 (2%)	2 (3%)	2 (1.6%)

RHAI = right hepatic artery injury.
*Single case with thrombosis of posterior branch right portal vein following percutaneous transhepatic cholangiography.
†$P < 0.0001$ primary surgeon cases with vs. without RHAI, X^2.
‡$P < 0.0001$ primary surgeon cases with RHAI vs. biliary surgeon cases with RHAI, X^2.

Increase in Injury Severity and Right Hepatic Artery Injury

Because more than one biliary reconstruction was performed in many patients, the injury level often advanced proximally from one operation to the next. We evaluated the influence of RHAI on the increase in proximal extent of the bile duct injury between the initial injury and the subsequent successful reconstruction (Fig. 3). For injuries initially confined to the common bile duct or common hepatic duct, the incidence of RHAI was the same for patients with an increase in injury severity compared with those without. For injuries at or above the bifurcation of the common hepatic duct, 49% of those without injury propagation had RHAI, whereas 71% of those with injury propagation had RHAI ($P = 0.046$, Fisher exact test).

Mortality and Biliary Cirrhosis

There were three postoperative deaths. In two with associated RHAI, death resulted from hemobilia following a failed bile duct repair by the primary surgeon. The other occurred in an elderly patient without evidence of RHAI, who died of a myocardial infarction after a technically successful repair by a biliary surgeon (see Table 4). Three patients developed secondary biliary cirrhosis, two of whom had associated RHAI.

DISCUSSION

The incidence of RHAI during cholecystectomy is difficult to discern from the literature. Most reports on biliary reconstruction published before the laparoscopic era do not mention this complication, although there are a few useful observations. Chapman et al.,[6] for example, counted 18 (14%) hepatic artery injuries among 130 bile duct injuries. In an autopsy study, Halasz[20] found a hepatic arterial injury in 7% of persons who had undergone open cholecystectomies in the distant past. In a multi-institutional collection of 77,604 laparoscopic cholecystectomies, Deziel et al.[3] reported 44 cases (12%) of hepatic arterial injury

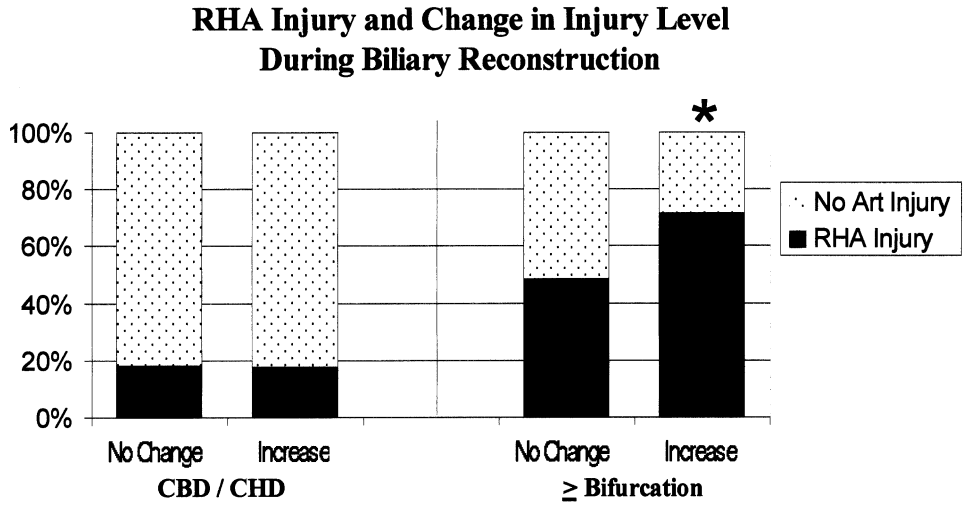

Fig. 3. Influence of RHAI on the change in the level of the bile duct injury from the initial injury (at laparoscopic cholecystectomy) to the level after successful biliary reconstruction. For injuries that initially involved the common bile duct (*CBD*) or common hepatic duct (*CHD*), RHAI had no effect. For injuries that were at or above the bifurcation, RHAI was associated with an increase in the subsequent injury level (*$P = 0.046$, injuries at or above the bifurcation, no change vs. increase, Fisher's exact test).

among 365 patients with major bile duct injuries. Davidoff et al.[4] thought that injury to the right hepatic artery was common in patients with class III injuries. Mathisen et al.[10] found RHAI among 24% of 32 bile duct injuries. Bachellier et al.[11] found 3 (20%) RHAI among 15 bile duct injuries.

There have been no systematic attempts to assess the consequences of RHAI. In the current study, 32% of patients with bile duct injury also had RHAI. If anything, the incidence of RHAI would be underestimated by our methods, for it is often impossible to determine the status of the right hepatic artery during operations to repair a bile duct injury, because the artery is often encased in inflammation resulting from tissue damage, bile collections, or infection.

RHAI is more common with class III (35%) and IV (64%) bile duct injuries compared with class I or II injuries (6% to 17%) as a consequence of the different injury mechanisms and patterns. During operations that result in class III or IV injuries, the right hepatic artery is in a position to be injured or, if the artery is seen, it may be misidentified as the cystic artery. During an operation that results in a class III injury, the common bile duct (mistaken for the cystic duct) is clipped and mobilized,[2] exposing the right hepatic artery, which lies behind the common hepatic duct. The surgeon is led to believe that the right hepatic artery is actually a posterior cystic artery, and it is often ligated based on that erroneous assumption. Factors that would influence the occurrence of RHAI include the level of the class III injury (more likely with higher injuries) and the point where the right hepatic artery crosses the common hepatic duct. We and others have noted an association between proximal bile duct injuries and RHAI.[1,2,13,14] Similar mechanisms could result in right hepatic artery with class IV injuries because of either deliberate ligation or injury during a dissection that is too close to the right hepatic duct. We recently published a detailed discussion of the mechanisms of bile duct injuries.[2]

Previous reports suggest that RHAI typically produces severe consequences.[12–19] For example, in one series of 49 bile duct injuries, the mortality rate was 38% with RHAI and 3% without.[14] Gupta et al.[12] reported that three of four patients with combined biliary and arterial injuries developed hepatic necrosis, and two of the four developed bile duct strictures. Several investigators[15–19] have said that right hepatic lobectomy may often be required as a consequence of RHAI.

Our data show that complications such as bleeding, hemobilia, abdominal and hepatic abscess formation, hepatic ischemia, and need for hepatectomy were more common among patients with RHAI compared with those without RHAI. Nevertheless, the incidence was lower (54%) than what might have been expected from the earlier studies cited above. For example, only 11% of our patients with RHAI developed hepatic ischemia, and only 5% required right hepatic resections. Furthermore, the mortality rate and incidence of biliary cirrhosis were unaffected by RHAI.

Hemobilia, which occurred in seven patients, deserves special mention. This complication can rapidly

become life-threatening and require massive blood transfusion.[21–30] Five cases of hemobilia followed biliary reconstructions by the primary surgeon, and two of these patients died. We suspect that the right hepatic artery had either been damaged at the original operation, and the healing process had been disrupted by the dissection performed in the second operation, or the artery had been injured during the repair. In either case it then bled into the new anastomosis. Hemobilia should be suspected whenever gastrointestinal hemorrhage follows cholecystectomy or a biliary reconstruction. Angiographic embolization is usually the best treatment.[23] Operative ligation accomplishes no more than embolization does, and it is much more difficult to perform.

Thirty-five percent of complications accompanying RHAI followed laparoscopic cholecystectomy, whereas 25% followed attempted biliary reconstruction. Bleeding, hemobilia, abdominal abscess, hepatic abscess, hepatic ischemia, and subsequent need for hepatectomy were more common (41%) among repairs by the primary surgeon but not those by a biliary surgeon. Among patients who underwent RHAI repair by a biliary surgeon, these complications were rare (3%). This suggests that something about how the operation is performed influences the risk of these complications.

Experimental studies provide relevant information. Even though the hepatic parenchymal blood supply comes predominantly from the portal circulation, and hepatic artery ligation is usually tolerated without clinical sequelae,[31–34] biliary obstruction in addition to RHAI injury may predispose to the development of hepatic necrosis. Doppman et al.[35] demonstrated hepatic necrosis and infarction in liver segments with biliary obstruction following hepatic artery embolization. Similarly, Yoshidome et al.[36] noted increased susceptibility to hepatic ischemia with obstructive jaundice. Okada[37] and Castro-e-Silva et al.[38,39] noted that hepatic artery occlusion in the setting of obstructive jaundice caused hepatic necrosis. These data may explain the development of hepatic ischemia, necrosis, and abscess formation in patients with persistent biliary obstruction.

Following RHAI, blood flow through the small vessels that supply the right hepatic duct could theoretically be compromised, although intrahepatic and hilar plate vessels provide collateral vessels.[7,9,33,34] Operations that disrupt the network of communications at the hilar plate would be expected to produce a relative ischemia to the bile duct and a greater risk of stricture formation. We noted an association between RHAI and propagation of proximal bile duct injuries (bifurcation or higher), but not for injuries initially confined to the common bile duct or common hepatic duct. Any contribution to stricture formation from RHAI is difficult to quantify, however, because RHAI is more common among high biliary injuries, and high biliary injuries are also more difficult to repair.

Although others have reported an association between RHAI and failure of the biliary repair,[8,12,13] we found no such association. Repairs by the primary surgeon were apparently not affected by RHAI, but the outcome was quite poor in either case. By contrast, the success rate achieved by biliary surgeons was high and similar with or without RHAI.

CONCLUSION

This large study has shown that RHAI occurred more often with class III and IV injuries, and less often with class I and II injuries. RHAI was more commonly associated with abscess formation, intraoperative bleeding, postoperative bleeding, hemobilia, right hepatic lobe ischemia, and subsequent need for hepatectomy. RHAI did not increase the mortality rate or decrease the success rate of the biliary repair, although it was associated with injury propagation in proximal bile duct injuries. Among patients treated by the primary surgeon, RHAI was associated with a higher incidence of postoperative abscess formation, bleeding, hemobilia, hepatic ischemia, and the need for hepatic resection. An increase in the complication rate was not seen in patients treated by a biliary specialist.

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Discussion

Dr. K. Lillemoe (Baltimore, MD): I would like to congratulate Drs. Stewart and Way for another major contribution to our understanding of this very significant problem. They have analyzed their database very nicely and have been able to detect an incidence of hepatic artery injury far higher than most of us have

seen reported. I would agree with Dr. Stewart that this number is probably an underestimate of what actually probably takes place.

If you go back to the first classic article out of Duke University and their excellent drawing describing this injury,[4] you can see the injury to the right hepatic artery being predicted. Although the injury doesn't bother us clinically, most patients, when you look at cholangiograms where there are 10 to 20 clips, you realize that there was probably some bleeding.

When you deal with these patients early on transfer to your institution, oftentimes with a bile leak, and you detect that there is ischemia of the liver, which is the result of likely a hepatic artery injury, how often have you been forced to intervene, such as debride or drain collections? Has this problem influenced your management and thus delayed your definitive repair? Have you noticed any difference based on the anatomic variant of a replaced right hepatic with these injuries?

I have one final question regarding the very dreaded complication of hemobilia. You stress the importance of arteriography and embolization, but after successful immediate control of the bleeding, do you think most of these patients require reexploration and a definitive procedure to deal with it? In a couple of these patients whom we have managed with arterial embolization, the embolization was temporizing but not a permanent, long-lasting, effect.

Dr. L. Stewart: Interestingly, hepatic ischemia was not really that common in this series; the incidence was only 11% among patients with right hepatic artery injury. The most common finding associated with it was hepatic abscess, which was generally successfully treated with percutaneous drainage. Regarding patients who present with biliary fistulas, which are the majority, you have to gain control of that biliary fistula with drainage, and that is our routine. The first thing we do is stabilize the patient, drain all of the abdominal bile collections, and any hepatic abscess would similarly be percutaneously drained. The goal is to get the patient well; after this we perform complete cholangiography of the biliary tree to plan reconstruction.

With regard to hemobilia, we believe that the proper thing to do is to proceed directly to angiography, and this is also the consensus in the literature. The primary surgeon or an emergency room physician treated the two patients with hemobilia who died in this series. In one patient, operative exploration was attempted and failed. The other patient did not make it to that point. I think the operating room is the wrong place to be.

Dr. Lillemoe asked if something should be done after hepatic embolization. I think you have to see how the patient does. In most situations nothing further is needed, but you have to follow the patient's course.

Your second question, regarding a replaced right hepatic artery, brings up an important point. We found that this could lead to a class II injury. During dissection in the triangle of Calot, this vessel can be injured and then clips applied leading to injury of the hepatic duct. We found that there were a number of patients with class II injuries that were associated with a replaced right hepatic artery.

Dr. D. Fromm (Detroit, MI): For a number of years people believed that the right hepatic artery could be ligated with impunity. This may be an erroneous concept. I am curious about the cases of hepatic necrosis that you observed. Were these patients hypotensive during the time of their operations when ligation of the right hepatic artery occurred?

If one recognizes that damage to the right hepatic artery occurred at the time of cholecystectomy, do you recommend reconstruction of the artery?

Dr. Stewart: With regard to hepatic necrosis, there were four patients who required hepatectomy in this series. Two of these cases were basically a direct result of the laparoscopic cholecystectomy; the patients had immediate hepatic necrosis, and as part of their initial resuscitation went on to hepatectomy. The other two cases actually occurred following repairs by the primary surgeon where the patients did not initially have hepatic necrosis; following repair, these patients then subsequently developed hepatic necrosis.

What is interesting is that there are animal studies in the literature that suggest if you ligate a segment of the biliary tree and then thrombose the right hepatic artery, the segment that you have ligated will develop hepatic necrosis. There are several very nice studies detailing this, and they are referenced in the manuscript. So it seems that in the setting of biliary obstruction, the liver is much more susceptible to ischemia with the loss of the hepatic artery perfusion, and I suspect that is the mechanism in these situations.

There is debate in the literature about whether repair of the right hepatic artery should be done, and we did not find evidence that this needs to be done based on the analysis of our data. However, if that is the situation, and it is straightforward, I do not see a downside to it, but I do not think it is absolutely necessary. We did not find that it significantly influenced the success of biliary reconstruction.

Central Pancreatectomy With Pancreaticogastrostomy for Benign Pancreatic Pathology

David T. Efron, M.D., Keith D. Lillemoe, M.D., John L. Cameron, M.D., Charles J. Yeo, M.D.

Benign lesions of the neck and proximal body of the pancreas pose an interesting surgical challenge. If the lesions are not amenable to simple enucleation, surgeons may be faced with the choice of performing a right-sided resection (pancreaticoduodenectomy) or a left-sided resection (distal pancreatectomy) to include the lesion, resulting in resection of a substantial amount of normal pancreatic parenchyma. Central pancreatic resection has been reported with Roux-en-Y pancreaticojejunostomy reconstruction; however, this interrupts small bowel continuity and obligates an additional anastomosis. We have reviewed our experience with central pancreatectomy with pancreaticogastrostomy (PG) for benign central pancreatic pathology. Between January 1999 and December 2002, 14 central pancreatectomies were performed with PG reconstruction. There were 7 women and 7 men with a mean age of 60.9 years. Five resections were performed for islet cell tumors, three were performed for noninvasive intraductal papillary mucinous neoplasms, two were performed for serous cystadenoma, and one each was performed for a simple cyst, pseudocyst, mucinous metaplasia, and focal chronic pancreatitis. Seven out of 14 patients experienced a total of 10 complications. Pancreatic fistulae manifested by drainage of amylase-rich fluid from the operatively placed drains developed in 5 patients (36%). Reoperation or interventional radiologic procedures were not required in any patient with a fistula. Postoperative follow-up demonstrated 13 out of 14 patients to be alive and well without evidence of pancreatic insufficiency. One patient died at home on postoperative day 57 of cardiac pathology. Central pancreatectomy with PG is a safe and effective procedure that allows for preservation of pancreatic endocrine and exocrine function without disruption of enteric continuity. The complication of pancreatic fistula was managed conservatively via maintenance of operatively placed drains. (J GASTROINTEST SURG 2004;8:532–538)

KEY WORDS: Benign pancreatic lesions, central pancreatectomy, pancreaticogastrostomy

Central pancreatectomy has recently been described by several authors as an alternative to distal pancreatectomy or pancreaticoduodenectomy for benign lesions of the neck or proximal body of the pancreas.[1–7] This procedure has the advantages of avoiding the morbidity and mortality associated with pancreaticoduodenectomy, preserving splenic function by avoiding the splenectomy that frequently accompanies distal pancreatectomy, and preserving maximal pancreatic endocrine and exocrine function. The vast majority of cases that have been reported in the literature describe pancreatic-enteric reconstruction of the left-sided pancreatic remnant using a Roux-en-Y limb of jejunum to construct a pancreaticojejunostomy (PJ).

Pancreaticogastrostomy (PG) was reported by Sherwin and Tripodi in a canine model[8] and used clinically by Waugh and Clagett as a means of implanting the pancreatic remnant into the gastrointestinal (GI) tract.[9] Numerous studies have reported the efficacy of PG as an alternative method of reconstruction after pancreaticoduodenectomy.[10–16] In the setting of central pancreatectomy, PG has the advantage of avoiding the disruption of enteric continuity necessary with Roux-en-Y reconstruction and obviating the need for the jejuno-jejunostomy required for

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Roux-en-Y reconstruction. Here we describe our experience with central pancreatectomy using PG for distal pancreatic reconstruction.

PATIENTS AND METHODS

Patients who underwent central pancreatic resection with PG reconstruction were identified from departmental and individual surgeon experience. A retrospective review of hospital records was undertaken. The study was approved by the Institutional Review Board for Human Research and complied with Health Insurance Portability and Accountability Act (HIPAA) regulations.

Between January 1999 and December 2002, 14 central pancreatectomies were performed with PG reconstruction. There were 7 women and 7 men with a mean age of 60.9 years (range 37–84 years). Lesions were identified most frequently by CT scan succeeded by magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound, and transabdominal ultrasound. Five resections were performed for islet cell tumors (three nonfunctional, two insulinomas), three were performed for noninvasive intraductal papillary mucinous neoplasms (two IPMN-adenoma, one borderline), two were performed for serous cystadenoma, and one each was performed for a simple cyst, pancreatic pseudocyst, mucinous metaplasia, and focal chronic pancreatitis (Table 1). Resected lesions exhibited an average diameter of 2.2 cm. Figure 1 demonstrates CT scans from 4 patients with lesions resected via central pancreatectomy. Though central pancreatectomy was considered possible for all patients preoperatively, the final decision to proceed was made intraoperatively after assessment of anatomy and pathology.

A midline abdominal incision is typically used. The abdomen is explored for synchronous pathology. The lesser sac is entered by dividing the gastrocolic ligament and the stomach is retracted in a cephalad manner. The pancreas is identified and the neck or proximal-body lesion is localized (Fig. 2). If there is any difficulty localizing the lesion, intraoperative ultrasound can be used to locate and define the pathology. The pancreas is elevated off the superior mesenteric vein-portal vein and divided proximally yielding an appropriate proximal margin free from the lesion. The pancreas is dissected out of the retroperitoneum and away from the splenic vein and artery leaving these vessels intact. The pancreas is then divided distal to the lesion, again insuring an appropriate negative margin. The specimen is sent to pathology for margin analysis (Fig. 3, inset).

If the margins are negative and the pathology is confirmed as benign, the proximal pancreatic stump is closed with horizontal mattress sutures. Care is taken to identify and specifically ligate the pancreatic duct. The distal pancreatic remnant is then anastomosed to the posterior wall of the stomach (Fig. 3). In 12 patients the PG anastomosis was constructed in two layers with an outer layer of 3-0 interrupted silk and an inner running layer of 3-0 vicryl. In 2 patients the anastomosis consisted of a single layer of interrupted silk sutures. No pancreatic duct stents were used in any of the patients. Closed suction silastic drains were operatively placed near the PG anastomosis and the pancreatic remnant. The number of drains

Table 1. Demographics, symptoms, and pathologic data

Patient	Sex	Age (yrs)	Symptoms	Pathologic diagnosis	Size (cm)
1	F	62	Light-headedness	Islet cell tumor, nonfunctional	1.1
2	M	50	Chronic pancreatitis	Simple cyst	3.5
3	M	65	Indicated during work-up of acute pancreatitis, nonresolving	Pseudocyst	4.0
4	F	77	Nonspecific abdominal pain	Mucinous metaplasia	1.5
5	M	84	Hypoglycemia	Insulinoma	1.5
6	F	51	Epigastric pain	Serous cystadenoma	3.5
7	F	56	Asymptomatic	Islet cell tumor, nonfunctional	2.2
8	F	72	Abdominal pain	IPMN-borderline	2.2
9	M	37	Hypoglycemia	Insulinoma	1.5
10	M	65	Recurrent pancreatitis	Focal chronic pancreatitis	3.0
11	F	63	Asymptomatic	Serous cystadenoma	2.2
12	M	52	Flank/back pain	IPMN-adenoma	2.5
13	F	70	Asymptomatic	IPMN-adenoma	1.4
14	M	48	Mild steatorrhea	Islet cell tumor, nonfunctional	0.8

IPMN = intraductal papillary mucinous neoplasm.

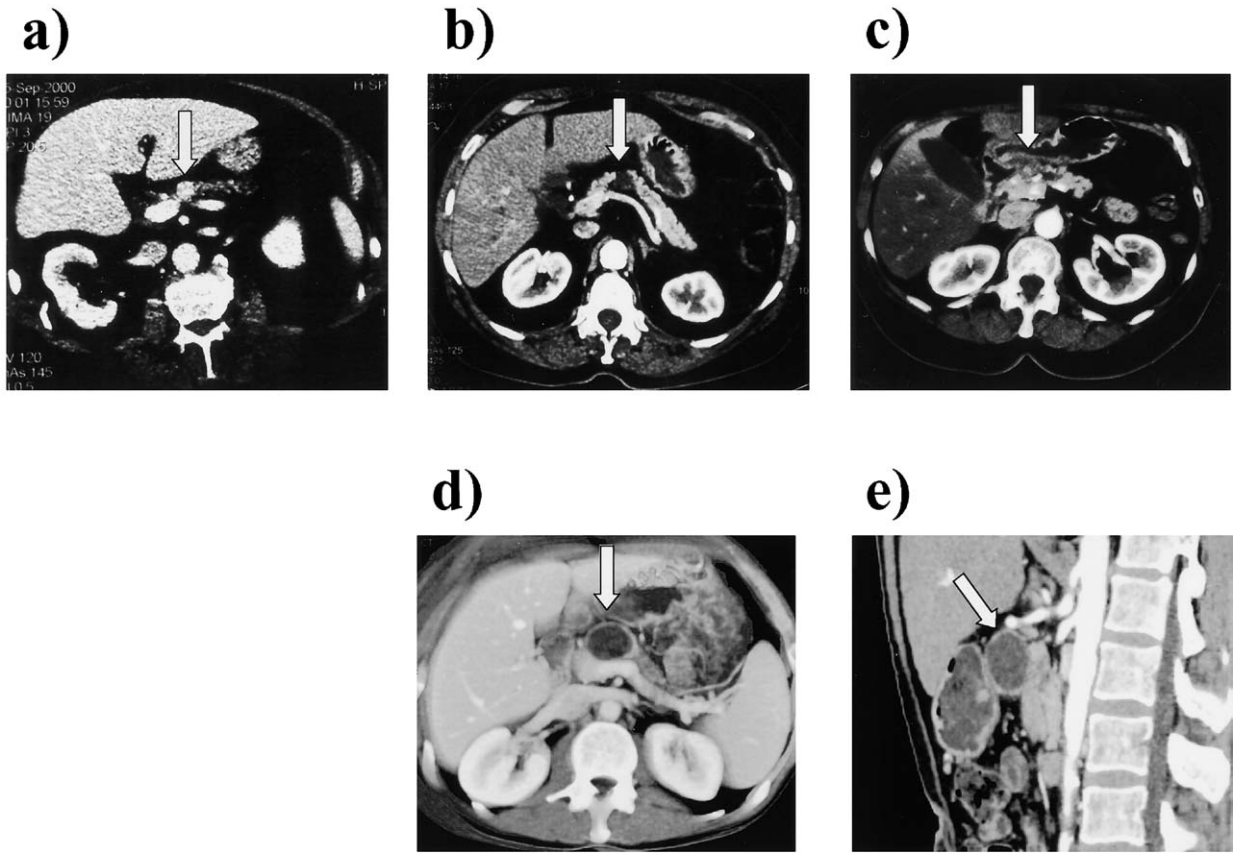

Fig. 1. CT scans demonstrating lesions resected via central pancreatectomy. (**A**) Hypervascular lesion in the neck of the pancreas; pathology: islet cell tumor. (**B**) Cystic lesion in the mid-body with dilated distal duct; pathology: IPMN. (**C**) Cystic lesion in the neck of the pancreas; pathology: serous cystadenoma. (**D**) axial and (**E**) coronal of a three-dimensional reconstruction CT scan of a cystic lesion of the pancreatic neck; pathology: simple cyst (*arrows* demonstrate lesions).

were placed at the discretion of the operating surgeon. The use of octreotide was also at the discretion of the individual surgeon and quite variable between patients. In recent years octreotide has not been used. Data are given as mean ± standard deviation.

RESULTS

The operative and hospital data are listed in Table 2. The mean operative time was 229 minutes with a mean estimated blood loss of 412 ml. Only 4 patients received red blood cell transfusion. An average of 2 peripancreatic drains were employed (range 1–4) for an average duration of 10.9 days (6.7 days for patients without fistula). The mean postoperative length of hospital stay was 11.1 days (9.9 days for patients without fistula).

Seven patients experienced a total of 10 complications (Table 3). Two patients returned to the operating room (OR). One patient with an upper GI bleed recognized on the night of surgery was taken back 6 hours postoperatively for suture ligation of a bleeding vessel at the PG. This was approached via an anterior gastrotomy. The second patient returned to the OR on postoperative day 17 for a mechanical small bowel obstruction that occurred as a result of acute herniation of bowel through the midline fascia at a site of fascial dehiscence.

One patient suffered a late postoperative upper GI bleed at the PG (identified on postoperative day 10. This patient had been anticoagulated for a prosthetic heart valve and the bleed was managed with transfusion, reversal of anticoagulation, and endoscopic cauterization. The patient was subsequently discharged, but died from complications of severe cardiac disease on postoperative day 57.

Postoperative pancreatic fistula developed in 5 patients. All fistulae were controlled by the operatively placed drains and required no further intervention. The development of a pancreatic fistula increased the length of hospital stay by 3.5 days (9.9–13.4 days).

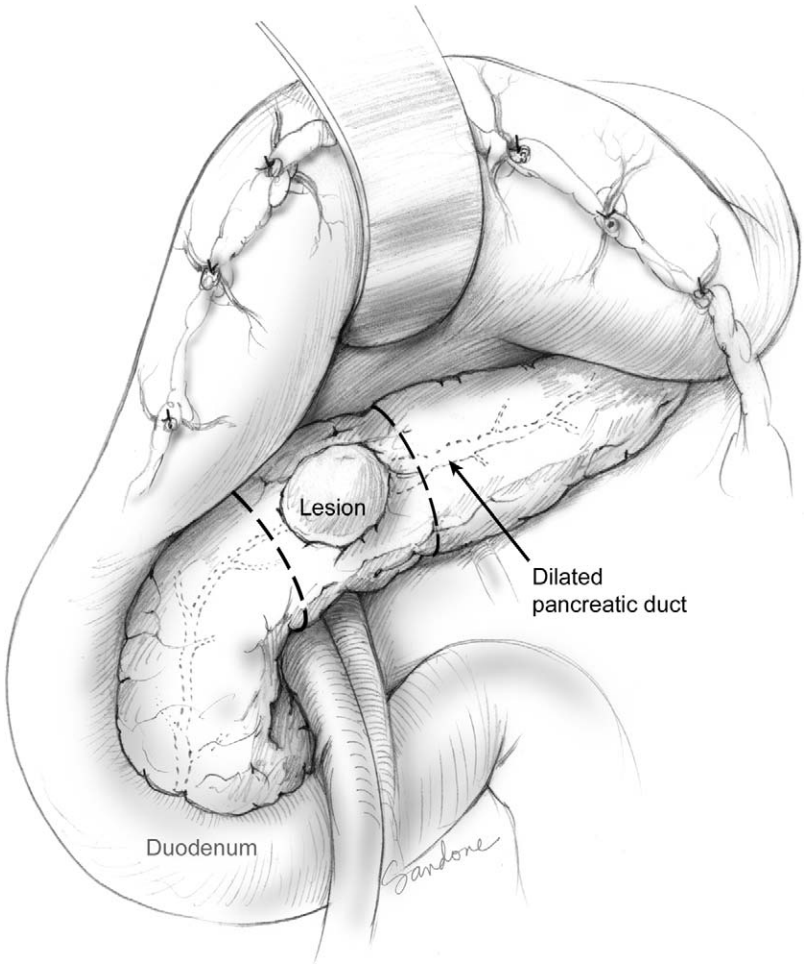

Fig. 2. A view of the pancreas with a benign cystic lesion in the neck and proximal body of the pancreas. The gastrocolic ligament has been divided and the stomach retracted in a cephalad manner. The *dashed lines* depict lines of parenchymal transection. A dilated pancreatic duct is illustrated distal to this benign cystic lesion.

All drains were removed and fistulae sealed by postoperative day 30. Only 1 patient experienced a persistent pancreatic leak after drain removal and this patient demonstrated closure of the leak with short duration of intravenous antibiotic, parenteral nutrition, and NPO (nothing by mouth) status.

Other complications included a urinary tract infection in 1 patient and a perioperative cerebrovascular accident in another patient. Postoperative follow-up of 12.3 (±12.5) months (range 1–42 months) demonstrated 13 out of 14 patients to be alive and well without evidence of pancreatic endocrine or exocrine insufficiency. At the time of the last follow-up, none of the patients were taking exogenous pancreatic supplements and none of the patients were rendered diabetic by this procedure.

DISCUSSION

Previous reported series of central pancreatectomy have largely described reconstruction featuring anastomosis of the distal pancreatic remnant to a Roux-en-Y jejunal limb. Between 1995 and 2000 four series from single institutions[1,3,4,5] reported patients who underwent central pancreatic resection for various benign lesions. These series ranged from 10–24 patients and were reconstructed using a Roux-en-Y PJ. Overall complication rates in these series ranged from 13%–40% with no perioperative mortality. In the largest series of central pancreatectomy, Sauvanet and the members of the French Pancreas Club retrospectively reported a multi-institutional collection of 53 central resections, 26 of which were reconstructed via a Roux-en-Y PJ and 25 of which underwent PG

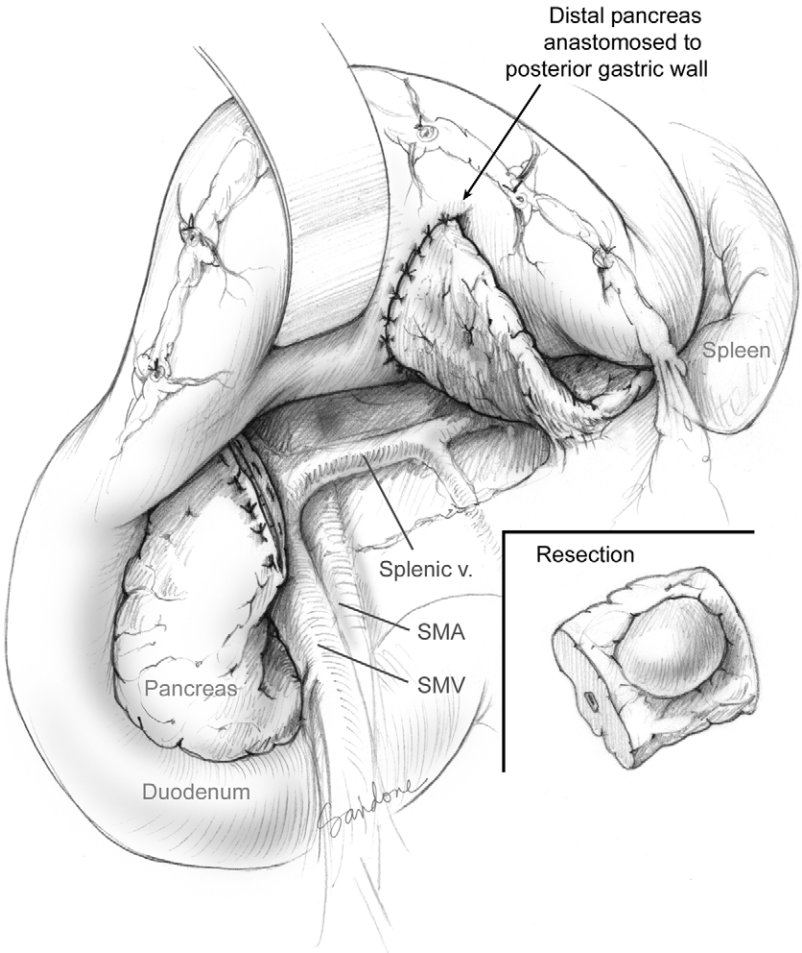

Fig. 3. A view of the completed pancreaticogastrostomy (PG) and oversewn proximal pancreatic remnant. The inset depicts the specimen properly oriented and ready to be sent to pathology for diagnosis and margin assessment.

anastomosis (in the remaining 2 patients the pancreatic remnant was oversewn).[2] They reported no appreciable difference in postoperative course or complications, but felt that the PG was a technically easier operation as there was no need to construct the Roux loop. Their overall complication rate was 41% with 1 postoperative death (2%).

A number of studies have specifically examined the use of PG vs. PJ reconstruction of the distal pancreatic remnant after pancreaticoduodenectomy.[10–12] Both methods have been demonstrated to be safe and well

Table 2. Operative/hospital data

Mean operative time	229 minutes (±49)
Mean estimated blood loss	412 ml (±326)
Mean number of drains	2 (range 1–4)
Average drain duration	10.9 days (±8.5)
Without fistula	6.7 days (±1.5)
With fistula	18.6 days (±10.8)
Average length of postoperative hospital stay	11.1 days (±6.3)
Without fistula	9.9 days (±5.8)
With fistula	13.4 days (±7.0)

(mean ± standard deviation)

Table 3. Complications

Patients without complications	7 (50%)
Patients with complications	7 (50%)
Reoperations	2
Pancreatic fistula	5
Upper GI bleed	2
Small bowel obstruction	1
Cerebrovascular accident	1
Urinary tract infection	1

GI = gastrointestinal.

tolerated and there seem to be no considerable differences between PG and PJ both in perioperative complications and long-term outcome. Several authors have suggested that PG may be a superior method of pancreaticoenteric anastomosis after pancreaticoduodenectomy,[13–16] but this has not been supported by prospective randomized study.[10]

In the current retrospective review, endocrine function of the patient was not specifically assessed with oral glucose tolerance tests. Four series have reported the use of oral glucose tolerance testing to postoperatively assess endocrine function in patients after central pancreatectomy.[1–4] New onset diabetes after central pancreatectomy was reported as developing in only 4 out of 100 patients. Two of these patients were determined to have chronic pancreatitis or fibrosis on pathology, likely contributing to their glucose intolerance.[2,4] Diabetes after resection of an excessive amount of pancreatic parenchyma developed in 1 patient. The remaining patient who was rendered diabetic became so after conversion of the central resection to a pancreaticoduodenectomy as a result of a recurrence of an IPMN.[2] No patient in our series exhibited evidence of postoperative endocrine dysfunction, however, our follow-up is relatively short (mean = 12.3 months). Nonetheless, by preserving pancreatic parenchyma on both the right and left sides of the gland, it would be anticipated that central pancreatectomy would be accompanied by a lower risk of diabetes as compared with larger resections such as pancreaticoduodenectomy or distal pancreatectomy. Further, central pancreatectomy seems to be a better solution, when applicable, than distal pancreatectomy, because there is more preservation of both endocrine and exocrine function.

One potential disadvantage of PG after pancreaticoduodenectomy is the possible loss of exocrine function. Pessaux and associates recently demonstrated that even though the vast majority of PG anastomoses maintained patency (68%), evidence of exocrine insufficiency was seen in up to 95% of patients after pancreaticoduodenectomy with PG.[17] Yet, despite these findings, this does not seem to lead to substantial changes in postoperative physiology or quality of life.[18–20] Central pancreatectomy patients most likely preserve adequate exocrine function because the head and uncinate process are left intact with normal exocrine drainage.

By far the most challenging technical complication after pancreatic surgery remains the pancreatic fistula. It is well tolerated if adequately controlled and usually seals with conservative measures (NPO status, parenteral nutrition, octreotide). Pancreatic leaks after pancreaticoduodenectomy have been indicated to occur in 5%–30% of patients, varying based upon underlying pathology, pancreatic texture, and surgeon experience.[21] This is further complicated by the liberal interpretation of what constitutes a pancreatic fistula, as no standard definition has been universally accepted. Leak rates for distal pancreatectomy may also be as high as 25%.[22–24] Central pancreatectomy, by definition, retains both the oversewn proximal pancreatic remnant (right-sided gland) as well as a distal pancreaticoenteric anastomosis yielding two sources of pancreatic leakage. Fortunately, the risk of fistula does not seem to be strictly additive, but it is likely that leak rates for central pancreatectomy will always exceed rates for single-sided pancreatic resection. In the reported series of central pancreatectomy,[1–7] fistula rates ranged from a low of 4% to a high of 36%.

Upper GI bleeding developed in 2 patients in our series. In the first patient the bleed occurred immediately postoperatively and was controlled with return to the OR and suture ligation. This patient was 1 of 2 that underwent a single layer reconstruction via PG and was believed by the surgeon to have been a technical complication. The second patient demonstrated a delayed onset bleed (postoperative day 10) and carried the additional risk of requiring anticoagulation for a mechanical heart valve. Though difficult to draw meaningful conclusions given the small size of our series, previous studies of PG anastomoses do not predict a higher risk of GI bleed from this method of reconstruction.[10–12]

In this series, none of the patients underwent central resection without confirmation of benign pathology and negative resection margins. Intraoperative frozen section was used to rule out malignancy and confirm negative margin status of the pancreatic remnants (both proximal and distal). For patients with IPMNs this poses a difficult question: is central pancreatectomy appropriate? IPMN has been identified as a premalignant lesion. A number of the series of central pancreatectomy have reported this procedure with patients exhibiting IPMNs.[1–3,5,6] Sauvanet reported that 2 of the 5 patients who underwent central resection for IPMNs demonstrated local recurrence identified within 2 years.[2] In our series, 3 patients demonstrated IPMN on pathology; 2 patients were 70 years or older whereas 1 patient was 52 years of age. Also, two of the IPMNs were identified as adenomas on pathologic review whereas one was identified as borderline. There were no lesions that demonstrated severe dysplasia or carcinoma in situ. Clearly, until more definitive data are seen, the possibility of pancreatic cancer developing in these patients, who remain at risk, will require continued surveillance.[25]

CONCLUSIONS

Central pancreatectomy with PG is a safe and effective procedure that allows for the preservation of pancreatic endocrine and exocrine function without the disruption of enteric continuity. In our experience, the complication of pancreatic fistula was managed conservatively via maintenance of operatively placed drains and did not require invasive intervention to allow healing.

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Alimentary Tract Surgery in the Nonagenarian: Elective vs. Emergent Operations

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The objective of this study was to compare elective with emergent surgery in patients over the age of 90 years. We retrospectively reviewed the records of patients over 90 years of age who underwent alimentary tract surgery between 1994 and 2002 at a community teaching hospital. Of 100 patients (mean age 92 years; range 90 to 98 years), 82 were women and 18 were men. Seventy-three percent were admitted from private homes or assisted-living facilities, and 27% came from a skilled-nursing facility (SNF). Major comorbid conditions existed in 93%. Procedures included right hemicolectomy (22%), adhesiolysis and/or small bowel resection (19%), cholecystectomy (14%), left-sided or sigmoid colectomy (11%), and perineal proctectomy (8%). Overall morbidity and mortality were 36% and 15%, respectively. Postoperative complications included respiratory failure and pneumonia (11%), arrhythmias (9%), delirium (7%), congestive heart failure and myocardial infarction (6%), and urinary complications (4%). Twenty-eight percent of the operations were elective, and 72% were emergent. Morbidity and mortality were higher in the emergent group (41% and 19%, respectively) than in the elective group (26% and 4%, respectively; $P = 0.04$), especially for patients with an emergent surgical problem who came from a nursing home (22%). Average length of stay was 12 ± 10 days (range 2 to 69 days) with little difference between elective and emergent cases. Sixty-four percent of patients were discharged to skilled-nursing facilities. Alimentary tract surgery can be performed safely in nonagenarians, and they should not be denied surgical care solely because of age. (J GASTROINTEST SURG 2004;8:539–542)

KEY WORDS: Surgery, elderly, gastrointestinal

The population is growing increasingly older. At present, one of eight Americans is over 65 years of age. Population trends suggest that by 2020, Americans aged 65 years and older will comprise 20% of the population. Americans over the age of 85, who numbered 4.2 million in 2000, are expected to reach 8.9 million by 2030.[1] Consequently, extremely elderly patients (defined as 90 years of age or older) are undergoing surgical procedures, with a concomitant higher incidence of adverse events and surgical complications. In all patients, independent of age, emergency surgery carries a higher rate of morbidity and mortality than does elective surgery. Despite an increasingly older population, studies of surgical outcomes in the elderly have been limited.[2–10] Our study examined a population of patients over the age of 90 who underwent gastrointestinal surgery at a community teaching hospital. Our goal was to evaluate mortality and morbidity trends and to compare and contrast these in operations performed electively and emergently.

MATERIAL AND METHODS

The records of all patients 90 years of age and older, who underwent alimentary tract surgery (excluding oropharyngeal procedures) at a 514-bed community teaching hospital between July 1994 and September 2002, were reviewed retrospectively. Data

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examined included age, sex, length of hospital stay, comorbid conditions, place of residence (i.e., nursing home vs. independent home living), operative duration and findings, type of operation, final pathologic findings, posthospital course, mortality rate, and surgical complications. All hospital records were obtained including the location of the prehospital and postdischarge domicile. Two groups of patients were compared: those undergoing elective vs. those undergoing emergent procedures. Elective cases were defined as those in which patients had an outpatient workup and were admitted for operation. Emergent cases were defined as those in which patients were admitted through the emergency room and went to the operating room within less than 24 hours from the time the decision to operate was made. We also grouped patients by location of the operation along the gastrointestinal tract, which included foregut (including the biliary tract), midgut, and hindgut procedures. Data were evaluated statistically using Fisher's exact test.

RESULTS

A total of 100 patients met the inclusion criteria. Patients ranged in age from 90 to 98 years. The mean and median ages of the patients in our study were 92 and 91.5 years, respectively. Eighty-two patients were women and 18 were men. Twenty-eight of the cases in our series were elective and 72 cases were emergent. The average length of hospital stay in the study was 12 ± 10 days (range 2 to 69 days) with the length of stay being slightly greater in the emergent group (12 days [range 3 to 70 days]) as compared with the elective group (11 days [range 2 to 58 days]).

The charts of four patients (one elective operation and three emergent operations) did not specify whether these patients had been admitted from home, an assisted-living facility, or a skilled-nursing facility (SNF). Most remaining patients were admitted from their homes or from assisted living: 73% (70 of 96) of patients. Twenty-seven percent (26 of 96 patients) came from SNFs. This was a similar trend in both elective and emergent operations with 73% (19 of 27 patients) of elective cases and 74% (51 of 69 patients) of emergent cases being admitted from home.

Most patients (93%) had some underlying comorbidity (Table 1). Hypertension was the most prevalent comorbidity (54%), followed by coronary artery disease and/or congestive heart failure (39%), and arrhythmias (27%) (Table 2). Most of the patients undergoing elective operations (86%) had two or more comorbid conditions. Seventy-five percent of patients operated on emergently had two or more comorbid conditions. There was no difference statistically in any comorbidity between patients undergoing elective vs. emergent procedures or in the number of comorbid conditions.

Table 1. Percentage of patients with comorbid conditions: Elective vs. emergent surgery

Total comorbidities	Elective	Emergent	Total
0	7%	7%	7%
1	7%	18%	15%
2	29%	32%	31%
3	36%	25%	28%
4	21%	18%	19%

The cases were grouped according to whether they involved the stomach, duodenum, and biliary tree (foregut); the small bowel (midgut); or the colon (hindgut). There were a total of 22 foregut cases, 21 midgut, and 57 hindgut cases. Of these, there were three elective foregut, 0 elective midgut, and 25 elective colon cases; there were 19 emergent foregut, 21 emergent midgut, and 32 emergent colon cases. Common procedures included right hemicolectomy (22%), adhesiolysis and/or small bowel resection for small bowel obstruction (19%), open or laparoscopic cholecystectomy (14%), left-sided or sigmoid colectomy (11%), and perineal proctectomy (8%).

The overall mortality rate in the population of patients aged 90 and older was 15%. The mortality rate in the elective group was 4% (1 of 28 patients), and the mortality rate in the emergent group was significantly higher (19% [14 of 72 patients]; $P = 0.04$). The overall morbidity rate for this patient population was 36% (31 of 85 patients). The morbidity rate was 26% (7 of 27 patients) in the elective group and 41% (24 of 58 patients) in the emergent group. The difference in morbidity rates between the two groups was not statistically significant.

Patients had a wide range of complications. Cardiopulmonary complications were most prevalent affecting 22 (26%) out of 85 patients. Respiratory

Table 2. Percentage of patients with particular comorbid conditions: Elective vs. emergent surgery

	Elective	Emergent	Total
Hypertension	60	51	54
Coronary artery disease	14	26	23
Congestive heart failure	14	17	16
Arrhythmias	32	25	27
Pulmonary (COPD, etc.)	18	11	13
CVA/TIA	11	15	14
Musculoskeletal	39	24	28
Psychiatric disease	25	14	17
History of neoplasm	11	17	15
Hypothyroidism	14	21	19
Diabetes mellitus	7	7	7

COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; TIA = transient ischemic attack.

failure (defined as the patient's need for mechanical ventilation for more than 24 hours postoperatively) and pneumonia were common complications in 9 (11%) of 85 patients. Arrhythmias occurred in 8 of 85 patients, and 5 of 85 patients had congestive heart failure or myocardial infarction. Urinary complications, including urinary tract infection and urinary retention, occurred in 4 of 85 patients. Delirium affected 6 (10%) of 58 patients in the emergent group and less in the elective group for a total incidence of 7%. There were no other neurologic complications in the series.

Twenty-eight percent of cases were elective, most commonly for a colonic mass (61%) or rectal prolapse (18%). Of the patients with a colonic mass, 35% had associated symptomatic anemia and 29% had symptomatic bleeding. Seventy-two percent of cases were emergent. The most common indication for emergent operation was acute abdomen (67%), followed by symptoms of bowel obstruction, including nausea and vomiting and abdominal distention (19%).

The largest group of patients in our study was those who underwent colon operations. Most underwent a right hemicolectomy (24 patients); eight patients had a low anterior resection, a sigmoid resection, or a left hemicolectomy, and eight patients had a perineal proctectomy. Right hemicolectomy was the most commonly performed procedure for both elective (14 patients) and emergent (10 patients) reasons. Five loop colostomies were performed for emergent indications, including large bowel obstruction secondary to colon cancer, ovarian cancer, and tuberculosis. Thirty (53%) of 57 patients were operated on for nonmalignant conditions such as diverticulitis, appendicitis, or rectal prolapse. Of those who were operated on for malignancy and for whom the TNM stage was available, 89% (24 of 27 of the patients) were T3 or greater at the time of surgery. Thirty-seven percent of patients had positive lymph nodes at the time of surgery.

Survivors were discharged from the hospital to a nursing home in 64% of cases. Of the elective group, 48% went to their homes whereas only 29% of the emergent group were discharged to home.

DISCUSSION

As the population continues to age and perioperative care becomes increasingly sophisticated, more extremely elderly patients are receiving surgical attention. Our study found that in most cases, the elderly were able to tolerate gastrointestinal surgery, and most left the hospital after either elective or emergent surgery.

Elderly patients arriving from a nursing home represent a unique population. These patients are often frail and have multiple associated comorbid conditions, and they often have a short life expectancy.[3] Interestingly, however, admission from SNFs was not a positive predictor of poorer prognosis in our study. Comparing admissions from home vs. SNF, patients have similar mortality rates: 13% (9 of 70 patients) from home vs. 15% (4 of 26 patients) from a SNF but have slightly higher morbidity: 39% (24 of 61 of patients) from home vs. 32% (7 of 22 patients) from a SNF. Interestingly, the length of stay was much higher in the patients admitted from home (13.5 days) as compared with those from SNFs (8.4 days). This may be due to the small number of patients in this group or may be due to the fact that patients from a nursing home had their discharge planning taken care of before they entered the hospital. Our results suggest that patients from SNFs should not be treated any differently from elderly patients admitted from home when contemplating surgical procedures if comorbid conditions are equal and surgical intervention is compatible with their wishes and advanced directives.

Several studies have reviewed the mortality and morbidity in the elderly. Comparing our data to a study on elderly patients undergoing gastrointestinal surgery prior to 1980,[4] we find a shift from approximately 20% of cases in the elderly being emergent to 72% in our study. Previous mortality rates were 6.7% in the elective population and 20% in the emergent population. Our overall mortality rate is similar to those previously reported. Our decrease in mortality is especially interesting because our patients were all over 90 years of age, whereas previous studies consisted of patients over the age of 70. Rigberg et al.[5] reviewed patients who underwent gastrointestinal surgery who were over the age of 90. Of 32 patients who underwent any gastrointestinal surgical procedure, 69% of their cases were emergent and 31% were elective. The elective group had 0% mortality and 20% morbidity compared with rates of 14% mortality and 68% morbidity in their emergent group. Comparable data from our study showed elective mortality and morbidity rates of 4% and 26% and emergent mortality and morbidity rates of 19% and 41%. Improvements in mortality in the study by Rigberg et al.[5] in 2000 and our study may result from such factors as advances in ICU care, better nutritional support, and better understanding of physiologic processes in the geriatric population.

Colon operations in the elderly are associated with a higher mortality rate than is seen in younger population. Violi et al.[6] showed a stepwise increase in mortality as a patient's age increases from 60 years to

over the age of 80: for patients under age 60, mortality and morbidity rates were 0.5% and 5.9%, respectively, whereas for patients older than 80, mortality and morbidity were 8.5% and 33%, respectively. In our series, 57% of cases were hindgut cases, including appendectomies. Of these, 25 were elective and 32 were emergent; 30 were for benign disease, and the remaining 27 cases were for colon masses. Colorectal procedures are common in the elderly because of the higher rates of colon cancer in this population. Cancer operations are more often emergent in the elderly and even if elective, tumors tend to present at a more advanced stage and are more often less differentiated.[7] In our series, more cases were emergent (n = 32) than elective (n = 25), and in our series most colon operations (n = 30) were for benign disease.

Colorectal surgery was at one time considered to be hazardous with very high mortality rates[8]; however, recent studies have demonstrated that surgery is safe and that age should not be the only reason to deny treatment.[9] Comparing our data with those of Spivak et al.,[9] we find that we have a larger proportion of emergent cases than was described in their study, which had a ratio of 81% elective to 20% emergent operations. Their mortality rates for elective and emergent cases (3% and 21%, respectively) match our mortality rates (4% and 24%, respectively). The one difference in our study population was age—that is, our patients were all older than 90, whereas theirs were over the age of 80. Our study, as well as the previous studies, reveal that colorectal surgery can be performed safely in the elderly population.[9,10]

The elderly are a diverse group of patients with comorbidity and quality of life issues that make them a more challenging group of patients than their younger counterparts.[3] When measuring outcomes, quality of life needs to be a major factor when planning elective or emergent surgery in the elderly population. Although most elderly patients are admitted from an independent environment, most do not return to their homes after major abdominal surgery.

CONCLUSION

Elective surgery in the population over the age of 90 seems to be tolerated well with low mortality and acceptable morbidity. Although emergent procedures carry higher morbidity and mortality, most patients tolerate the operation and leave the hospital.

Elective procedures in this population of patients should not be postponed solely because of age but only after fully assessing each patient's comorbid conditions. The patient's preoperative location of residence should not be a factor in deciding on an interventional course. Frank conversations are needed between the surgeon, the patient, and the patient's family prior to any intervention so that expectations are understood and advanced directives are carried out appropriately.

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Safety and Reliability of Tattooing Colorectal Neoplasms Prior to Laparoscopic Resection

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Accurate tumor localization is critical to performing minimally invasive colorectal resection. This study reviews the safety and reliability of tattooing colorectal neoplasms prior to laparoscopic resection. We retrospectively reviewed 50 consecutive patients with colorectal neoplasms who underwent endoscopic tattooing prior to laparoscopic resection. Data were obtained from medical charts, endoscopy records, and pathology reports. No complications related to endoscopy or tattooing were incurred. Five neoplasms (10%) were in the ascending colon, five (10%) were in the transverse colon, eight (16%) were in the descending colon, 23 (46%) were in the sigmoid colon, and nine (18%) were in the rectum. Tattoos were visualized intraoperatively and accurately localized the neoplasm in 44 patients (88%). Six patients (12%) did not have tattoos visualized laparoscopically and required intraoperative localization. On average, the pathology specimens in this series had a 15 cm proximal margin, a 12 cm distal margin, and 15 lymph nodes. In the context of laparoscopic colorectal resection, preoperative endoscopic tattooing is a safe and reliable method of tumor localization in most cases. Localizing colon and proximal rectal lesions with tattoos may be preferable to other localization techniques including intraoperative endoscopy.
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Key words: Tumor localization, endoscopic tattoo, colorectal cancer, laparoscopic surgery

Accurate tumor localization remains a critical aspect of the minimally invasive approach to colorectal resection. There are a number of methods used to localize colorectal neoplasms before and during resection (Table 1). Barium enema can be used to localize larger tumors, but localizing small tumors with barium enema can be difficult. Because of its relatively poor resolution, barium enema is a poor method for localizing polypectomy sites. Colonoscopy can accurately localize lesions but is heavily dependent on the experience of the endoscopist. Combining preoperative colonoscopy with fluoroscopy can overcome this but involves radiation and requires special equipment in the endoscopy suite. Some advocate placing mucosal clips at the time of preoperative colonoscopy and using fluoroscopy to facilitate localization. Clip migration is the main problem with this approach and makes this method inherently unreliable. Intraoperative colonoscopy can be used for localization but has several drawbacks. Colonoscopy in the operating room can be time-consuming, technically difficult, and cumbersome because of positioning of the patient on the table. In addition, colonic insufflation, even with proximal bowel occlusion, can sacrifice intraperitoneal domain, limit operative exposure, and severely handicap the laparoscopic surgeon. In the setting of laparoscopic surgery, preoperative endoscopic tattooing can potentially overcome many of the deficits mentioned above.

In 1958, Sauntry and Knudtson[1] first described colorectal tattooing with the use of a blue dye to track rectal polypectomy sites. Later, in 1975, Ponsky and King[2] published their often-cited case report of a

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Table 1. Methods for localizing colorectal neoplasms before and during laparoscopic resection

Barium enema
Preoperative colonoscopy (with or without fluoroscopy)
Placement of mucosal clips followed by fluoroscopy
Intraoperative colonoscopy
Preoperative tattooing

patient in whom they used India ink to localize a sigmoid polyp prior to colectomy. Over the next 20 years, a number of case reports were published reviewing the accuracy, utility, and complications of tattooing colorectal lesions in the context of open surgery.[3–6] During this interval a variety of water-soluble and permanent dyes were studied, and the applications for endoscopic tattooing were broadened to include localization of both upper and lower gastrointestinal sources of hemorrhage.[7–9]

Most of the literature describing complications of colonic tattooing involves India ink. The incidence of clinically relevant complications from India ink injections is well below 1%.[5,10] These short-term, rare complications include submucosal abscess, fever, localized peritonitis, and inflammatory pseudotumor formation.[11,12] Histologic consequences of India ink injection have also been reported. These findings include fat necrosis and tissue edema with neutrophilic infiltration and are typically found in clinically asymptomatic patients.[13] The inflammatory complications from the injections are thought to be caused by impurities in the ink or possibly by contaminants. Introduction of gastrointestinal flora into the wall of the colon has also been suggested as a mechanism.

In the late 1990s, endoscopists began reporting small reviews of their early experiences tattooing lesions prior to laparoscopic colorectal resection.[14] With laparoscopic colectomy becoming more prevalent, the safety and reliability of colorectal tattooing in the context of laparoscopic surgery must be further evaluated.

METHODS

We retrospectively reviewed 50 consecutive patients with colorectal neoplasms who underwent endoscopic tattooing prior to laparoscopic resection. Data were obtained from medical charts, endoscopy records, and pathology reports.

Patients underwent a mechanical bowel preparation prior to colonoscopic tattooing. We employed the Spot endoscopic marker (GI Supply, Camp Hill, PA), which is an inexpensive, readily available, sterile carbon particle suspension. This dye is approved by the United States Food and Drug Administration and comes ready to use in prepackaged syringes. Tattoos were placed using a 25-gauge sclerotherapy needle, and the dye was injected tangentially at multiple circumferential sites distal to the neoplasm or polypectomy site. Enough dye was injected to raise a submucosal bleb at each injection site (usually 1 to 4 cc of ink). Serosal violation was avoided by keeping the needle flush with the bowel wall. To raise a bleb, the needle was withdrawn from the tissue slowly while injecting until a bleb began to form. Then, with the needle held in position, the injection was completed.

RESULTS

Fifty patients underwent tattooing and subsequent colorectal resection over a 3-year period. The average time between tattooing and resection was 4 days (range 1 to 30 days). Thirty patients (60%) were tattooed the day before resection. No complications related to endoscopy or tattooing were incurred.

The series includes 38 patients (76%) with colorectal cancer and 12 patients (24%) with colorectal adenomas not amenable to endoscopic removal. Five neoplasms (10%) were in the ascending colon, five (10%) were in the transverse colon, eight (16%) were in the descending colon, 23 (46%) were in the sigmoid colon, and nine (18%) were in the rectum. On average, the pathology specimens in this series had a 15 cm proximal margin, a 12 cm distal margin, and 15 lymph nodes.

Thirty patients (60%) underwent laparoscopic-assisted colectomy with either extracorporeal ileocolic anastomosis or intracorporeal colocolostomy, depending on the location of the neoplasm. During these operations the mesentery and vascular pedicle are divided and the colon is fully mobilized laparoscopically. Then the bowel is exteriorized to allow delivery of the specimen prior to anastomosis. Two of the laparoscopic-assisted patients were converted to open resections because of extensive adhesions from prior surgery. Twenty patients (40%) underwent "hybrid" resections for rectal and distal sigmoid lesions.[15] These operations used the laparoscopic approach to divide the inferior mesenteric artery, proximal colon, and mesentery and to mobilize the splenic flexure. Hybrid cases concluded with a planned inferior laparotomy to complete the dissection, divide the distal bowel, deliver the specimen, and perform the anastomosis.

Tattoos were visualized intraoperatively and accurately localized the neoplasm in 44 patients (88%).

Early in our experience, three of these patients with sigmoid lesions underwent intraoperative colonoscopy to confirm accurate tattoo placement. Six patients (12%) did not have tattoos visualized laparoscopically. Two of these patients underwent hybrid operations for rectal neoplasms and had lesions that were palpable during the open portion of their cases obviating the need for intraoperative endoscopy. The remaining four patients required intraoperative colonoscopy to localize their lesions during resection; three patients had sigmoid neoplasms, and one patient had an hepatic flexure lesion. Gross examination revealed that tattoos were absent on the serosa but present on the mucosa in four of the six cases, and dye was absent on the serosa and mucosa in the other two.

DISCUSSION

There is a well-articulated reluctance among surgeons to proceed with laparoscopic resection on the basis of preoperative colonoscopy alone. The authors routinely localize colorectal neoplasms, including polyp cancers, prior to laparoscopic resection. Excluded from this practice are patients with larger tumors that are anticipated to be readily visible via the laparoscope, patients with distal rectal tumors whose margin of resection is determined by the levator ani muscles, and patients undergoing abdominoperineal resection. In addition, patients with lesions proximal to the hepatic flexure may not require localization beyond a complete colonoscopy. In this situation, it is usually sufficient to estimate the location of a tumor by recognizing its anatomic relationship to the ileocecal valve.

Review of the present series emphasizes the safety and reliability of colorectal tattooing in the context of laparoscopic resection. No complications related to colonoscopy or tattoo placement were incurred. Preoperatively placed tattoos adequately localized nearly 90% of the tumors and obviated the need for intraoperative localization in most cases. In addition, the proximal margins, distal margins, and numbers of lymph nodes in the operative specimens in the series were adequate and comparable to resection specimens previously reported in other series.[16]

As mentioned, tattoos failed to localize colorectal lesions in six patients undergoing resection. Inspection of the resection specimens revealed that these failures were likely due to technical errors at the time of tattoo placement. Tattoos were absent on the serosa but present on the mucosa in four of these patients, and dye was absent on the serosa and mucosa in the other two. These findings attest to the importance of using appropriate technique while raising the submucosal bleb to avoid spraying the dye endoluminally.

The timing of preoperative tattooing deserves special consideration. Properly placed tattoos are long lasting and can be placed reliably at the time of diagnostic colonoscopy in anticipation of future operation.[10] Alternatively, patients can undergo endoscopy with tattooing the day prior to a planned laparoscopic resection. This latter timeline takes advantage of the usual preoperative bowel preparation and obviates the need for additional bowel preparation specifically for localization purposes. It should be noted that colonic insufflation the day before the operation does not persist or sacrifice intra-abdominal domain at the time of surgery.

The safety and reliability of colonoscopic tattooing, as well as the significant shortcomings of other localization techniques reviewed earlier, make tattooing the preferred method for tumor localization prior to colorectal laparoscopic resection. The decision to localize with tattoos rather than another method is also influenced by the oncologic perspective of laparoscopic colorectal resection. Specifically, an accurate tattoo helps the laparoscopist avoid manipulating a cancer intraoperatively and aids the surgeon by marking an appropriate margin of tissue for resection.[3,4] In the event of tattoo failure, the authors use intraoperative colonoscopy for localization.

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Effect of High-Dose Steroids on Anastomotic Complications After Proctocolectomy With Ileal Pouch–Anal Anastomosis

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This review was designed to determine whether "high-dose" steroid therapy (≥20 mg prednisone/day) increases the likelihood of anastomotic complications after restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA). The hospital records of 100 patients undergoing proctocolectomy with IPAA were reviewed. Patient characteristics were analyzed to determine what factors were associated with higher rates of anastomosis-related complications. Seventy-one of our patients were given diverting ileostomies, whereas the remaining 29 underwent a single-stage procedure. Fifty-four percent of the patients in our review were taking steroids preoperatively, 39 of whom were on high-dose therapy. The overall anastomosis-related complication rate was 14%. There was no significant difference in complication rates with respect to age, steroid use, steroid dose, use of a diverting ileostomy, type of anastomosis, duration of disease, or presence of backwash ileitis. A trend toward higher leakage rates was found in patients undergoing single-stage procedures (10.3% vs. 2.8%, $P = 0.14$) as well as in patients undergoing single-stage procedures on high-dose steroids (22% vs. 5.0, $P = 0.22$). Nevertheless, neither of these trends was found to be statistically significant, which was likely influenced by the small sample size. Our data suggest that there may be an increase in anastomotic leakage rates in patients on high-dose steroids undergoing a single-stage proctocolectomy with IPAA. Nevertheless, our rate was not as high as the rates seen by other investigators and did not reach statistical significance. During preoperative counseling, patients on high-dose steroids should be informed of this uncertain but real risk of anastomotic leakage. (J GASTROINTEST SURG 2004;8:547–551)

KEY WORDS: Restorative proctocolectomy, postoperative complications, ulcerative colitis, adenomatous polyposis coli

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) and diverting ileostomy has become the standard procedure for many patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP) who desire a continence-preserving procedure. More recently, a single-stage procedure (without the formation of a diverting ileostomy) is being performed in a select group of patients. These patients are typically those individuals considered good surgical candidates who do not have contraindications such as preoperative steroid use.[1–4] In addition, previous studies have suggested that a dose of prednisone greater than 20 mg per day ("high-dose") is associated with an increased risk of IPAA leakage.[5,6] The goal of this study was to assess whether high-dose preoperative steroid therapy is associated with anastomotic complications in patients undergoing restorative proctocolectomy and IPAA. We hypothesized that 20 mg or more of prednisone per day would increase anastomotic complications in patients who underwent a restorative proctocolectomy.

MATERIAL AND METHODS

The hospital records of 100 patients who underwent restorative proctocolectomy and IPAA performed

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by a single surgeon between 1995 and 2001 were reviewed. All patients were included regardless of preoperative condition or postoperative course. The mean follow-up time was 34 months (range 4 to 82 months). The data collected included age, sex, preoperative diagnosis, duration of disease, comorbid conditions, presence of backwash ileitis, preoperative steroid use, type of anastomosis, presence or absence of diverting ileostomy, and postoperative complications.

Anastomotic complications were defined as an anastomotic leak or stricture. Pelvic pouch leaks were determined to be present when there was radiographic or clinical evidence of anastomotic disruption or presence of a pelvic abscess. In this study, anastomotic strictures were defined as those needing repeated digital or operative dilations and did not include thin anastomotic webs. Yates-corrected chi-square and Fisher's exact test were used to evaluate categorical data. Statistical significance was set at $P < 0.05$.

RESULTS

All of the patients in our review underwent a proctocolectomy (or completion proctocolectomy) with formation of a J-pouch reservoir for the IPAA. Of the 100 patients, 87 had the diagnosis of UC, nine had FAP, three had Crohn's disease, and one had indeterminate colitis. Overall, 14 patients in our review had anastomosis-related complications. These included five anastomotic leaks and nine anastomotic strictures (Table 1). There were no case-related deaths and no patients in our review required pouch excision.

Fifty-four patients in our review were taking steroids preoperatively, of whom 39 were on high-dose therapy (≥20 mg prednisone/day). Of the five anastomotic leaks, three (5.6%) occurred in the steroid group, whereas two (4.3%) were found in the nonsteroid group (NS; $P = 0.99$). No leaks were observed in the "low-dose" (1 to 20 mg prednisone/day) steroid group. All three patients taking steroids who had anastomotic leaks were taking high-dose steroids (3 [7.7%] of 39 patients). However, this was not significantly different from the 3.3% leakage rate in patients taking no or low-dose steroids ($P = 0.59$). In addition, no significant difference was found when comparing leakage rate and duration of disease, age, type of anastomosis, or presence of backwash ileitis (see Table 1). Comorbid conditions and preoperative albumin levels were also not found to be associated with anastomosis-related complications (data not shown).

Most of our patients were given temporary ileostomies (71%), and these patients were similar in respect to age, sex, comorbid conditions, and duration of disease as compared to those patients spared an ileostomy. Indications for a diverting ileostomy included patient preference, tension at the anastomotic site, anastomotic leak noted at the time of surgery, or the surgeon's clinical judgment during the procedure. Of the 29 patients who underwent a single-stage procedure, 13.8% had an anastomosis-related complication vs. 14.1% of the patients with diverting ileostomies (NS; $P = 0.99$). With regard to anastomotic leaks, a higher rate was seen in patients with single-stage procedures in comparison to those who had an ileostomy (10.3% vs. 2.8%; $P = 0.14$). In addition, of the nine patients on high-dose steroids who underwent a single-stage procedure, two (22%) had postoperative leaks, which was higher than the 5.0% leakage rate observed in the remaining 20 patients who also had a single-stage procedure (NS; $P = 0.44$). Among those patients who had an ileostomy, the leakage rate in patients on high-dose steroids was not significantly different from those who were taking

Table 1. Anastomotic complications

Risk factors (no. of patients)[†]	Leak	Complications* Stricture	Complications* Overall complication rate
Steroid			
Yes (54)	3 (5.6%)	4 (7.4%)	7 (13.0%)
No (46)	2 (4.3%)	5 (10.9%)	7 (15.2%)
Prednisone			
<20 mg (63)	2 (3.3%)	6 (9.5%)	8 (12.7%)
≥20 mg (37)	3 (7.7%)	3 (8.1%)	6 (16.2%)
Ileostomy			
Yes (71)	2 (2.8%)	8 (11.3%)	10 (14.1%)
No (29)	3 (10.3%)	1 (3.4%)	4 (13.8%)
Duration of disease[‡]			
≤10 yr (54)	3 (5.6%)	5 (9.3%)	8 (14.8%)
>10 yr (37)	2 (5.4%)	3 (8.1%)	5 (13.5%)
Age			
≤40 yr (51)	1 (2.0%)	4 (7.8%)	5 (9.8%)
>40 yr (49)	4 (8.2%)	5 (10.2%)	9 (18.4%)
Anastomosis			
Stapled (91)	5 (5.5%)	9 (9.9%)	14 (15.4%)
Hand-sewn (9)	0	0	0
Backwash ileitis			
Yes (7)	0	1 (14.3%)	1 (14.3%)
No (92)	5 (5.4%)	7 (7.6%)	12 (13.0%)
Total (100)	5 (5.0%)	9 (9.0%)	14 (14%)

*The chi-squared and Fisher's exact P values for all listed categories are not significant ($P > 0.05$).
[†]Data not available when totals do not equal 100.
[‡]In the nine patients with unknown duration of disease, the overall complication rate was 11.1%.

low-dose or no steroids (3.6% vs. 2.3%; $P = 0.99$) (Fig. 1).

Nine of our patients developed anastomotic strictures. None of these strictures were related to pouch leak or sepsis. There was no association between stricture rate and steroid use, duration of disease, age of the patient, or presence of backwash ileitis (see Table 1). A higher rate of stricture was seen in patients with diverting ileostomies (8 [11.3%] of 71) when compared to patients without ileostomies (1 [3.4%] of 29). This, however, did not reach statistical significance ($P = 0.40$).

All five of the patients who developed an anastomotic leak had the preoperative diagnosis of UC. Although three of the patients with leaks presented with sepsis, the remaining two patients were asymptomatic. Notably, all three patients with symptomatic leaks had initially undergone a single-stage procedure, whereas the two patients with asymptomatic leaks had undergone diverting ileostomies. Of the three patients with symptomatic leaks, two were taking steroids, whereas one was not. Of the two patients with asymptomatic leaks, one patient was on steroids preoperatively and the other was not.

All three patients with sepsis resulting from anastomotic leakage underwent urgent surgery with creation of a loop ileostomy and drainage of the pelvic abscess. They all subsequently recovered uneventfully and later underwent closure of their ileostomies. The two asymptomatic leaks were found on routine radiographic studies. In one the leak was not apparent on physical examination 1 month after it was discovered, and the patient underwent an ileostomy takedown without any repair and has done well. The other patient with an asymptomatic leak underwent a local repair of the leak and ileostomy takedown in the same setting. This patient has also recovered without event.

DISCUSSION

A proctocolectomy with IPAA has become the procedure of choice for patients requiring excision of the colon and rectum for UC and FAP. Although patients with FAP invariably undergo surgery following diagnosis, patients with UC commonly have surgery after the discovery of a premalignant lesion or after medical therapy has failed. When first envisioned, this procedure was accompanied by a diverting ileostomy.[7] This was done to divert enteric contents away from the newly formed pouch in order to minimize complications of an anastomotic breakdown. Although earlier reports have supported this practice,[8,9] subsequent studies have suggested that IPAA without temporary ileal diversion can be safely performed for a subset of patients undergoing surgery.[1,4,10–14] These patients include those who have adequate preoperative nutritional status and no risk factors that would hinder anastomotic healing (including preoperative steroid use).

Patients with UC are often taking steroids prior to undergoing proctocolectomy with IPAA. Because steroid use has been associated with a substantially

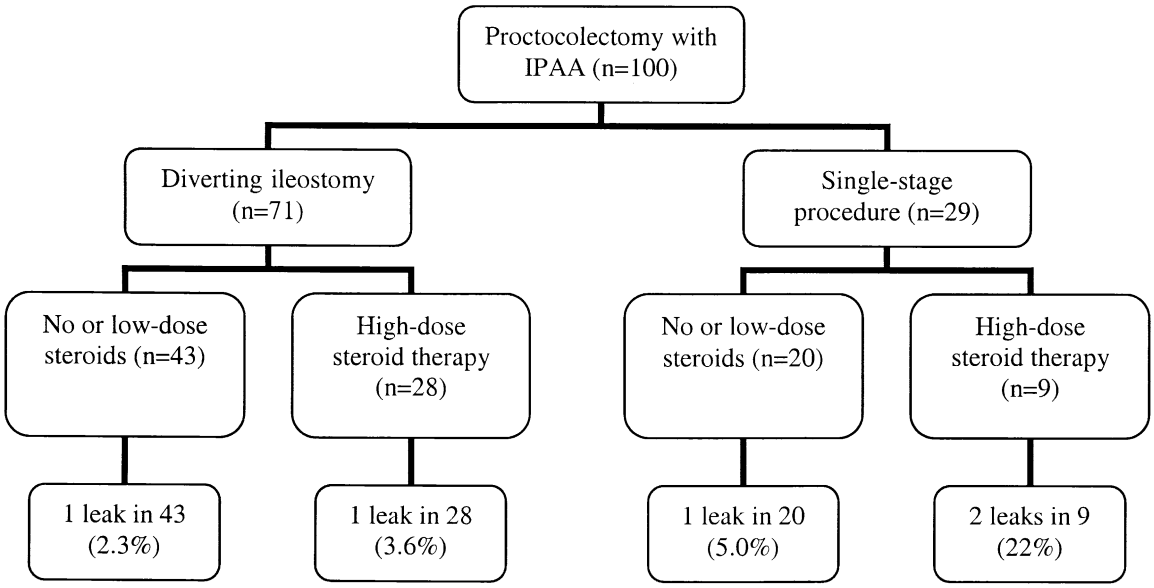

Fig. 1. Anastomotic leakage rate by presence of ileostomy and steroid dose. IPAA = ileal pouch–anal anastomosis.

increased risk of anastomotic leakage following large bowel resection,[15] previous studies have advocated the use of a diverting ileostomy with IPAA in patients on steroids.[12,16] More recently, however, leakage rate after IPAA was not found to be related to steroid use or dosage,[17] and steroid dose was not found to be an important factor in postoperative complications following IPAA.[18]

Although the association between preoperative steroid use and complications following IPAA remains controversial, patients on high-dose steroids undergoing a single-stage proctocolectomy with IPAA consistently have had high complication rates.[5,6] Ziv et al.[5] analyzed 67 patients undergoing IPAA and found no difference in early septic complications between groups with no, low-dose (1 to 20 mg prednisone/day), and high-dose (20 mg prednisone/day) steroid doses. They did, however, show that in their patients who underwent *single-stage* procedures, early septic complications occurred in 3.8%, 20%, and 50% in the no, low-dose, and high-dose steroid use groups, respectively ($P = 0.004$). They concluded that an ileostomy should be included in all patients taking high-dose steroids preoperatively.

In a study by Tjandra et al.,[6] 50 patients who underwent a single-stage IPAA were compared to 50 patients who had the procedure with diverting ileostomy. Nine of their patients had anastomotic leaks, eight of whom were taking high-dose steroids. In their patients who were spared an ileostomy, 86% on high-dose steroids had septic complications compared to 2% taking no steroids or low-dose steroids ($P < 0.001$). Based on these results, they recommend a diverting ileostomy in all patients taking more than 20 mg of prednisone per day undergoing an IPAA.

The goal of our study was to assess whether preoperative high-dose steroid use increases anastomotic complications after proctocolectomy with IPAA. In our sample of 100 patients undergoing restorative proctocolectomy, our anastomosis-related complication rate was 14%, which is comparable to other studies.[13,16] There was no significant difference in complication rate with respect to age, steroid use, steroid dose, use of a diverting ileostomy, type of anastomosis, duration of disease, or presence of backwash ileitis.

When we examined anastomotic leak rates, however, several trends were noted. When stratifying by the use of a diverting ileostomy, the rate of leaks in patients undergoing a single-stage procedure was higher than in those with ileostomies (10.3% vs. 2.8%). This association between higher leakage rates in patients undergoing single-stage procedures has been reported,[19] but (as in this study) this trend was recently found not to be statistically significant.[10] In addition, among the five anastomotic leaks in this study, all leaks in patients with ileostomies were asymptomatic, whereas all of the symptomatic leaks were found in patients without diverting ileostomies. These findings confirm previous reports that ileostomies do not significantly decrease the rate of anastomotic leaks, but do lessen the severity of their presentation.[20]

In this study, patients on high-dose steroids undergoing single-stage procedures were found to have a higher leak rate than those in the low-dose or no steroid use group (22% vs. 5%). In contrast to the studies by Ziv[5] and Tjandra,[6] our findings did not reach statistical significance (Table 2). It is, however, difficult to draw concrete conclusions from any of these studies because the number of patients on high-dose steroids undergoing a single-stage procedure was small. In our study we had nine patients who underwent the single-stage procedure and were on high-dose steroids, whereas Ziv et al.[5] similarly had 10 and Tjandra et al.[6] had only seven. In addition, our comparison of patients without diverting ileostomies based on steroid dose had a statistical power of only 16%. It would require 45 patients on high-dose steroids and 100 patients on low-dose or no steroids (all without diverting ileostomies) to approach a power of 80%.

CONCLUSION

For patients who require a proctocolectomy and desire a continence-preserving procedure, the formation of an IPAA is usually the procedure of choice.

Table 2. Comparison of anastomotic breakdown rates in patients undergoing a single-stage procedure in the current and previous studies

Comparative study	Anastomotic disruption rate	*P* value*
Ziv et al.[5] (1996)		
No or <20 mg prednisone (n = 36)	3/36 (8.3%)	
≥20 mg prednisone (n = 10)	5/10 (50%)	0.015
Tjandra et al.[6] (1993)		
No or <20 mg prednisone (n = 43)	1/43 (2.3%)	
≥20 mg prednisone (n = 7)	6/7 (85.7%)	<0.001
Current study		
No or <20 mg prednisone (n = 20)	1/20 (5.0%)	
≥20 mg prednisone (n = 9)	2/9 (22.2%)	0.44

*Fisher's exact test.

It is common for these patients to be on steroids preoperatively, and many centers invariably perform diverting ileostomies in these patients. We were unable to confirm the very high complication rates seen in these patients. Therefore, in our experience, steroid therapy alone does not preclude someone from being a candidate for a single-stage procedure. Our data suggest that there may be an increase in the rate of anastomotic leaks in patients on high-dose steroids undergoing a single-stage procedure. This complication rate, however, was not as great as rates seen by other investigators and did not reach statistical significance. Studies on this topic have very small numbers, but all suggest that high-dose steroids may impair wound healing and lead to increased leak rates. The prudent surgeon would counsel his/her patients accordingly when discussing the need for a diverting ileostomy in a patient on high-dose steroids.

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Cost and Effectiveness of Follow-up Examinations in Patients With Colorectal Cancer Resected for Cure in a French Population-Based Study

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The cost of follow-up examinations for patients having undergone potentially curative surgery for colorectal cancer is considerable. The aim of this study was to provide a thorough assessment of the cost and effectiveness of the follow-up tests used during the 5 years after surgical resection for colorectal cancer and its recurrences. We studied medical and economic data from the records of 256 patients registered in the Herault Tumor Registry who underwent potentially curative surgical resection in 1992. Recurrence, curative recurrence, survival, and the cost of follow-up tests were assessed respectively for at least 5 years. We analyzed the cost and effectiveness of follow-up tests in patients who received either follow-up with carcinoembryonic antigen (CEA) monitoring as advocated by the 1998 French consensus conference recommendations (standard follow-up) or a more minimal follow-up schedule. Nine patients died in the postoperative period. The 5-year survival rates in the standard and minimal follow-up groups were 85% and 79%, respectively ($p = 0.25$). Cost-effectiveness ratios were 2123 in Dukes' stage A patients, 4306 in Dukes' stage B patients, and 9600 in Dukes' stage C patients. Cost-effectiveness ratios for CEA monitoring and abdominal ultrasonography per patient alive in the standard follow-up group were 1238 and 2261.5, respectively. Cost-effectiveness ratios for CEA monitoring and abdominal ultrasonography per patient alive in the minimal follow-up group were 1478 and 573, respectively. There were no survivors 5 years after a recurrence when the recurrence was detected by physical examination, chest X-ray, and colonoscopy in either follow-up group. Dukes' classification is a poor indicator of patient selection. The follow-up tests should only include CEA monitoring and abdominal ultrasonography for the diagnosis of recurrence. (J GASTROINTEST SURG 2004;8:552–558)

KEY WORDS: Cost, effectiveness, follow-up, examinations, colorectal cancer

INTRODUCTION

Colorectal cancer is a public health problem. It is the highest-ranking cancer in France, both sexes combined, with nearly 33,000 new cases per year.[1] Surgery is the primary treatment for most colorectal cancers. Adjuvant chemotherapy and radiotherapy are recommended for specific subgroups.[2] After primary treatment, 20%–55% of the patients have recurrences.[3–6] As patients who will have recurrence after primary treatment cannot be differentiated, all patients with colorectal cancer having undergone potentially curative resection are subject to follow-up. The aim is to improve survival by providing potentially curative treatment for earlier diagnosed recurrences. Guidelines for this costly follow-up regimen have been set.[7–10] However, its impact on survival has not been clearly evidenced.[11–14] This obviously useful medico-economic analysis in a healthcare system with limited resources will enable gastroenterologists, surgeons, and oncologists to determine the best balance between optimal follow-up and available resources.

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The objective of this work was to provide the first population-based study with a recent unbiased medico-economic assessment of tests for the follow-up of colorectal cancer after potentially curative resection.

PATIENTS AND METHODS

Inclusion Criteria

We studied records from the Herault Tumor Registry, which records all invasive malignant tumors diagnosed in subjects residing in the department of the Herault in the south of France. Cases of colorectal cancer diagnosed between January 1, 1992 and December 31, 1992 were identified from validated registry data and constituted the study population. This was a retrospective study including 324 medical files recorded by 46 gastroenterologists and 302 surgery files recorded by 44 surgeons in collaboration with 147 general practitioners in the Herault. Data on the patients' clinical status were collected at the end of 1997. For clinical situations unknown at the time, birth, death records, and national statistics data (INSEE repertoire) were consulted or, with the primary care physician's consent, the patients or their families were contacted to complete the data set. The study population included all cases of invasive adenocarcinoma recorded in the final data set of 382 cases of cancer of the colon and the rectum. Of these 382 patients with colorectal cancer, 256 had undergone potentially curative resection in the Herault in 1992.

Mean patient age was 68.4 years (range 29–91): 68 years for 148 men and 69.5 years for 108 women. One hundred ninety-seven patients (70% of the initial population) had cancer of the colon and 69 patients (30%) had cancer of the rectum. All patients (n = 256) had undergone potentially curative surgery. The postoperative mortality rate was 4% (10 patients). Of the 69 patients with cancer of the rectum, 42 (61%) were given radiotherapy. Preradiotherapy and postoperative radiotherapy were respectively used for 48% (n = 33) and 17% (n = 12) of rectal cancers after potentially curative resection. Postoperative radiochemotherapy was used for 17% (n = 12) of rectal cancers after potentially curative resection. Adjuvant chemotherapy was given to 60 patients (28.6%) with colorectal cancer. Chemotherapy was given to 21% of the patients with Dukes' stage B colorectal cancer (tumor infiltrating the subserous, the serous, or more) and to 44% of the patients with colorectal cancer presenting lymph node metastasis.

Data Collection

Data concerning all of the follow-up tests were collected until diagnosis of recurrence, death of patients for an unrelated cause, or the end of the fifth year of follow-up for recurrence-free patients. The number and form (asymptomatic/symptomatic) of recurrences, the 5-year survival rate after diagnosis of recurrence, and the metachronous colorectal tumors were identified.

Definitions

Follow-up Schedules. Patients were divided into two groups. Group 1 had a standard follow-up using, as a baseline, the tests advocated by the consensus conference[8] with carcinoembryonic antigen (CEA) monitoring every 4–6 months for 3 years, then once a year for 2 years. They also had a physical examination every 3 months for 2 years, then every 6 months for 3 years, a colonoscopy every 3 years, an ultrasonography exploration every 4–6 months for 3 years, then once a year for 2 years, and an annual chest x-ray. Patients in group 2 had a minimal follow-up schedule. That is, at the most, they had CEA monitoring and ultrasonography exploration once a year for 3 years, a physical examination every 6 months for 5 years, a colonoscopy every 3 years, and a chest x-ray once a year for 2 years.

Cost. All explorations and tests performed during follow-up were identified using the French Health Service codes. Corresponding costs were calculated by applying the 1998 cost coefficients. Only the direct cost of the tests and physical examinations were taken into account. The cost was the mean cost of tests until diagnosis of recurrence, death of patients for an unrelated cause, or the end of the fifth year of follow-up for recurrence-free patients. The cost of follow-up for diagnosing a recurrence and for 5-year survival for recurrence-free patients were calculated for each Dukes' stage, for both follow-up strategies, and for each test performed during follow-up.

Effectiveness. The effectiveness was considered by the number of patients alive 5 years after the detection of recurrence by indicated modality divided by the total of recurrences detected in a minimal or standard schedule.

Cost-Effectiveness. Cost-effectiveness ratios were calculated for each Dukes' stage and for minimal or standard schedules according to the following formula: cost/effectiveness. By calculating the cost-effectiveness ratios, a comparison was made between the tests of two monitoring schedules.

Statistical Methods

Comparison of categorical variables was performed by χ^2 analysis. Continuous, non-normally

distributed variables were analyzed with the Mann–Whitney U test. Normally distributed data were analyzed with the Student *t* test. Kaplan–Meier 5-year survival plots were calculated for specific survival (including disease-related mortality) for the study population and for patients after diagnosis of recurrence. The BMDP 1993 version (SPSS Inc., Chicago, IL) and the SAS 6.06 version (SAS Institute, Cary, NC) software were used.

RESULTS

Patient Variables

Sixty-nine patients (30% of the 231 patients who could be classified into one of the follow-up groups) had a standard follow-up schedule and 162 (70%) had a minimal follow-up schedule. Table 1 shows the type and number of tests performed for each follow-up group. Apart from age, however, there was no statistical difference among any of these patient variables between the two groups (Table 2). Postoperative chemotherapy differed significantly between the two groups in Dukes' stage C patients: 17/20 (85%) in the standard follow-up group and 15/44 (34%) in the minimal follow-up group ($p = 0.001$). Twenty-five patients could not be satisfactorily classified into one of the two groups: 10 patients had recurrent disease and died from colorectal cancer during the first 10 months, 10 patients died from another disease during the first 10 months, and 5 patients were lost to follow-up at 2–9 months.

Recurrence

At 60 months' follow-up (minimal or standard), 143 patients were recurrence-free, 12 were alive but had recurrence, 47 had died from colorectal cancer, and 29 had died from another disease. At the 5-year follow-up, 59 patients (26%) had recurrence, 27 patients (46%) had multiple recurrences, 12 patients (20%) had loco-regional recurrence, 4 patients (7%) had peritoneal metastasis, and 15 patients (27%) had hepatic metastasis. Fifteen of the patients (22%) in the standard follow-up group and 44 patients (27%) in the minimal follow-up group had recurrent disease ($p = 0.27$). Radical reoperations were performed on 30.5% (18/59): 33% (5/15) in the standard follow-up group and 29.5% (13/44) in the minimal follow-up group ($p = 0.7$). Ages were evenly distributed between the patients who underwent potentially curative treatment for their recurrent colorectal cancer and those who had no potentially curative treatment for their recurrent colorectal cancer: 68.8 (SD: 11) years vs. 68.5 (SD: 10) years, respectively ($p = 0.9$). Six patients with recurrence (40%) were asymptomatic at the time of detection in the standard follow-up group, whereas 17 patients (36%) were asymptomatic at the time of detection in the minimal follow-up group

Table 1. Mean number of examinations per patient (with standard deviation) in the Herault area during the 5 years after resection for the cure of colorectal cancer

Follow-up	Standard (n = 69)	Minimal (n = 162)
Physical examination	20 (3)	7 (2.7)
Ultrasound	6 (1.1)	2 (0.7)
Colonoscopy	5 (3.5)	2 (1.1)
Chest x-ray	4 (1.4)	1 (0.6)
CEA	12 (3.7)	3 (2)
Liver tests	10 (4.2)	3 (1.6)
Blood chemistry and cell counts	12 (2.8)	4 (0.9)
CA 19-9	10 (3.5)	3 (1.4)

CA 19-9 = cancer antigen 19-9 test; CEA = carcinoembryonic antigen.

Table 2. Patient variables and follow-up modalities

	Minimal		Standard		
Follow-up	**n**	**%**	**n**	**%**	***p***
Sex					
Male	92	*58%*	37	*54%*	0.8
Female	70	*42%*	32	*46%*	
Age	69	(±11)	64	(±10)	***0.014***
Macroscopic type					
Expanded	17	*10.5%*	8	*11.5%*	0.8
Infiltrated	145	*89.5%*	61	*88.5%*	
Histology					
Differentiated	146	*90%*	65	*95%*	0.3
Undifferentiated	16	*10%*	4	*5%*	
Dukes'					
A (T1-2 N0 M0)	50	*31%*	28	*40.5%*	0.09
B (T3-4 N0 M0)	68	*42%*	21	*30.5%*	
C (T1-4 N1-2 M0)	44	*27%*	20	*29%*	
Location					
Colon	124	*73%*	45	*65%*	0.1
Rectum	38	*27%*	24	*45%*	
Emergency surgery					
Yes	18	*11%*	6	*9%*	0.6
No	144	*89%*	63	*91%*	
Postoperative chemotherapy					
Yes	26	*16%*	32	*46%*	***0.001***
No	136	*84%*	37	*54%*	

($p = 0.7$). Radical reoperations were performed on 27% (10/37) of patients with symptomatic recurrence and 36% (8/22) of patients with asymptomatic recurrence ($p = 0.6$).

Survival

The specific 5-year survival rate (disease-related mortality) for all colorectal cancer patients in the Herault was 75%. The 5-year survival rate (disease-related mortality) after diagnosis of recurrence for patients who had recurrences within 5 years was 12% (±4.8). The 5-year survival rates in the standard and minimal follow-up groups were 85% and 79%, respectively ($p = 0.25$). The 5-year survival rates of patients with symptomatic recurrence and of those with asymptomatic recurrence were 22% and 25%, respectively ($p = 0.46$).

Effectiveness of Follow-up Tests

Physical examination, CEA monitoring, chest x-ray, colonoscopy, and abdominal ultrasonography were the diagnostic modalities that detected the first signs of recurrent diseases. Twenty-three recurrences (39%) were detected by physical examination with or without symptoms; none of the patients were alive 5 years after the diagnosis of a recurrent disease. Nine recurrences (15%) were detected by an elevated CEA level; 3 patients were still alive 5 years after the diagnosis of a recurrent disease. Twenty-three recurrences (39%) were detected by abdominal ultrasonography; 7 patients were still alive 5 years after the diagnosis of a recurrent disease. Two cases of pulmonary metastasis were detected by chest x-ray; none of the patients were alive 5 years after the diagnosis of a recurrent disease. Colonoscopy led to the diagnosis of two local recurrences; none of the patients were alive 5 years after the diagnosis of a recurrent disease. Colonoscopy led to the diagnosis of 7 metachronous cancers; 6 of these patients were still alive 5 years after the diagnosis of a recurrent disease. Tables 3 and 4 illustrate the diagnostic modalities that detected the first signs of recurrent diseases in each follow-up group.

Cost of Follow-up

The total cost of follow-up was 164,470 euros. The mean cumulative cost of follow-up was 842 euros per patient at the 5-year follow-up. The mean cost per patient per year was 290, 194, 134, 123, and 101 euros for the 1st, 2nd, 3rd, 4th, and 5th years, respectively. Tables 3 and 4 illustrate the costs of each follow-up test.

Cost-Effectiveness of Follow-up

Cost-effectiveness ratios were 2123 in Dukes' stage A patients, 4306 in Dukes' stage B patients, and 9600 in Dukes' stage C patients (see Table 5). Cost-effectiveness ratios for CEA monitoring and abdominal ultrasonography per patient alive in the standard follow-up group were 1238 and 2261.5, respectively (Table 6). Cost-effectiveness ratios for CEA monitoring and abdominal ultrasonography per patient alive in the minimal follow-up group were 1478 and 573, respectively (Table 6). There were no survivors 5 years after a recurrence when the recurrence was detected by physical examination, chest x-ray, and colonoscopy in either follow-up group. CEA monitoring was more cost-efficient in the standard follow-up group than in the minimal follow-up group and abdominal ultrasonography was more cost-efficient in the minimal follow-up group than in the standard follow-up group.

DISCUSSION

As in other population-based studies, this study includes systematic identification of medical practices and their impact on survival. This underlines the importance of quality medical case management. Given the precision of the data collected, this is the first French population-based study to deal specifically with the issue of the cost and efficiency of colorectal cancer follow-up tests over a 5-year period.

Table 3. Cost and effectiveness of diagnostic modalities demonstrating the first signs of recurrent disease and patients alive 5 years after the diagnosis of recurrence in patients with standard follow-up (n = 69)

	n	Cost (euros)	Recurrences (n)	Radical resection of recurrences	Patients alive 5 years after recurrence diagnosis
Physical examination	900	15,207	3 *20%*	0	0
Abdominal ultrasound	352	20,284	4 *27%*	3	2
Colonoscopy	247	14,223	1 *6.5%*	0	0
Chest x-ray	199	5,979	1 *6.5%*	0	0
CEA assay	577	11,083	6 *40%*	2	2

CEA = carcinoembryonic antigen.

Table 4. Cost and effectiveness of diagnostic modalities demonstrating the first signs of recurrent disease and patients alive 5 years after the diagnosis of recurrence in patients with minimal follow-up (n = 162)

	n	Cost (euros)	Recurrences (n)	Radical resection of recurrences	Patients alive 5 years after recurrence diagnosis
Physical examination	700	11,754	20 *45.5%*	0	0
Abdominal ultrasound	178	10,257	19 *43%*	12	5
Colonoscopy	213	12,274	1 *2.3%*	0	0
Chest x-ray	103	3,095	1 *2.2%*	0	0
CEA assay	284	5,455	3 7%	1	1

CEA = carcinoembryonic antigen.

The particularity of this study lies in the fact that the choice of minimal or standard follow-up schedules was left to the attending physician. This approach not only provided an inventory of practices, but also an assessment of their effectiveness in terms of a population as opposed to a hospital series or a random study in which patients are selected. Consequently, the results must not be taken out of context, i.e., the population concerned. However, these conclusions will be used as the basis for further randomized studies to define the examinations to be carried out.

Compared with the number of tests that would have been prescribed in accordance with current recommended guidelines, or the number reported in randomized studies, clinicians in the Herault generally prescribed minimal follow-up regimens and the overall survival rate for Dukes' stages A, B, and C was 75%. No significant difference was found in comparison with the overall survival rate in randomized studies (70%–75%).[11–15] To date, no study has provided sufficient evidence of survival benefit in colorectal cancer patients with intensive follow-up. Five randomized studies published in the literature have analyzed the impact of intensive follow-up, but none of them were based on scientific evidence.[11–15] Moreover, the populations were not profiled, the sample sizes were relatively small, and the methodologies differed significantly. Four of these studies came to a significantly similar conclusion: potentially curative resection of recurrence is not correlated with increased survival.[11–14] In our series, 28% of potentially curative resections performed showed no significant difference between the two follow-up schedules. Furthermore, asymptomatic patients had no more potentially curative resections than symptomatic patients. On the basis of our experience, there was no evidence to show that an earlier diagnosis of asymptomatic or even symptomatic colon and rectum carcinoma recurrence leads to a reasonable probability of curative therapy or a greater chance of cure.

Given the lack of evidence-based studies concerning the impact of postoperative follow-up after resection of colorectal cancer, various surveillance strategies are used in practice, some of which entail considerable costs. The mean cost of follow-up per patient with each of the protocols routinely used in the United States between 1982 and 1994 have been calculated in the literature.[16] The type and the number of follow-up tests varied significantly depending on the follow-up strategies with a 28-fold difference in costs by center (ranging from $561–$16,492). In the Herault, cost-effectiveness ratios

Table 5. Cost and effectiveness of follow-up and Dukes' stages

Dukes' stage	n	Cost* (euros)	Recurrences (n)	Effectiveness†	Cost-effectiveness ratio
A	72	637	10 (14%)	0.3	2123
B	98	732	24 (24.5%)	0.17	4306
C	61	768	25 (41%)	0.08	9600

*The mean cost of tests until diagnosis of recurrence, death of patients for an unrelated cause, or the end of the fifth year of follow-up for recurrence-free patients.

†Patients alive 5 years after the detection of recurrence by indicated modality divided by the total number of recurrences detected in minimal or standard schedules.

Table 6. Cost-effective ratios of follow-up tests

	Follow-up modalities	Mean cost* (euros)	Effectiveness†	Cost-effectiveness ratio
Abdominal	minimal	63	0.11	573
Ultrasound	standard	294	0.13	2261
CEA assay	minimal	34	0.025	1478
	standard	161	0.13	1238

CEA = carcinoembryonic antigen.

*The mean cost of tests until diagnosis of recurrence, death of patients for an unrelated cause, or the end of the fifth year of follow-up for recurrence-free patients.

†Patients alive 5 years after the detection of recurrence by indicated modality divided by the total number of recurrences detected in minimal or standard schedules.

increased by referring to stage instead of parietal and lymph node involvement related to the primary tumor and follow-up did not lead to an increased survival rate. Therefore, neither the standard nor the minimal follow-up schedule were as useful for stage C patients as for earlier stage patients. The first explanation is that stage C patients did not have optimal initial treatment: only 44% of stage C patients had chemotherapy. Follow-up cannot compensate for inadequacies in diagnosis and therapy. It should only be proposed after optimal initial treatment. In our study, the follow-up schedule was influenced by whether or not postoperative chemotherapy had been carried out. The second explanation is that Dukes' classification is not an effective tool in differentiating recurrence-free patients from patients with unresectable recurrence for whom follow-up is of no benefit. The next step in research concerning the follow-up of colorectal cancer is to find different prognostic indicators to determine which selected group of patients will benefit most from follow-up by detecting early curable recurrent cancer. To date, we cannot recommend evidence-based clinical guidelines for follow-up as a function of the primary stage of colorectal cancer. However, Bleeker and associates have shown that the association of abdominal ultrasonography and colonoscopy was more cost-effective than CEA monitoring, chest x-ray, and physical examination in patients with Dukes' stage C colorectal cancer.[17]

In the literature, it is shown that only one-third of recurrences or metastases are detected by physical examination.[18–20] In our study, physical examination detected 39% of recurrence, but was one of the least effective tests with no survivals among patients with recurrence. The most effective indicator of recurrence in the literature are the CEA levels,[18,21] but CEA monitoring is only marginally cost-efficient and is not helpful for most patients.[22] In our series, all patients with recurrence detected by CEA monitoring who had a radical resection were alive 5 years after the diagnosis of recurrence and CEA monitoring was one of the most cost-effective tests, especially in the standard follow-up group. Performances of ultrasonography (sensitivity = 0.8) are inferior to performances of the CT scan (sensitivity = 0.91)[23,24], but the convenience of ultrasonography explains why it is more commonly used as the primary test. These performances were optimal for stage C patients.[17] In our studies, ultrasonography was shown to be the most effective test for both the diagnosis of recurrence and the diagnosis in patients alive 5 years after the diagnosis of recurrence, particularly for the minimal follow-up group. Ultrasonography seems to be suitable for the follow-up of hepatic secondary tumors and because it is both less expensive and quicker than other imaging procedures, it should be used as the first-line confirmatory procedure in asymptomatic patients.[25] Although not currently recommended by the American Society of Clinical Oncology, ultrasonography should therefore be included in follow-up schedules for colorectal cancer after potentially curative resection.

Helicoid CT-scan with injection is essentially recommended in France after liver and abdominal ultrasonography in cases where there is technical difficulty, doubt, or negative exploration with a high CEA level. The need for induced irradiation, injection of the iodine-containing contrast product, and the cost tend to make it a second intention examination in many countries. However, some authors, notably in the United States, advocate using it systematically in follow-up.[26] The main advantage of this is the very high sensitivity to tumors of over 1 cm (sensitivity = 0.91%). Unfortunately, performances are much lower for tumors under 1 cm (sensitivity < 0.56%).[27]

The effectiveness of the chest x-ray has not been proven even though it is found to detect one-half of pulmonary metastases.[28] Only 3%–7% of recurrences were detected by chest x-ray with a rate lower than 1% for potentially curative resection.[19] In our series, 4% of recurrences were detected by chest x-ray.

In regard to loco-regional recurrence, colonoscopy is the least sensitive test.[29] Its sensitivity is lower than barium enema, namely because barium enema objectifies images of extrinsic compression.[26] In our study, the effectiveness of colonoscopy was poor for both the diagnosis of recurrence and the survival of patients with recurrence. However, colonoscopy could be beneficial in some cases. First, it could be beneficial in the case of patients who did not undergo full preoperative colonoscopy due to an obstructing tumor and second, it could be beneficial in the case of patients for whom screening for other forms of cancer (metachronal cancers) or polyps is required.

The main benefits are gained by selective use in young patients with continuing polyp formation leading to a high risk of developing metachronous cancer.[28] In our series, the sole benefit was in screening metachronous cancers. Seven patients had metachronous colorectal cancer and 6 of these patients were still alive 5 years after diagnosis.

On the basis of our experience, we conclude the following: (i) the sole indicator of selection, Dukes' classification, is a poor tool of selection and estimation of follow-up, (ii) we suggest that the follow-up tests should only include CEA monitoring and abdominal ultrasonography for the diagnosis of recurrence in new controlled studies, and (iii) colonoscopy performed every 3 years would only be called

for in the case of screening for other forms of cancer (metachronal cancers) or polyps.

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Clinical Characteristics of Familial Adenomatous Polyposis and Management of Duodenal Adenomas

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The aim of this study was to evaluate the clinical characteristics of patients with familial adenomatous polyposis (FAP) undergoing surgical treatment over a 10-year period and specifically to evaluate the incidence and clinical outcome of patients treated for duodenal adenomas. Patients with FAP who underwent surgical treatment for colonic polyposis at the University of Louisville from January 1992 to July 2002 were investigated. Surgical treatment included colectomy and ileal J-pouch–anal anastomosis (IPAA) or completion proctectomy with or without IPAA in those who had previously undergone subtotal colectomy elsewhere. All patients underwent screening gastroduodenoscopy at 3-year intervals beginning at the time of diagnosis or referral. Postoperative morbidity, mortality, and functional outcome were evaluated, as well as the occurrence of extracolonic manifestations and results of treatment for duodenal adenomas when required. Fifty-four patients were included in the study (mean age 28 ± 2 years). Twenty-seven of them (50%) underwent colectomy and IPAA as the initial operation. Twenty-seven patients had previously undergone subtotal colectomy. Eight of these 27 patients had cancer in the rectum, of which three were T4 and one was T2N1 cancer. Twenty-two patients underwent a completion proctectomy and three required abdominoperineal resection. Twenty of the 54 patients developed duodenal adenomas. The mean age of diagnosis of duodenal disease was not significantly different from that of patients who were still free of duodenal polyps (40 ± 11 vs. 34 ± 12 years). Seven of these 20 patients underwent local excision of duodenal polyps (either endocopically or transduodenally); four of these patients developed recurrent disease. Six patients underwent pancreaticoduodenectomy for duodenal adenomas with severe dyplasia. These patients experienced an increased number of bowel movements, from five per day (range 4 to 8) to 10 per day (range 6 to 15). One patient required pouch excision and end ileostomy to control diarrhea. Our data demonstrate the following: (1) patients with FAP who have undergone prior subtotal colectomy and ileorectal anastomosis have a high risk of developing advanced cancer in the rectal stump; (2) duodenal adenomas are common in patients with FAP and may occur at an early age; (3) screening duodenoscopy should be initiated at the time of diagnosis of FAP; (4) local excision of duodenal adenomas is associated with a high risk of local recurrence; and (5) even though pancreaticoduodenectomy is the treatment of choice for advanced duodenal adenomas, this procedure may adversely affect pouch function in some patients. (J GASTROINTEST SURG 2004;8:559–564)

KEY WORDS: Familial adenomatous polyposis, rectal cancer, ileal pouch–anal anastomosis, pancreaticoduodenectomy, duodenal adenomas

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized predominantly by the formation of colonic adenomas. When left untreated, colonic polyps progress to cancer. In the past, patients with FAP were commonly treated with subtotal colectomy and ileorectal anastomosis, which did not eliminate the risk of rectal cancer. We believe that the current treatment of choice is total colectomy with ileal J-pouch–anal anastomosis (IPAA), an operation that leads to a meaningful prolongation of life in these patients.

Patients with this genetic disease may also experience extracolonic manifestations many years after their initial colonic surgery. These patients are often

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referred to as having Gardner's syndrome. Duodenal polyps, and intra-abdominal desmoids in particular, are among the manifestations that may have the most profound adverse effect on prognosis. Even though colorectal cancer is still the most common cause of death in patients with FAP, in the future it will likely be surpassed by the increasing mortality secondary to duodenal cancer and intra-abdominal desmoids.[1,2] The prevalence of duodenal polyps increases with time after the initial diagnosis of the disease,[3–6] which is not appreciated by many clinicians. Eighty to 98% of these patients will eventually develop duodenal adenomas.[7,8] Involved in these considerations are the number and size of the polyps, their histology and the severity of the dysplasia, and a very complex array of factors for each patient. Because these adenomas may progress to duodenal cancer, aggressive screening and endoscopic or surgical treatment is indicated if duodenal adenomas are identified. Controversy exists as to which is the best type of treatment for these polyps. The aim of this study was to evaluate the clinical characteristics of patients with FAP treated over a 10-year period, to determine the incidence of the extracolonic manifestations associated with the greatest morbidity and mortality—that is, duodenal adenomas and intra-abdominal desmoids, and to assess the outcome of treatment in patients with duodenal adenomas.

MATERIAL AND METHODS

Patients with FAP who underwent surgical treatment for colonic polyposis at the University of Louisville by a single surgeon over a 10-year period from January 1992 to July 2002 were investigated. Surgical treatment at our unit included either IPAA or abdominoperineal resection if a locally advanced rectal cancer was identified. Completion proctectomy was performed only when dysplasia, cancer, or multiple new polyps were discovered. IPAA was performed either primarily at the time of colectomy or with completion proctectomy in patients with FAP who had undergone prior subtotal colectomy elsewhere. In the majority of cases, IPAA was performed with rectal mucosectomy and hand-sewn anastomosis with a diverting loop ileostomy if anastomotic tension was present. All patients underwent screening gastroduodenoscopy at 3-year intervals. An end-viewing scope was initially used. If biopsy-proved adenomatous change was identified, a side-viewing duodenoscope was used for subsequent examinations. Endoscopic retrograde cholangiopancreatography (ERCP) was performed to investigate the papilla if indicated. The guidelines for ERCP vary substantially and have been discussed in recent articles[9,10] and a major monograph.[11] Within our department is an uncommon depth of expertise with ERCP, and three surgeons regularly perform more than a dozen pancreatoduodenectomies per year, which in turn, permits individualized patient management. Duodenal adenomas were considered to be advanced when they were larger than 10 mm, had a tubulovillous or villous microscopic appearance, or exhibited dysplasia.[8,12]

Intra-abdominal desmoids were diagnosed either at the time of surgery or by CT scanning if patients developed symptoms of abdominal pain or small bowel obstruction. Postoperative morbidity, mortality, and functional outcome were evaluated, as well as the occurrence of extracolonic manifestations and the results of treatment for duodenal disease when required.

Statistical analysis was performed using the *t*-test to compare the patients' ages in those with and without duodenal adenomas. The Kaplan-Meier estimation technique was used to assess the cumulative probability of developing duodenal adenomas. Statistical analysis was performed with the use of SPSS for Windows 11.01.

RESULTS

Fifty-four patients were included in the study. The mean age of patients at the initial operation for colonic polyposis was 28 ± 8 years (range 13 to 47 years). Twenty-seven patients (50%) underwent total proctocolectomy and IPAA as their first operation. In two of these patients, an unsuspected stage I carcinoma was identified in the surgical specimen. The remaining 25 patients (48%) had undergone prior subtotal colectomy and ileorectal anastomosis elsewhere and were referred to our institution for treatment of rectal disease. Twenty-two of these patients underwent completion proctectomy with IPAA, whereas three patients underwent abdominoperineal resection for locally advanced rectal cancer and eventually died of recurrent disease. The mean interval between the initial procedure and the completion proctectomy was 16 ± 9 years (range 1 to 36 years). In eight of these patients, rectal carcinoma was present: T4 in three of them and T2N1 in one.

Duodenal Adenomas

Twenty patients (37%) developed duodenal adenomas, whereas 34 patients (63%) are free of duodenal disease a mean of 7 years (range 0 to 35 years) from the time of diagnosis of FAP. The cumulative probability of developing duodenal disease relative to the initial colonic surgery for FAP is shown in Fig. 1.

Fig. 1. Cumulative probability of developing duodenal adenomas following initial colon surgery. *Solid line* represents the probability of onset of duodenal adenomas; *dotted lines* show the probability within a 95% confidence interval. FAP = familial adenomatous polyposis.

Twenty years after the initial operation for FAP, it is estimated that 54% of patients will develop duodenal adenomas. The interval between the initial operation for colonic polyposis and the onset of duodenal polyposis, based on the Kaplan-Meier estimation, is for our patients 21 ± 2 years (95% confidence interval 17 to 25 years). There was no statistically significant difference between the age of onset of duodenal adenomas and the age of those patients currently free of duodenal disease (40 ± 11 years vs. 34 ± 12 years). Thirteen of the 20 patients with duodenal polyps had dysplastic adenomas. The presence of dysplasia was confirmed by at least two independent pathologists. The management of duodenal adenomas requires judgment, experience, and a full range of technical skills with individualization of therapy. Patient understanding and attention to follow-up plans are essential.

Local Procedures. Five patients underwent endoscopic polypectomy (two with argon fulguration); three of these patients required subsequent repeated procedures for recurrent disease. Two patients underwent transduodenal local excisions (one ampullectomy, one polyp excision). One of these patients had severe postoperative pancreatitis that required surgical treatment and a subsequent duodenal recurrence that required endoscopic fulguration. Overall, four patients had recurrence after local excision. The mean time to recurrence was 19 months after endoscopic polypectomy (range 6 to 24 months).

Radical Excision. Four patients underwent pancreaticoduodenectomy for treatment of dysplastic duodenal polyps that were believed not to be amenable to endoscopic or local procedures an average of 4.2 years (range 2 to 7 years) after IPAA. After pancreaticoduodenectomy, the number of bowel movements per day doubled, from a mean of five per day (range 4 to 8 per day) to 10 per day (range 6 to 15 per day). Two of these four patients required scheduled somatostatin to control the frequency of bowel movements and maintain acceptable bowel function. One of these patients subsequently underwent excision of the ileal pouch because of recalcitrant diarrhea with incontinence and perianal excoriation. The other patient had unrecognized small bowel obstruction after IPAA; reoperation disclosed adhesions and small desmoid tumors and has been followed by relief of pain and normalization of bowel function (4 bowel movements per day). The other two patients required strict food restrictions and heavy use of antidiarrheal medication. Three of the four patients treated with pancreaticoduodenectomy experienced weight loss (9 to 25 kg) postoperatively (i.e., over the first 2 postoperative years), and one patient had several episodes of pancreatitis requiring hospital readmission.

Intra-Abdominal Desmoids

Intra-abdominal desmoids developed in seven patients (13%), four of whom required either surgery and/or chemotherapy because of the malignant behavior of these tumors with recurrent small bowel obstruction. No deaths have occurred thus far secondary to either duodenal disease or intra-abdominal desmoids. One patient, thought to be ill as a result of a desmoid tumor, at operation actually had another primary adenocarcinoma with mesenteric lymph node metastases plus four additional large benign jejunal villous adenomas.

DISCUSSION

Virtually all patients with FAP who do not receive treatment are at risk of developing colorectal cancer. Colorectal cancer remains the leading cause of death in patients with FAP, accounting for 58% to 73% of all FAP deaths.[1,2] There are still a significant number of patients who initially undergo subtotal colectomy with preservation of the rectum or even part of the colon. In our series, 25 (48%) of the 52 patients who underwent surgery for FAP had a prior subtotal colectomy, and 32% were found to have cancer in the rectal stump. For this reason we believe that the treatment of choice is early prophylactic total proctocolectomy with IPAA rather than colectomy with ileorectal anastomosis, which is often based on the number of polyps within the rectum and the likelihood of attentive compliance in follow-up by the patient.

Because of the underlying genetic cause of this disease, the prolongation of life in these patients as a result of colectomy and IPAA does, however, permit time for the growth of tumors in other organs, in particular in the duodenum. There is a high prevalence of duodenal polyps in patients with FAP that increases with age[4,13] and can be as high as 98% at age 75 years. In our series the prevalence of duodenal disease was only 35%. This may be due to the fact that our patient population is still relatively young. Others have also reported that the severity of duodenal polyposis increases with age.[14] Our data demonstrate that duodenal polyps are discovered after a mean interval of 21 years from the time of the initial surgery for FAP. The age at diagnosis of duodenal adenomas among our patients was not significantly higher than the age of those patients who have not yet developed duodenal adenomas. These data suggest that patients should begin duodenal screening early, preferably at the time the disease is diagnosed.

The incidence of duodenal cancer in FAP patients ranges from 3% to 4%, which is 100 to 300 times greater than the general population.[5,15,16] Most of these cancers arise from "advanced duodenal polyps"; patients with Spigelman class IV adenomas have a 36% risk of developing duodenal cancer.[17] Treatment of duodenal adenomas is advised because of the high risk of progression to cancer that is associated with advanced polyps, the poor prognosis of overt duodenal cancer,[16,18,19] and the favorable prognosis for early-stage lesions treated surgically or endoscopically.[16] The unpredictable behavior of duodenal polyps, and the lack of predictive factors that accurately indicate which adenomas will progress to cancer, suggest the importance of early screening duodenoscopy. We believe that this should be performed even in young patients, despite the evidence that progression of duodenal adenomas occurs in a minority of patients.[20,21]

In selected cases, screening for duodenal abnormalities and polyps includes the use of ERCP to rule out the presence of ampullary adenomas. This procedure, even in experienced hands, has a risk of morbidity[22] and even death resulting from post-ERCP pancreatitis.[1,23] In our series, overall, 25% of the patients with duodenal adenomas had pancreatitis. In one patient pancreatitis was the first symptom of ampullary adenoma, which required pancreatic duct stenting. Pancreatitis, if severe, may be lethal and therefore should be considered as a cause of further morbidity[24] in the natural history of these patients and a potential cause of death, as was observed by Belchetz et al.[1] We observed one case of pancreatitis following screening with ERCP, one case as a postoperative complication after transduodenal ampullectomy (these two required surgery to drain intra-abdominal fluid collections), and one case of pancreatitis after pancreaticoduodenectomy. On the other hand, of the last 707 consecutive ERCPs reported to a quality control group, 697 were successful and four resulted in significant pancreatitis.[25]

Recent data suggest that medical treatment with cyclooxygenase 2 inhibitors may result in a significant reduction in the size and number of duodenal adenomas,[26] but polyp excision is still considered the best option for advanced adenomas (i.e., polyps larger than 10 mm with tubulovillous or villous appearance and dysplastic changes).[8,12] The proper treatment for duodenal adenomas remains controversial. The risk of recurrence is high after endoscopic or transduodenal excision,[5,18,19,23] and endoscopic ablation is technically difficult.[27] In our series, three of seven patients who underwent local excision had an early recurrence in the duodenum. Duodenal excision via pancreaticoduodenectomy or as a pancreas-sparing duodenectomy[28,29] is considered an option in patients with advanced duodenal polyposis. In our series, 12% of FAP patients had advanced duodenal polyposis or cancer and required pancreaticoduodenectomy. This

is similar to the 12% reported by Ruo et al.[30] It has been postulated that pancreaticoduodenectomy with partial gastric resection and vagotomy may have adverse effects on the quality of life with dumping syndrome, fatty stools, and difficulty in gaining weight postoperatively.[31,32] In patients who have previously undergone a total colectomy with IPAA, the results following pancreaticoduodenectomy may be worse,[33] as was also seen in our patients. These patients may have a significant increase in the number of bowel movements and may even experience fecal incontinence. Severe diarrhea, which can be resistant even to aggressive antidiarrheal therapy, interfered with daily activity in three of our four patients who underwent pancreaticoduodenectomy. One patient eventually required pouch excision and construction of an end ileostomy because of difficulty in controlling bowel movements and severe perineal excoriation. Quality-of-life issues have not been evaluated in these patients. This is important, however, because these patients undergo pancreaticoduodenectomy at a fairly young age. A single case of what was thought to be pouch dysfunction secondary to the pancreatoduodenectomy proved at reoperation to be severe perineal small bowel obstruction due to a single adhesion; the severe diarrhea disappeared after adhesiolysis only.

Patients with FAP can also be impaired by the presence of intra-abdominal desmoids that represent another potential cause of morbidity and mortality. The prevalence of abdominal desmoids in patients with FAP is 10%.[34] In patients who have undergone prophylactic total colectomy, desmoids were said to be the cause of death in 30%.[2] Their etiology is unknown and their clinical behavior is unpredictable. Both surgical and medical treatment is often disappointing. In our series, symptomatic desmoids were diagnosed at a mean age of 41 years. No deaths from desmoids have thus far occurred, but four of seven desmoids demonstrated an aggressive behavior requiring surgery to relieve small bowel obstruction plus aggressive chemotherapy. One of these patients ultimately required pouch excision and end ileostomy.

CONCLUSION

Our data demonstrate that a significant number of patients who undergo IPAA after a prior subtotal colectomy and ileorectal anastomosis have advanced cancer present within the retained rectal stump, which remains the leading cause of death in these patients. With prolongation of their lives as a result of colectomy, FAP patients subsequently have a high risk of developing duodenal cancer, even at an early age. For this reason screening duodenoscopies are recommended beginning at the time of disease diagnosis. The proper treatment of duodenal adenomas is controversial. Pancreaticoduodenectomy, which is an option for patients with advanced duodenal polyposis, may be associated with a significant worsening of bowel function in patients who have previously undergone IPAA.

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Diffuse Pancreatic Adenocarcinoma Identified in an Adult With Annular Pancreas

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Annular pancreas is a congenital anomaly resulting from malrotation of the pancreatic ventral bud. Although annular pancreas in the adult is rare, it may be recognized with increased frequency as a result of more liberal use of pancreatic imaging studies in patients with chronic abdominal pain and suspected chronic pancreatitis. Malignancy in the setting of annular pancreas is an uncommon event that has been reported previously but has almost always been related to the annular (ventral) segment. We report an interesting case in which pancreatic adenocarcinoma diffusely involving the dorsal (nonannular) segment presented in a middle-aged female patient. This unusual presentation points out the importance of considering neoplasia as part of the differential diagnosis and the possibility of pancreatic pathology in the dorsal, nonannular segment when there is no obvious duodenal or biliary obstruction involving the annular ventral segment. (J GASTROINTEST SURG 2004;8:565–568)

KEY WORDS: Pancreas, annular, adenocarcinoma, pancreatitis

Annular pancreas is a rare embryologic abnormality resulting from malrotation of the pancreatic ventral bud. Since it was first reported by Tiedermann[1] in 1818, the identification of associated anomalies, coexisting medical conditions, and the diagnosis and treatment of annular pancreas has improved. This congenital abnormality is usually diagnosed in the newborn infant, where it presents as obstruction of the duodenum. In adults, annular pancreas has been associated with peptic ulceration, duodenal obstruction, pancreatitis, and obstructive jaundice. Malignancy in the setting of annular pancreas is an unusual event. We report herein an interesting case in which pancreatic adenocarcinoma diffusely involving the dorsal (nonannular) segment presented in a middle-aged female patient.

CASE REPORT

A 52-year-old woman presented with a 12-month history of epigastric abdominal pain. She was initially thought to have chronic cholecystitis and underwent laparoscopic cholecystectomy with intraoperative cholangiography. No gallstones were found, and when her pain persisted postoperatively associated with slightly elevated pancreatic enzyme levels (amylase, 115 U/L; lipase, 245U/L), an abdominal computed tomography (CT) scan was obtained. This study demonstrated mild enlargement of the pancreatic head and body with peripancreatic edema, focal pancreatic head hyperdensities, and dilatation of the pancreatic duct. Circumferential soft tissue around the duodenum was evident but was not appreciated on initial interpretation (Fig. 1). There was no evidence of dilation of the biliary duct system. The patient was referred to the Pancreatic Diseases Center at the University of Cincinnati Medical Center. An endoscopic retrograde cholangiopancreatography (ERCP) was performed, which on injection of the major papilla revealed a ventral pancreatic duct that encircled the duodenum. The dorsal duct was not visible on this injection, which is consistent with complete pancreatic divisum. The minor papilla and dorsal pancreatic duct were unable to be cannulated or visualized (Fig. 2). The persistent pain was attributed to chronic pancreatitis associated with annular pancreas and pancreas divisum. At operation the preoperative diagnosis of annular pancreas was confirmed (Fig. 3), and this tissue, although somewhat firm to palpation, appeared surprisingly unremarkable. However, the

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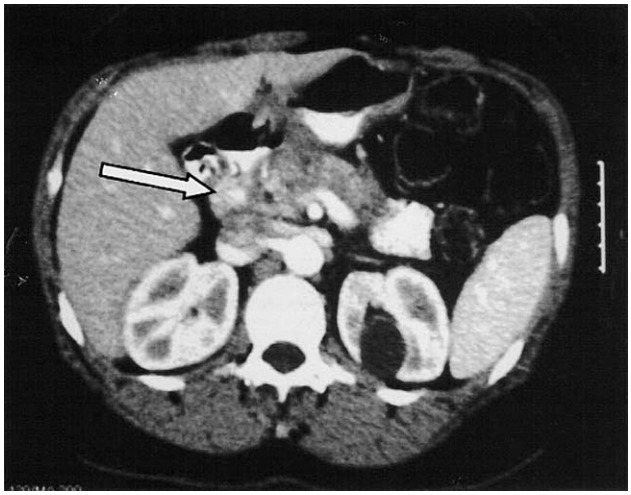

Fig. 1. Abdominal CT scan illustrating mild enlargement of the pancreatic body and head with peripancreatic edema and focal pancreatic head hyperdensities.

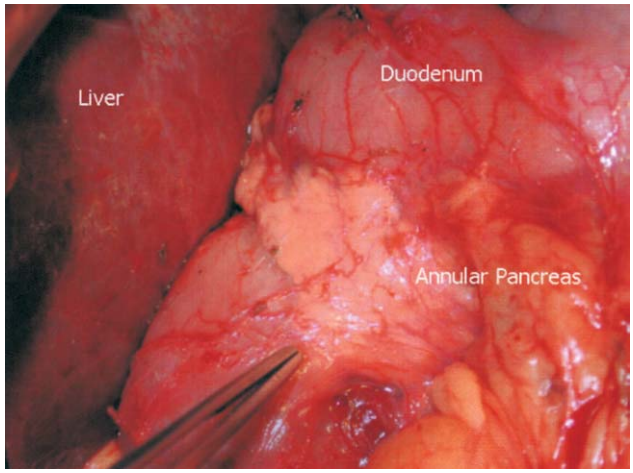

Fig. 3. Intraoperative photograph demonstrating the presence of the annular pancreas with relatively normal-appearing pancreatic tissue.

dorsal segment of the gland, particularly in the head, was markedly indurated and diffusely hard. A frozen section was obtained from the inferior border of the pancreas at the level of the superior mesenteric vein, which demonstrated findings consistent with chronic pancreatitis. Pancreaticoduodenectomy was performed to remove the presumed inflammatory head mass. Frozen section of the transected pancreatic margin at this time revealed adenocarcinoma. Additional distal resection was performed, but again frozen-section analysis of the margin revealed adenocarcinoma. A completion (total) pancreatectomy was performed. Final pathogic examination demonstrated diffuse, moderately well–differentiated infiltrating pancreatic adenocarcinoma (T3N0Mx). Interestingly, the annular portion of the pancreas showed only mild chronic pancreatitis but no evidence of neoplasia (Fig. 4). The postoperative course was unremarkable, and the patient was discharged on postoperative day 14. Subsequently the patient began adjuvant chemoradiation, which was poorly tolerated and ultimately discontinued. She died 9 months after the operation of recurrent carcinoma.

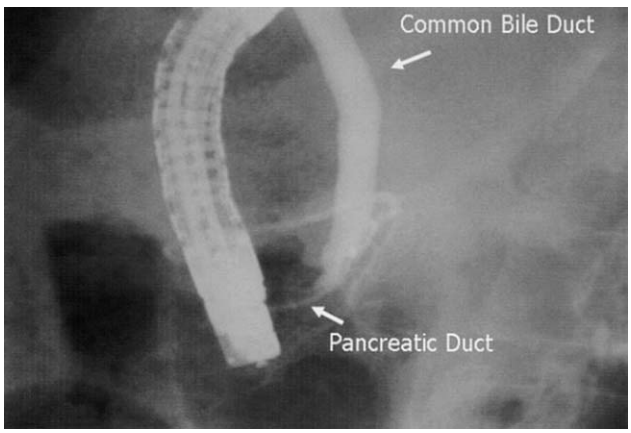

Fig. 2. ERCP demonstrating pancreatic duct encircling the second portion of the duodenum associated with the annular pancreas.

DISCUSSION

Annular pancreas is an unusual congenital abnormality that, based on autopsy series, is estimated to occur in approximately 1 in 6500 cases. More recently, among patients undergoing ERCP (which represents a subset of individuals with a higher prior probability of pancreatic pathology), approximately 1 in 1000 cases is found to have annular pancreas.[2,3]

During normal development of the pancreas in the first 4 to 8 weeks of gestation, the rotation and fusion of the ventral and dorsal pancreatic bud results in the formation of the pancreas and the main duct of Wirsung; the minor duct of Santorini represents the vestigial remnant of the dorsal duct.[4] Thus the ventral bud forms the bulk of the head and uncinate process, whereas the remainder of the head, neck, body, and tail of the pancreas is formed by the dorsal bud. Developmental arrest in which the ventral bud fails to completely rotate is the basis of annular pancreas, although the genetic and molecular basis for this anomaly remains obscure. Typically the annular (ventral) segment surrounds the duodenum just proximal to the ampulla of Vater.[5] Affected infants may have associated conditions including Down's syndrome, duodenal or esophageal atresia, tracheoesophageal

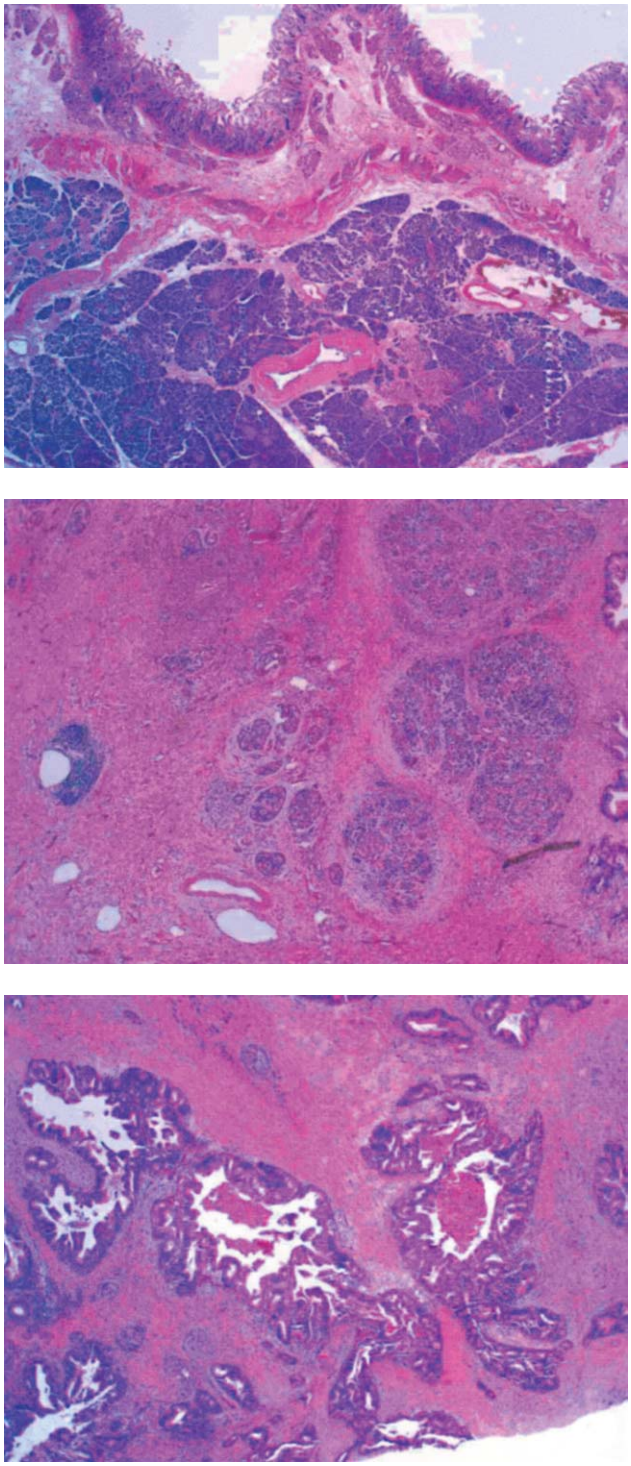

Fig. 4. top, Photomicrograph of an annular pancreas. (Hematoxylin & esoin stain; original magnification ×10.) **middle**, Photomicrograph of the annular portion of the pancreatic gland with chronic pancreatitis. (Hematoxylin & esoin stain; original magnification ×10.) **bottom**, Photomicrograph of diffuse, moderately differentiated infiltrating adenocarcinoma of the remaining gland. (Hematoxylin & esoin stain; original magnification ×20.)

fistula, intestinal malrotation, and various cardiac anomalies.[6] The most common presentation of annular pancreas in children is duodenal obstruction during the postnatal period.[7]

Annular pancreas in adults typically does not present until the third to fifth decade of life.[8,9] Although annular pancreas in the adult is rare, it may be recognized with increased frequency because of the more liberal use of abdominal CT scans and ERCP in patients with chronic abdominal pain and suspected chronic pancreatitis. The presentation of symptomatic annular pancreas in adults most commonly involves jaundice, pain, or duodenal obstruction. The development of chronic pancreatitis affecting the annular (ventral) bud is the factor that leads to gradual obstruction of the duodenum or impingement on the ampullary apparatus, leading to the clinical presentation.

Malignancy developing in the setting of annular pancreas has been reported previously, but this has almost always been related to the annular (ventral) segment. The propensity of malignancy to affect the ventral segment has been attributed to the presence of chronic inflammatory changes associated with pancreatitis. Kiernan et al.[6] reviewed 281 cases of annular pancreas in 1980, and more recently Yogi et al.[10] reviewed 170 cases from the Japanese literature in 1999. Of these reported cases, only 10 were associated with malignancy and consisted of pancreatic carcinoma, ampullary carcinoma, and insulinoma.[10–15] To our knowledge there is only one other English language report of a patient with pancreatic cancer arising in the dorsal (nonannular) segment.[5] This unusual presentation of pancreatic adenocarcinoma in the dorsal segment of a patient with annular (ventral) pancreas points out the importance of considering neoplasia as part of the differential diagnosis. Of note, the patient developed malignancy without jaundice, indicating that the main common bile duct (which is associated with the ventral bud) can be spared from involvement despite the presence of extensive, diffuse tumor involvement in the dorsal bud.

Although annular pancreas presenting in the adult remains a relatively uncommon clinical occurrence, recognition of the entity will increase as the threshold for pancreatic imaging in minimally symptomatic or even asymptomatic patients decreases. In symptomatic patients, the possibility of pancreatic pathology in the dorsal, nonannular segment should be considered in situations where there is no obvious duodenal or biliary obstruction involving the annular ventral segment.

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Cyst Fluid Tumor-Associated Trypsin Inhibitor May Be Helpful in the Differentiation of Cystic Pancreatic Lesions

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In clinical practice it is important to differentiate pseudocysts from cystic pancreatic tumors, especially potentially malignant mucinous cystic tumors. We investigated three new markers—tumor-associated trypsin inhibitor (TATI) and the free α and β subunits of human choriogonadotropin (hCGα and hCGβ, respectively)—in the cyst fluid of patients with cystic pancreatic lesions and compared the concentrations of these markers to those of carcinoembryonic antigen (CEA), CA 19-9, CA 242, CA 125, CA 15-3, alpha-fetoprotein, and tissue polypeptide antigen in order to distinguish benign cysts from malignant cysts. Between 1995 and 2001, a total of 34 patients operated on for cystic pancreatic lesions at Tampere University Hospital were included. Cyst fluid was aspirated at operation and stored at −70 C. The histologic diagnosis was pseudocyst in 23 patients, serous cystadenoma (SCA) in four patients, benign mucinous cystadenoma (MCA) in four patients, cystic papillary neoplasm (CPN) in one patient, glucagonoma in one patient, and malignant endocrine islet cell carcinoma (EC) in one patient. Significantly higher concentrations of TATI were found in patients with MCA and EC (2239 ± 149 μg/L [mean ± SEM]) than in patients with pseudocyst (55 ± 29 μg/L; $P = 0.001$) and in patients with SCA (36 ± 23 μg/L; $P = 0.01$). The patient with CPN and the patient with glucagonoma had relatively low levels of TATI (30.7 and 46.5 μg/L). Mean CEA was higher in patients with MCA compared to those with pseudocysts (19,993 ± 9418 vs. 53 ± 20 μg/L, $P = 0.002$) and SCA (0.4 ± 0.1 μg/L; $P = 0.02$), but in the patient with malignant EC, the patient with CPN, and the patient with glucagonoma, CEA was normal. HCGα, hCGβ, CA 19-9, CA 242, CA 125, CA 15-3, alpha fetoprotein, and tissue polypeptide antigen could not distinguish between MCA vs. pseudocyst or SCA, because both normal and elevated values were seen in all groups. To our knowledge, this is the first time that TATI has been quantitated in the cyst fluid of patients with cystic pancreatic lesions. It appears to be a potential marker in the differential diagnosis of benign from malignant cystic pancreatic lesions. (J GASTROINTEST SURG 2004;8:569–574)

KEY WORDS: Cystic pancreatic lesions, TATI, tumor markers

The most common cystic lesions of the pancreas are pseudocysts, accounting for 80% to 90% of all cystic pancreatic lesions. Of the remaining 10%, the majority are cystic neoplasms.[1] The most frequent histologic types of these neoplasms are mucinous cystadenoma (MCA) or serous cystadema (SCA). Mucinous tumors are malignant or premalignant lesions, whereas serous cystadenomas are considered benign with virtually negligible risk for malignancy.[2] To select the appropriate treatment, it is important to differentiate pseudocysts from cystic tumors, especially from potentially malignant tumors. Although the patients with pseudocysts usually have a typical disease history (previous period of acute pancreatitis or chronic pancreatitis), typical radiologic findings, such as calcifications in the pancreatic parenchyma but not in the cyst wall, or typical findings of chronic pancreatitis in magnetic resonance cholangiopancreatography or in endoscopic retrograde cholangiopancreatography,[3] up to 37% of cases of neoplastic

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cysts are misdiagnosed as pseudocysts initially.[4] Although clinical and radiologic evaluation is highly important, this is occasionally not enough to draw correct conclusions in a high-risk patient.

Results of cytologic examination of fine-needle aspirate, when positive, may help in the decision-making process, but the negative predictive value of cytologic findings is poor.[3,5] Cystic fluid amylase activity is typically high in patients with pseudocysts, but high levels have been measured in neoplasms as well.[3–5] Cyst fluid concentration of carcinoembryonic antigen (CEA) is the most frequently used tumor marker, but similar to amylase values and cytologic findings, it is not reliable in individual patients because the sensitivity is not satisfactory.

Tumor-associated trypsin inhibitor (TATI) is a polypeptide that is synthetized by several tumors and cell lines.[6] TATI has been used as a marker for ovarian, bladder, and kidney cancer,[7–10] but its role in diseases of the pancreas is unclear. TATI has been measured from serum, tissue, and bile in patients with pancreatic ductal adenocarcinoma and malignant biliary tract disease, but the sensitivity has remained low in those patients.[11–14]

Human choriogonadotropin (hCG) is normally secreted by trophoplastic cells during pregnancy, but in nontrophoblastic malignancies the levels are usually normal. However, the free β subunit of hCG (hCGβ) is frequently elevated in the serum of patients with various cancers of nontrophoblastic origin (e.g., ovary, colon, bladder, pancreas, uterine, and lung).[15–17] Elevated levels of hCGβ have been measured in 50% of patients with exocrine pancreatic cancer[18–20] and in 37% of the patients with endocrine gastroenteropancreatic tumors.[21]

To the best of our knowledge, TATI and hCGβ have not previously been found in the cyst fluid of patients with cystic pancreatic lesions. We investigated these new markers (hCGβ and TATI) and also the α subunit of hCG in the cyst fluid of patients with cystic pancreatic lesions, and compared them with previously used markers (i.e., CEA, CA 19-9, CA 242, CA 125, CA 15-3, alpha fetoprotein, and tissue polypeptide antigen).

PATIENTS AND METHODS

Between 1995 and 2002, a total of 34 patients (17 women and 17 men) with cystic lesions in the pancreas were operated on at Tampere University Hospital. The median age was 52 years (range 27 to 84 years).

Indications for operation included the following: symptomatic pseudocyst with chronic pancreatitis in 18 patients, unresolved large pseudocyst after acute pancreatitis in two patients, cystic neoplasm in 11 patients, and unclear cystic lesion in three patients. The clinical diagnosis was based on the disease history and CT findings.

During the operation, the cystic lesion was punctured to detect possible hemorrhagic complications of a pseudocyst and to draw a sample of the contents of the lesion. This sample was stored at −70 C for later assay. When the lesion was considered a probable pseudocyst, a 2 × 2 cm specimen was taken for frozen-section analysis to rule out cystic neoplasm by identifying no epithelium in the cyst wall. Based on the disease history, CT scans, and frozen-section analysis, resection was carried out when the lesion was considered a neoplastic cyst.

Final diagnosis was based on clinical follow-up of a minimum of 1 year, on histologic examination of a specimen from the suspected pseudocyst wall, and on the resected specimen when neoplasm was suspected. The final histologic findings included pseudocyst in 23 patients, SCA in four patients, MCA in four patients, cystic papillary neoplasm (CPN) in one patient, glucagonoma in one patient, and endocrine islet cell tumor (EC) in one patient.

Assays

Amylase was quantitated by means of an enzymatic calorimetric method (Roche, Hitatchi alfa-amylase test). TATI, hCGα, and hCGβ were all quantitated with in-house time-resolved immunofluorometric assays.[22] Detection limit of the hCGα assay is 2.8 pmol/L and that of the hCGβ assay is 0.5 pmol/L. Cross reaction of hCG in both assays is less than 0.1%. Interassay coefficient of variation is less than 15% in the hCGα assay (10 to 90 μg/L) and less than 12% in the hCGβ assay (2 to 40 pmol/L). Detection limit of the TATI assay is 0.2 μg/L. Interassay coefficient of variation is less than 10% in the concentration range 3 to 140 μg/L.

CEA and alpha fetoprotein levels were quantitated with time-resolved immunofluorometric assays (AutoDELFIA; Wallac, Turku, Finland). The detection limit of the CEA assay is 0.2 μg/L and the interassay coefficient of variation is less than 3% in the concentration range 3 to 90 μg/L. For alpha fetoprotein the detection limit is 0.1 kU/L and the interassay coefficient of variation is less than 3% in the concentration range 2 to 350 kU/L.

CA 125, CA 15-3, and CA 19-9 were quantitated with immunoenzymometric assays (Immuno1; Bayer, Tarrytown, NY). Detection limits of all assays are less than 1 kU/L. For CA 125, the total coefficient of variation is less than 4% (in the concentration range 15 to 500 kU/L); for CA 15-3 the total coefficient of

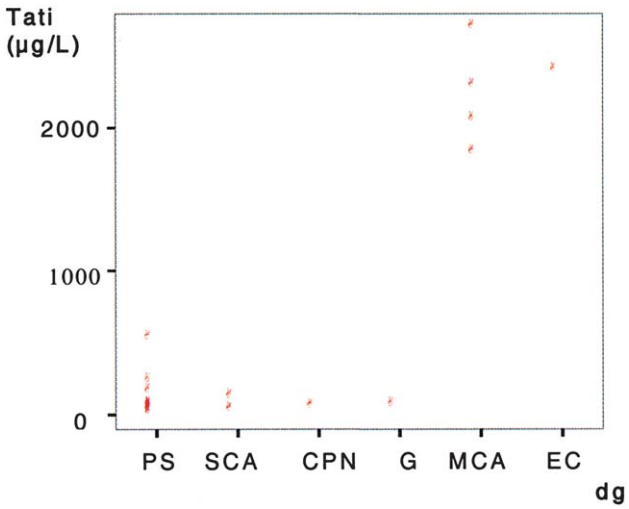

Fig. 1. Cyst fluid tumor-associated trypsin inhibitor (*TATI*) in patients with pseudocyst (*PS*), serous cystadenoma (*SCA*), cystic papillary neoplasm (*CPN*), glucagonoma (*G*), mucinous cystadenoma (*MCA*), and endocrine islet cell carcinoma (*EC*). dg = diagnosis.

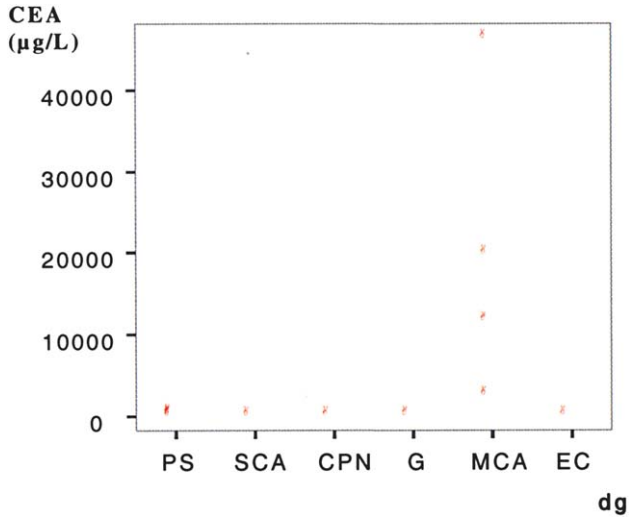

Fig. 2. Cyst fluid carcinoembryonic antigen (*CEA*) in patients with pseudocyst (*PS*), serous cystadenoma (*SCA*), cystic papillary neoplasm (*CPN*), glucagonoma (*G*), mucinous cystadenoma (*MCA*), and endocrine islet cell carcinoma (*EC*). dg = diagnosis.

variation is less than 6% (13 to 190 kU/L); and for CA 19-9 it is less than 3% in the concentration range 14 to 230 kU/L.

CA 242 was quantitated with a manual immunoenzymometric assay (CanAg; Gothenburg, Sweden). The detection limit is 1 kU/L, and the interassay coefficient of variation is less than 7% in the concentration range 13 to 134 kU/L.

TPA was quantitated with an immunoluminometric assay (LIAISON TPA-M; Sangtec Medical, Bromma, Sweden). Detection limit of the assay is 2 U/L and the interassay variation is less than 5% in the concentration range 55 to 620 U/L.

Statistical Analysis

Statistical analysis was performed using the Mann-Whitney U test and the Kruskal-Wallis test. Significance was considered as $P < 0.05$

RESULTS

In the four patients with MCA, serum concentrations of TATI were significantly higher than in the patients with pseudocyst (mean ± standard error of the mean [SEM], 2203 ± 186 vs. 46 ± 24 µg/L, $P = 0.002$) or SCA (36 ± 23 µg/L, $P = 0.02$) (Fig. 1). In the patient with EC, the TATI level was extremely high (2384 µg/L). The patient with CPN and the patient with glucagonoma had relatively low TATI levels (30.7 and 46.5 µg/L, respectively). When comparing subgroups (i.e., malignant or potentially malignant cystic lesions (i.e., EC, MCA, glucagonoma, or CPN) with benign cystic lesions (i.e., pseudocyst or SCA), we found that the patients with a malignant or potentially malignant cystic lesion had significantly higher TATI levels than those with a benign lesion (1609 ± 418 vs. 46 ± 21 µg/L; $P = 0.0001$).

Although the mean level of hCGβ was significantly higher in the patients with malignant or potentially malignant lesions (i.e., EC, MCA, glucagonoma, or CPN) compared to the patients with a benign lesion (i.e., pseudocyst or SCA) (257 ± 163 vs. 18 ± 9 pmol/L; $P = 0.01$), the patients with EC, glucagonoma, and CPN had normal levels of hCGβ, and one patient with pseudocyst had a very high level of hCGβ. We found no differences between these groups in the levels of hCGα (30 ± 12 vs. 40 ± 13 pmol/L; $P = 0.7$).

CEA levels were higher in all patients with MCA compared to those with pseudocyst (19,993 ± 9418 vs. 58 ± 20 µg/L; $P = 0.002$) or SCA (0.4 ± 0.1 µg/L; $P = 0.02$), but in the patient with a malignant endocrine islet cell carcinoma, CEA was normal (1.7 µg/L) (Fig. 2). The patient with CPN and the patient with glucagonoma both had low CEA levels (0.50 µ/L and 1.30 µg/L). CA 19-9 (Fig. 3), CA 242, CA 125, CA 15-3, alpha fetoprotein, and tissue polypeptide antigen were of no value in the differential diagnosis (Table 1).

Although the mean amylase level was significantly higher in the pseudocyst patients compared to the MCA patients (140,891 ± 65,567 vs. 14,475 ± 4,909 U/L; $P = 0.04$) or SCA patients (9,533 ± 186; $P = 0.03$), the dispersion was wide (Fig. 4).

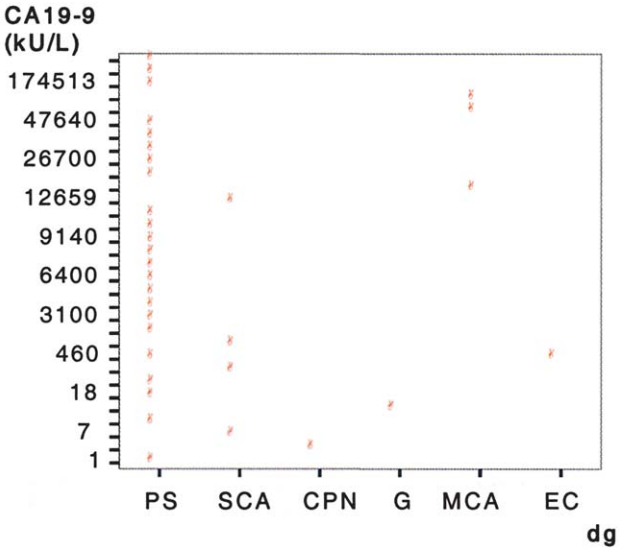

Fig. 3. Cyst fluid CA 19-9 in patients with pseudocyst (*PS*), serous cystadenoma (*SCA*), cystic papillary neoplasm (*CPN*), glucagonoma (*G*), mucinous cystadenoma (*MCA*), and endocrine islet cell carcinoma (*EC*). dg = diagnosis.

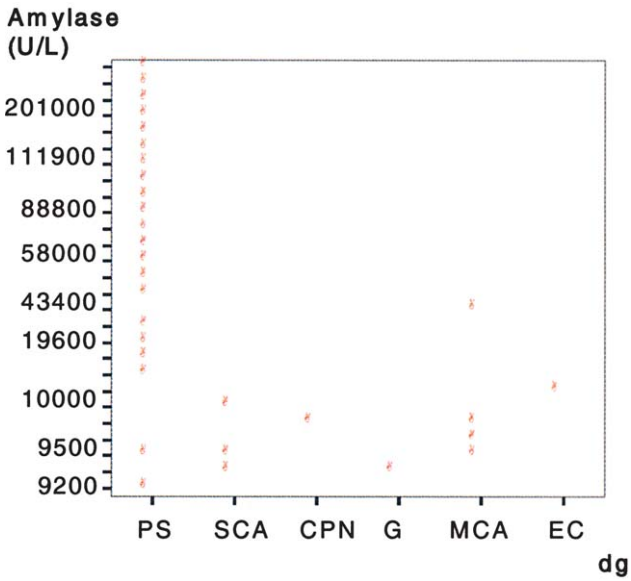

Fig. 4. Cyst fluid amylase activity in patients with pseudocyst (*PS*), serous cystadenoma (*SCA*), cystic papillary neoplasm (*CPN*), glucagonoma (*G*), mucinous cystadenoma (*MCA*), and endocrine islet cell carcinoma (*EC*). dg = diagnosis.

DISCUSSION

The present study is, to our knowledge, the first report documenting the cyst fluid levels of TATI in patients with cystic pancreatic lesions. TATI was isolated in 1982 from the urine of a patient with ovarian cancer by Stenman et al.[23] Later TATI was shown to be identical to pancreatic secretory trypsin inhibitor (PSTI).[24] Satake et al.[25] have measured elevated serum levels of TATI/PSTI both in benign and malignant disorders of the pancreas: in 77% of patients with acute pancreatitis, in 60% of patients

Table 1. CA 242, CA 125, CA 15-3, alpha fetoprotein, and tissue polypeptide antigen in patients with pseudocyst (PS), serous cystadenoma (SCA), mucinous cystadenoma (MCA), cystic papillary neoplasm (CPN), glucagonoma (G), and endocrine islet cell carcinoma (EC)

Tumor marker	PS (n = 23)	SCA (n = 4)	MCA (n = 4)	CPN (n = 1)	G (n = 1)	EC (n = 1)	*P* value*
CA 242 (kU/L)							
Mean ± SEM	281 ± 897	21 ± 23	936 ± 1459	3.5	80.1	6.6	0.14
Median	30.5	15.7	108.6	3.5	80.1	6.6	
CA 125 (kU/L)							
Mean ± SEM	813 ± 3647	776 ± 1470	427 ± 642	11	4.3	48.8	0.55
Median	10.8	60.7	168	11	4.3	48.8	
CA 15-3 (kU/L							
Mean ± SEM	7 ± 13	5 ± 3	138 ± 177	9.9	7.3	8.3	0.11
Median	1.9	6	82	9.9	7.3	8.3	
Alpha fetoprotein (kU/L)							
Mean ± SEM	1 ± 2	0.3 ± 0.7	0	0.6	0	0.6	0.43
Median	0	0	0	0.6	0	0.6	
Tissue polypeptide antigen (U/L)							
Mean ± SEM	6475 ± 15,074	58,100 ± 10,0783	23,230 ± 20,930	167	1240	926,800	0.14
Median	56,800	208,800	49,777	167	1240	926,800	

*Kruskall-Wallis test.

with chronic relapsing pancreatitis, and in 33% of patients with pancreatic cancer. According to their data, the sensitivity of TATI/PSTI in pancreatic cancer is poor.

Although clinical and radiologic examinations are highly important in the differential diagnosis of patients with cystic pancreatic lesions, it did not give us the correct diagnosis in 3 of 23 patients with pseudocyst. These three patients did not have any acute episodes of pancreatitis or chronic pancreatitis in their disease histories and no signs of chronic pancreatitis on CT scans or endoscopic retrograde cholangiopancreatography, which led to resection of the cauda of the pancreas instead of decompression. Instead, according to clinical and radiologic diagnosis, we did find all neoplasms, although we could not make a differential diagnosis between patients with serous cystadenoma, mucinous cystadenoma, cystic-papillary neoplasm, glucagonoma, or endocrine cancer according to clinical and radiologic evaluation. The risk for malignancy in patients with serous cystadenoma is extremely low, even lower than the operative mortality,[2,26] and it is not necessary to operate on these patients, at least not on high-risk patients.

We found very high cyst fluid TATI levels in all patients with mucinous cystadenoma and in the patient with endocrine cancer, whereas the levels in the cyst fluid were low in patients with pseudocyst , in patients with serous cystadenoma, in the patient with glucagonoma, and in the patient with cystic-papillary neoplasm. Although the patients with malignant or potentially malignant cystic lesions of the pancreas (i.e., EC, MCA, glucagonoma, or CPN) had significantly higher cyst fluid TATI levels than the patients with benign lesions (i.e., pseudocyst and SCA), the findings were inconsistent in the patients with glucagonoma and cystic papillary neoplasm. TATI levels were 46.5 and 30.1 μg/L, which both are over the cutoff value, but at the same level as in some of the patients with pseudocyst or serous cystadenoma. Glucagonoma is a very rare tumor of the pancreas with an incidence of one in every 20 million to one in 30 million.[27] It can be malignant as evidenced by local invasion or distant metastases. In our patient with glucagonoma, the histology was considered benign, but we do not know the possible malignant potential of this tumor. According to the study of Lomsky et al.,[28] in 366 autopsies of diabetic patients, the incidence of glucagonoma was 0.8%. This may mean that glucagonoma is underdiagnosed and possibly more often benign than we have thought. Cystic papillary neoplasm is also an uncommon tumor of the pancreas, accounting for less than 1% of all operatively treated pancreatic tumors.[29] Cystic papillary neoplasm was earlier considered to be benign, but patients with liver metastasis have been described.[29] TATI and CEA both had no value in the differential diagnosis of these rare tumors of the pancreas, glucagonoma and CPN.

CONCLUSION

The present small study shows that TATI is a promising marker in differentiating pseudocyst and serous cystadenoma from mucinous cystadenoma and malignant endocrine cystic tumors. It appears to be a better marker than hCGα or hCGβ and the previously measured CEA, CA 19-9, CA 242, CA 125, CA 15-3, alpha fetoprotein, and tissue polypeptide antigen.

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Effects of Preceding Gastrectomy on the Outcome of Pancreatoduodenectomy

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It is a complicated task to perform pancreatoduodenectomy for patients who previously had undergone gastrectomy. This paper reviewed our experience of eight pancreatoduodenectomies in gastrectomized patients. The indications for gastrectomy included gastric cancer in 3 patients, duodenal ulcer in 1 patient, and gastric ulcer in 4 patients. The interval between the two operations ranged from 15–254 months (average: 103 months). All patients underwent pancreatoduodenectomy, and the reconstruction after pancreatoduodenectomy was performed by the Whipple method, the Child method, or other complex Roux-en-Y type methods. All the patients recovered and were discharged without gastrointestinal disorder. The results suggest that the secondary pancreatoduodenectomy does not increase the mortality rate, although we should use the jejunal limb with less tissue damage at the anastomotic site of which circulation is well maintained for choledochojejunostomy and pancreaticojejunostomy. Furthermore, the jejunal limb should be lined carefully to avoid intestinal kinking and excess tension to the anastomosis.
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KEY WORDS: Pancreatoduodenectomy, gastrectomy

INTRODUCTION

Pancreatoduodenectomy (PD) involves various complex operative procedures. The principle of the surgical technique for one-stage pancreatoduodenectomy was established by Whipple and associates.[1] There have been two types of reconstruction procedure for the remnant alimentary tract after pancreatoduodenectomy: Billroth I type reconstruction method (Imanaga method) with gastrojejunostomy; pancreatojejunostomy, and choledochojejunostomy in that order[2,3]; and Billroth II–type reconstruction with choledochojejunostomy, pancreatojejunostomy, and gastrojejunostomy (Whipple method) or pancreatojejunostomy, choledochojejunostomy, and gastrojejunostomy (Child method), in that order.[1,4]

The mortality rate of pancreatoduodenectomy has declined to less than 5% for chronic pancreatitis and 3%–8% for pancreatic cancer.[5] The mortality rate is reported to be less than 1% at specialized centers with large patient numbers and experienced surgeons.[6] In contrast, overall morbidity rates remain high, ranging between 20%–70%.[5]

It is a complicated task to perform pancreatoduodenectomy for patients who previously had undergone gastrectomy. The adhesion and the modified anatomy of the remnant organs can be obstacles for pancreatoduodenectomy. Furthermore, it is easy to speculate that the reconstruction procedure requires experience because the adhesion of the intestine and the shortened mesentery frustrate the mobilization of the small intestine. We recently performed eight pancreatoduodenectomies in gastrectomized patients. This study retrospectively reviews such pancreatoduodenectomies undertaken in gastrectomized patients and explores the lessons learned from pancreatoduodenectomy in gastrectomized patients.

MATERIALS AND METHODS

We conducted a retrospective, descriptive analysis of pancreatoduodenectomy in patients who previously underwent gastrectomy for various indications. Among 156 patients who underwent pancreatoduodenectomy at the Department of Surgery and Surgical

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Basic Science (Kyoto University) from 1991–2000, 8 patients had undergone distal or total gastrectomy before the pancreatoduodenectomy (Table 1). Those 8 patients (7 men and 1 woman) ranged in age from 39–77 years (average: 55 years). The modes of reconstruction after pancreatoduodenectomy are listed and illustrated (Figs. 1–3).

RESULTS

The indications for preceding gastrectomy and the mode of the gastric resection are summarized in Table 1. The indications for gastrectomy included gastric cancer in 3 patients, duodenal ulcer in 1 patient, and gastric ulcer in 4 patients (Table 1). Distal gastrectomy was performed in 6 patients, where Billroth I anastomosis in 3 patients and Billroth II anastomosis in 3 patients were performed, respectively. Roux-en-Y anastomosis was performed for both total gastrectomies.

All patients underwent pancreatoduodenectomy. The indications for pancreatoduodenectomy are summarized in Table 1. The interval between the two operations ranged from 15–254 months (average: 103 months). Those patients who had undergone distal gastrectomy with Billroth I anastomosis had pancreatic ductal cell carcinoma, intraductal papillary mucinous tumors (IPMT), and duodenal gastrinoma. The reconstruction after pancreatoduodenectomy was made by the Whipple method in 2 patients and by the Child method in 1 patient (Fig. 1). Patients who had undergone gastrectomy with Billroth II anastomosis had bile duct cancer, islet cell tumor, and islet cell carcinoma. While preserving the existing gastrojejunostomy, the reconstruction after pancreatoduodenectomy was performed by the Whipple method in 1patient and by the Roux-en-Y method in 2 patients. The pancreatojejunostomy was performed at the elevated jejunum limb and at the origin of the jejunum for each type, respectively (Fig. 2).

Patients who had previously undergone total gastrectomy with Roux-en-Y anastomosis had pancreatic ductal carcinoma and pancreatic gastrinoma. After the second pancreatoduodenectomy, the previous esophagojejunostomy was preserved and the reconstruction was made by the Roux-en-Y type method using the origin of the jejunum or a new Roux limb (Fig. 3).

The operative time for the secondary pancreatoduodenectomy ranged from 8 hours and 20 minutes to 10 hours and 40 minutes (average: 9 hours and 6 minutes). The estimated blood loss ranged from

Table 1. List of the patients who underwent pancreatoduodenectomy after gastrectomy

	Gastrectomy				Pancreatoduodenectomy					
#	Age; gender	Indication	Mode of gastrectomy	Anastomosis	Age	Interval (months)	Indication	Reconstruction	Operative time	Complication
1	48; male	gastric cancer	distal	Billroth I	58	116	Pancreatic cancer	Whipple	10′ 40″	none
2	50; male	gastric cancer	distal	Billroth I	53	39	IPMT	Whipple	8′ 20″	none
3	28; female	gastric ulcer	distal	Billroth I	39	129	duodenal gastrinoma	Child	9′ 05″	none
4	31; male	duodenal ulcer	distal	Billroth II	52	245	bile duct cancer	Roux-en-Y type	9′ 39″	increased amylase in drainage
5	40; male	gastric ulcer	distal	Billroth II	44	46	islet cell tumor	Whipple	8′ 30″	afferent loop syndrome
6	62; male	gastric ulcer	distal	Billroth II	77	187	islet cell carcinoma	Roux-en-Y type	8′ 36″	none
7	65; male	gastric cancer	total	Roux-en-Y	69	43	pancreatic cancer	Roux-en-Y type	9′ 50″	afferent loop syndrome
8	45; male	gastric ulcer	total	Roux-en-Y	46	15	pancreatic gastrinoma	Roux-en-Y type	8′ 23″	none

IPMT = intraductal papillary mucinous tumors.

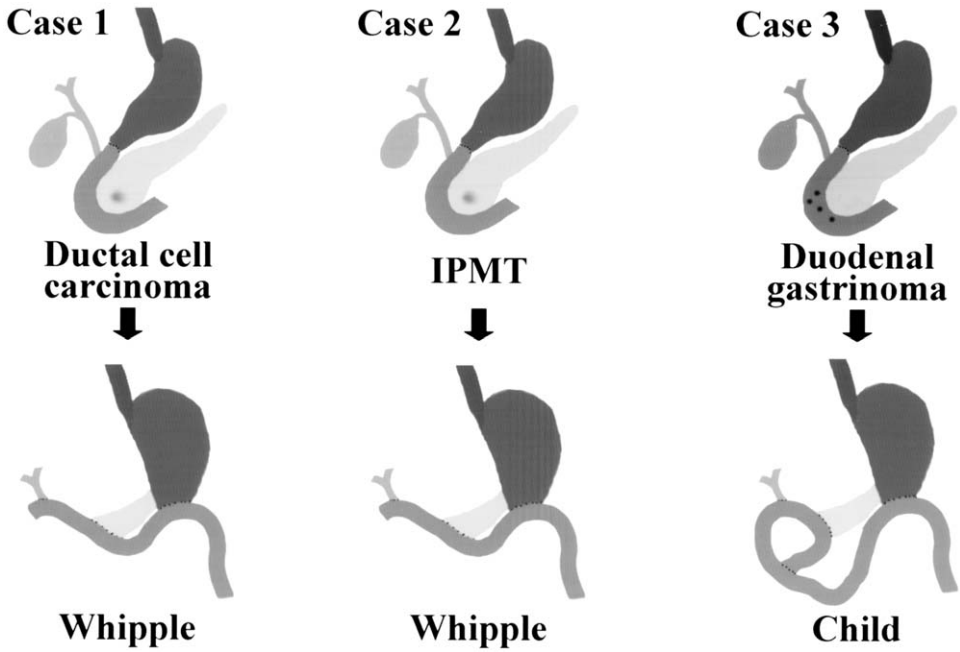

Fig. 1. Reconstruction methods after pancreatoduodenectomy for patients who previously underwent gastrectomy with Billroth I anastomosis.

630 g–2620 g (average: 1919 g). All the patients recovered and were discharged without gastrointestinal disorder. The length of hospital stay after the pancreatoduodenectomy ranged from 20–115 days (average: 56 days). During the postoperative course, afferent loop syndrome was recorded in 2 patients (cases 5 and 7), and increased amylase in the drainage was observed in 1 patient (case 4). In this case, a closed silicon drain was placed at the site of pancreaticojejunostomy. The amylase level in the drainage

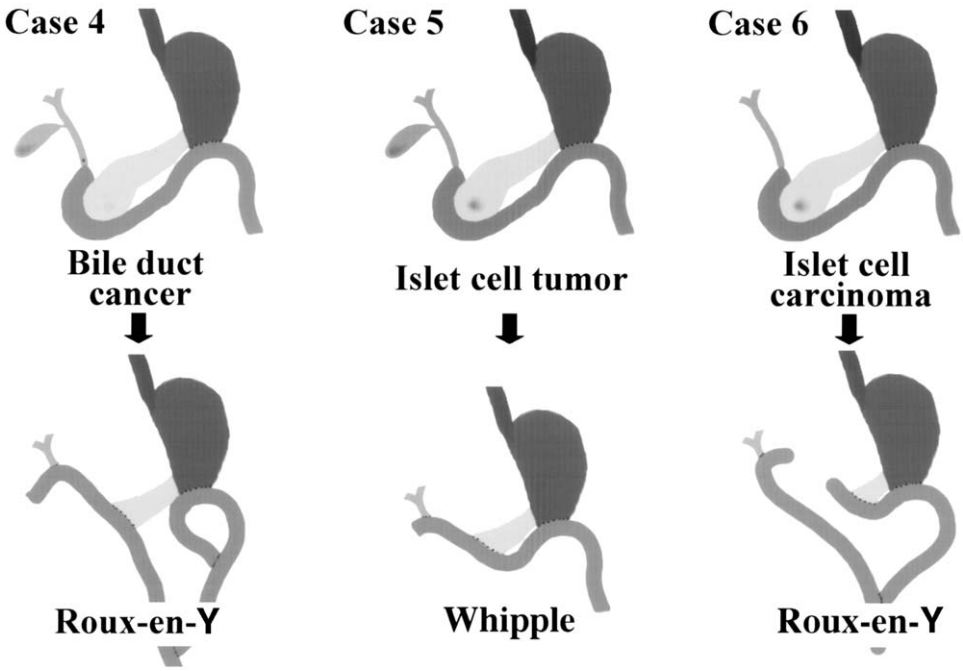

Fig. 2. Reconstruction methods after pancreatoduodenectomy for patients who previously underwent gastrectomy with Billroth II anastomosis.

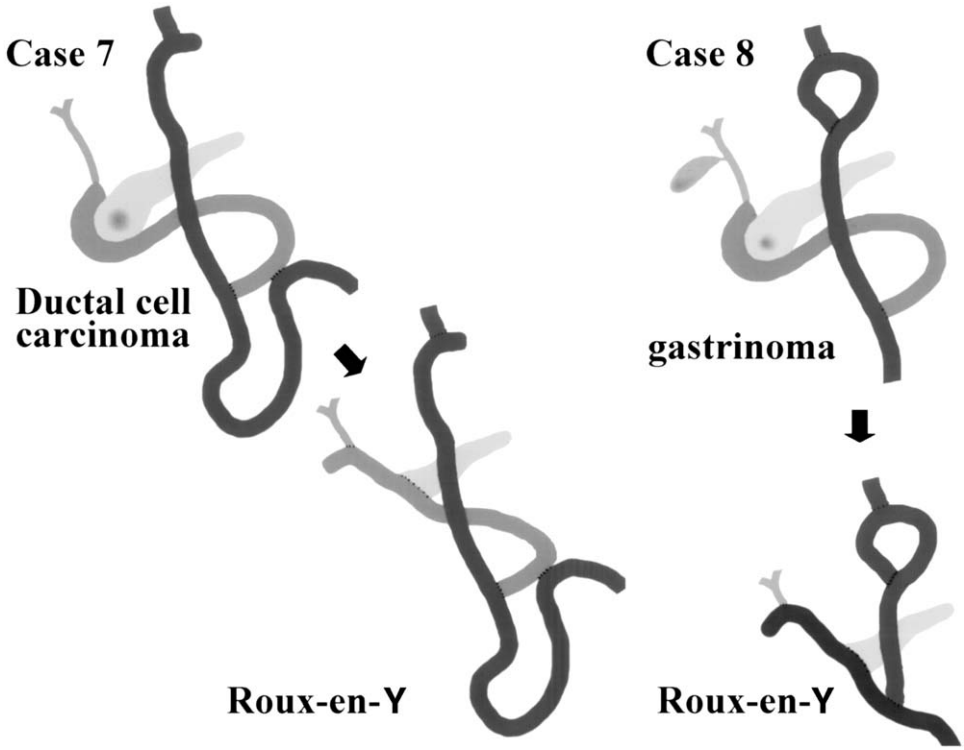

Fig. 3. Reconstruction methods after pancreatoduodenectomy for patients who previously underwent gastrectomy with Roux-en-Y anastomosis.

was normalized after 4 weeks of fasting without relaparotomy and surgical intervention.

DISCUSSION

It is a challenging task to perform a successful pancreatoduodenectomy on a patient who has a past history of major abdominal surgery. Preceding gastrectomy, in particular, affects the operative procedure of pancreatoduodenectomy because the intestinal adhesion and the modified anatomy of the upper abdomen may confound the operator and pose a risk for postoperative morbidity. We performed eight pancreatoduodenectomies for gastrectomized patients. As expected, the average operative time of 9 hours was considerably longer than the usual pancreatoduodenectomy procedure and the estimated blood loss was, to some extent, increased. An average hospital stay of 56 days for the second pancreatoduodenectomy is not significantly long as compared with those patients who underwent pancreatoduodenectomy for the first time. That is because under the Japanese insurance system, patients are generally allowed to stay in the hospital until they can live in their homes without professional support.

There was no mortality in the current series of patients, however, we observed afferent loop syndrome in 2 patients and increased amylase level in the drainage. As we have not encountered afferent loop syndrome after usual pancreatoduodenectomy, we speculate the reasons for the current patients are as follows. In case 5 (Fig. 2), the original gastrojejunostomy was preserved. The oral side of the jejunum was brought up to the hepatic hilus and choledochojejunostomy and pancreatojejunostomy were performed. Because this limb was slightly short (approximately 10 cm from the gastrojejunostomy), there the afferent loop might have been mildly kinked. In case 7 (Fig. 3), choledochojejunostomy and pancreatojejunostomy were performed in the same way. In this case, the jejunal limb associated with the choledochojejunostomy and pancreatojejunostomy was long enough and was not bent, however, the jejunal passage distal to the jejunojejunostomy was very poor because the patient experienced postoperative ileus twice after previous gastrectomy at another hospital. We have not experienced afferent loop syndrome or similar symptoms in our recent 160 consecutive pancreatoduodenectomies. Therefore, resurgery, especially under post-gastrectomized conditions, likely puts the patient at risk of developing afferent loop syndrome.

It is conceivable that patients after gastrectomy could have a relatively higher risk of anastomotic leakage at the sites of choledochojejunostomy and

pancreatojejunostomy than those who have undergone primary pancreatoduodenectomy because, in such patients, there may be higher intraluminal pressure at the site of anastomosis. One patient experienced an elevated amylase level in drainage. The amylase level in the drainage was normalized after 4 weeks of fasting without relaparotomy and surgical intervention. We have previously reported that the rate of pancreatic leakage—defined as (1) discharge from the peripancreatic drain with an amylase concentration of more than 1000 IU/ml at postoperative day 7 or (2) radiographic demonstration by fistulography or cholangiography—[7]was 10.6% for our consecutive 160 pancreatoduodenectomies. In the current series, one pancreatic leakage out of 8 patients (12.5%) was not significantly different from the previous analysis for conventional pancreaticojejunostomy ($P = 0.86$).

In a previous necropsy-based case control study where 439 autopsied individuals who had died of pancreatic carcinoma were compared with those who were matched for age at death, gender, and year of death, there was no relationship between pancreatic carcinoma and previous gastric resection,[8] although elderly patients are being referred for surgery in increasing numbers. Therefore, we will have more chance in the future to perform pancreatoduodenectomy in gastrectomized patients. In conclusion, the lesson from the current study is that secondary pancreatoduodenectomy does not increase the mortality rate, although we should use the jejunal limb with less tissue damage at the anastomotic site of which circulation is well maintained for choledochojejunostomy and pancreaticojejunostomy. Furthermore, the jejunal limb should be lined carefully to avoid intestinal kinking and excess tension to the anastomosis.

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Outcome of Radical Surgery for Carcinoma of the Gallbladder According to the Tumor Node Metastasis and Japanese Society of Biliary Surgery Stages

Antonio Frena, M.D., Ph.D., Giuseppe La Guardia, M.D., Federico Martin, M.D.

Primary carcinoma of the gallbladder is a progressive, lethal disease. Survival of patients with this neoplasm depends strictly on lymph node involvement and depth of tumor invasion. The aim of the study was to evaluate the results of our surgical series according to the tumor node metastasis and Japanese Society of Biliary Surgery classification systems. A retrospective analysis of our 15-year experience was performed. Of the 79 patients with gallbladder carcinoma observed at our institution between 1984 and 2001, a radical resection was carried out in 20 patients. Patients with stage I-II disease represent a minority of the cases of gallbladder carcinoma; the disease is localized in these patients, and surgical treatment provides the opportunity for good survival. Survival rates for patients with stage III-IV disease demonstrates that radical extended surgery offers the only chance for a relatively prolonged survival. (J GASTROINTEST SURG 2004;8:580–590)

KEY WORDS: Gallbladder cancer, extended cholecystectomy, liver surgery, TNM classification, JSBS (Japanese Society of Biliary Surgery) classification

Cancer of the gallbladder, the most frequent form of bile duct cancer,[1] is characterized by a very poor survival rate, and its surgical treatment is a matter of controversy. The high mortality rate associated with the disease is due to the rapid growth of the tumor, the late onset of symptoms, the early occurrence of lymph node spread, and the anatomic situation.[2–4] The proximity of the liver and major vascular structures often makes resection mandatory in an attempt to extirpate the disease. If to this we add the fact that various reviews of the literature in the past have provided evidence of 1-year survival rates close to zero,[5] one will readily understand the pessimism that has always characterized the approach to the treatment of such tumors. The aim of this report was retrospectively to analyze the data emerging in the follow-up of our own case series with a view to assessing the results, the adequacy of the surgical therapy implemented with a radical intent, and the differences, if any, between the procedures adopted in the past and the surgical strategy employed today for the purposes of enhancing patient survival.

PATIENTS AND METHODS

Between 1984 and 2001, we observed 79 patients with cancer of the gallbladder (63 women and 16 men; mean age 69 years [range 46 to 89 years]) in our department. The most frequent symptoms were right hypochondriac pain (57%) and jaundice (29%).

Twenty-eight patients were excluded from surgical treatment (in 12 cases after exploratory laparotomy) for the following reasons: 14 because of remote metastases, nine because of massive hepatic infiltration, three because of age and poor general condition, and two because of portal infiltration.

Thirty-one patients underwent palliative surgery for one of the following reasons: to relieve symptoms in 19 cases (biliary shunts for jaundice in 9, digestive tract shunts for gastric or duodenal obstruction in 4, and R2 cholecystectomy for pain in 6); in the other 12 cases, treatment consisted of simple cholecystectomy with the incidental finding of pT2 carcinoma, which was not followed by additional surgical treatment.

Twenty patients underwent radical resections (11 women and 9 men; mean age 67 years [range 58 to 83 years]). The surgical procedures are listed in Table 1.

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Table 1. Surgical procedure and stage in 20 patients undergoing radical surgery for gallbladder carcinoma

Patient	Age (yr)	Sex	AJCC stage	TNM	Operation
1	62	M	I	T1aN0M0	Cholecystectomy, common bile duct resection
2	68	F		T1bNXM0	Laparoscopic cholecystectomy
3	69	M	II	T2N0M0	Extended cholecystectomy (*two times*)
4	60	M		T2N0M0	Extended cholecystectomy
5	56	M		T2N0M0	Extended cholecystectomy (*two times*)
6	69	F	III	T3N0M0	Cholecystectomy, liver resection
7	68	M		T3N0M0	Cholecystectomy, liver resection
8	78	F		T3N1M0	Whipple procedure
9	75	M		T3N1M0	Cholecystectomy, liver resection, common bile duct resection
10	63	F		T3N0M0	Cholecystectomy, liver resection
11	70	F		T3N1M0	Extended cholecystectomy (*two times*)
12	64	F	IVa	T4N1M0	Cholecystectomy, liver resection, duodenal resection
13	53	F		T4N0M0	Cholecystectomy, liver resection
14	69	M		T4N1M0	Whipple procedure
15	65	M	IVb	T3N1M1	Cholecystectomy, liver resection
16	65	F		T4N1M1	Hepatopancreatoduodenectomy
17	83	F		T4N0M1	Cholecystectomy, right hemicolectomy
18	58	F		T2N2M0	Extended cholecystectomy (*two times*)
19	76	M		T2N2M0	Extended cholecystectomy
20	68	F		T4N2M0	Hepatopancreatoduodenectomy, partial colectomy

None of the patients received adjuvant postoperative chemotherapy.

The extent of the tumor was analyzed on the basis of the tumor node metastasis (TNM) classification (Table 2) and in accordance with the American Joint Committee on Cancer (AJCC) (Table 3) and the Japanese Society of Biliary Surgery (JSBS) (Table 4) staging systems. Survival was calculated according to the Kaplan-Meier method.

Table 2. TNM classification of gallbladder carcinoma

Tumor		
	Tx	Primary tumor cannot be assessed
	Tis	Carcinoma in situ
T1	T1a	Tumor invades lamina propria
	T1b	Tumor invades muscle layer
	T2	Tumor invades the perimuscular connective tissue
	T3	Tumor perforates the serosa or directly invades one adjacent organ, or both (extension 2 cm or less into liver)
	T4	Tumor extends more than 2 cm into the liver, and/or into two or more adjacent organs (any involvement of the liver)
Node		
	Nx	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in hepatoduodenal ligament
	N2	Metastasis in peripancreatic (head only), periduodenal, periportal, celiac, and/or superior mesenteric lymph nodes
Metastasis		
	Mx	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis

RESULTS

Mean survival for the 28 patients who did not undergo surgical treatment was 4.4 ± 2.8 months (range 1 to 11 months) with a 1-year actuarial survival of 0 (Fig. 1). For the 31 patients who did undergo palliative surgery, we can distinguish between two groups: the first group, which included 19 patients who were treated with biliary or digestive shunts or R2 cholecystectomy (patients with diffuse disease

Table 3. American Joint Committee on Cancer stage groupings

Stage 0	Tis N0 M0	Localized tumor
Stage I	T1 N0 M0	
Stage II	T2 N0 M0	
Stage III	T1 N1 M0	
	T2 N1 M0	
	T3 N0 M0	
	T3 N1 M0	Unresectable tumor
Stage IVa	T4 N0 M0	
	T4 N1 M0	
Stage IVb	Any T N2 M0	
	Any T any N M1	

Table 4. TNM compared to Japanese Society of Biliary Surgery and Japanese Society of Biliary Surgery stage groupings

Tumor		
Equal to TNM classification		
Node		
	n0	No regional lymph node metastasis
	n1	Metastasis in cystic duct and/or pericholedocal lymph node
	n2	Metastasis in hepatoduodenal ligament except n1, posterosuperior pancreatic head and/or along the common hepatic artery
	n3	Metastasis in peripancreatic head (except posterosuperior pancreatic), celiac, superior mesenteric, and/or para-aortal lymph nodes
Metastasis		
Equal to TNM classification		
Stage I		T1 n0 M0
Stage II		T1 n1 M0
		T2 n0 M0
		T2 n1 M0
Stage III		T1 n2 M0
		T2 n2 M0
		T3 n0 M0
		T3 n1 M0
		T2 n2 M0
Stage IVa		T4 n0 M0
		T4 n1 M0
		T4 n2 M0
		Any T n3 M0
Stage IVb		Any T n4 M0
		Any T any n M1

given first-intention palliative treatment for pain), the mean survival was 5.9 ± 6.2 months (range 1 to 26 months), whereas the actuarial 1- and 5-year survival rates were 12.7% and 0%, respectively. Remission of symptoms was achieved in 66.7% of the patients in whom biliary shunts were placed (in 3 cases, supplementary endoscopic and/or surgical procedures proved necessary), in 100% of the patients in whom digestive shunts were placed, and in 83.3% of the patients operated on for pain. The second group, which consisted of 12 patients in whom pT2 carcinoma was detected incidentally and who underwent simple cholecystectomy (patients without additional surgery operated on before 1995), had a mean survival of 35.0 ± 42.8 months (range 7 to 147 months), whereas the actuarial 1- and 5-year survival rates were 66.7% and 16.7%, respectively (Fig. 2).

Among the 20 patients undergoing radical resection, T1 tumor infiltration was found in two cases (T1a in one and 1 T1b in one), T2 infiltration in five cases, T3 infiltration in seven cases, and T4 infiltration in six cases; these patients were classified as stage 1 (2 patients), stage II (3 patients), stage III (6 patients), or stage IV (9 patients, 3 of whom were stage IVa and 6 stage IVb) according to the AJCC classification system (see Table 3). Lymph node involvement was present in 10 (50%) of 20 patients. The mean overall survival was 22.5 ± 28.0 months (range 3 to 102 months). The actuarial survival rates by local extent (T), lymph node involvement (N), and AJCC stage are shown in Figs. 3, 4, and 5, respectively.

There were no operative deaths. Histologic examination revealed adenocarcinoma in 15 patients, papilliferous adenocarcinoma in three, mucinous adenocarcinoma in one, and large cell adenocarcinoma in one.

DISCUSSION

The incidence of carcinoma of the gallbladder is increasing in the Western world. A recent French study[6] reported a standardized annual incidence of 0.6 cases per 100,000 men and 1.7 cases per 100,000 women. The American National Cancer Database report for the years 1985 to 1995 indicates an incidence of gallbladder carcinoma corresponding to 8.4% of all hepatobiliary neoplasms.[1] Surgery is currently the only valid therapeutic option for the management of these tumors in view of the poor results achieved with radiation therapy and chemotherapy.[7–10] Radical surgery offers practically the only chance of improving the prognosis.[11]

The almost total pessimism regarding any possibility of effective therapy that prevailed up until the 1970s gradually began to give way in later years to a more positive approach thanks to advances in surgical techniques, which allow the successful execution of extended resections. The low morbidity achieved in the past decade by extended operations involving the liver, bile ducts, and pancreas[12–16] has contributed to the changing attitude regarding treatment of these tumors.[17–20] The present debate, then, hinges on the attempt to standardize the various surgical treatments so as to be able to realistically relate the extent of the resection to the effective degree of prognostic improvement.[21,22]

In an initial analysis of our case series, we assessed the results in relation to the pTNM classification, where the T parameter plays a basic role. T1 carcinomas are mainly neoplasms detected incidentally in patients undergoing cholecystectomy for gallstone disease or acute cholecystitis.[23,24] These tumors have been reported more frequently within the past few years after standardization of the laparoscopic cholecystectomy procedure.[25–27] The anatomic/pathologic evidence[2,3] that T1 carcinomas (confined

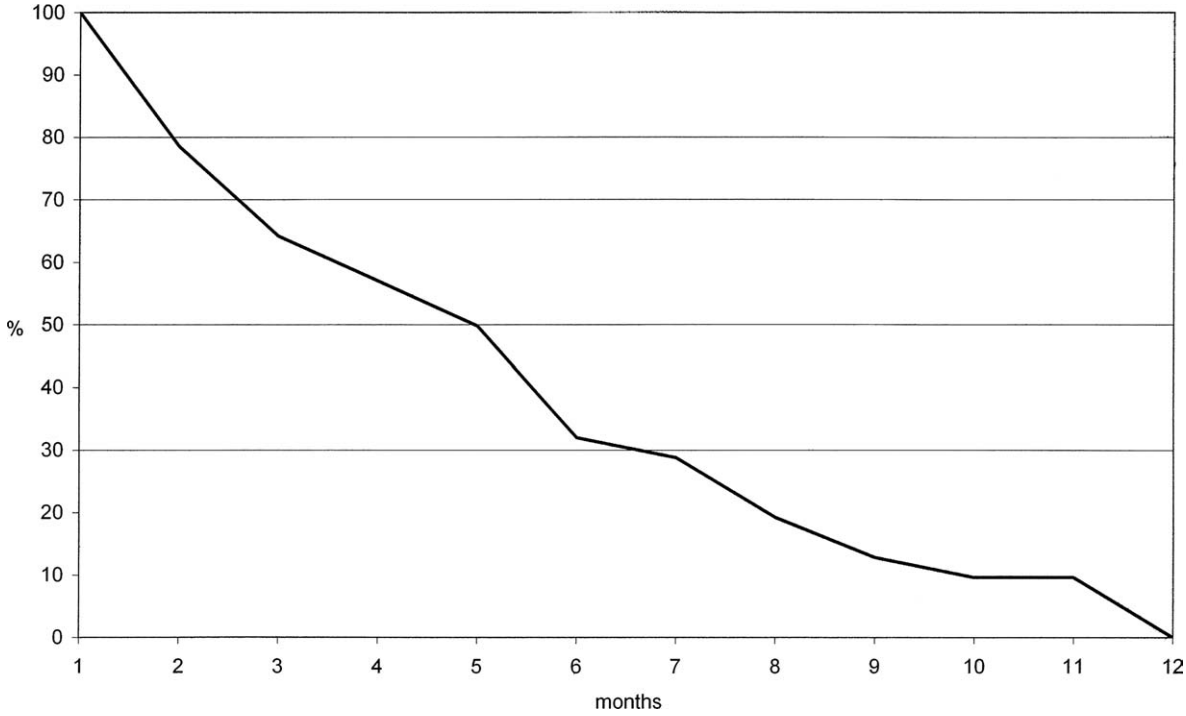

Fig. 1. Mean survival in the 28 patients who did not undergo surgical treatment.

to the mucosa—T1a, or to the muscularis—T1b) do not entail lymph node involvement has meant that simple cholecystectomy has come to be established as the treatment of choice for these tumors. Despite the fact that a number of reports of early recurrence after simple cholecystectomy for T1 carcinoma of the gallbladder have recently been published,[28–30] there can be no doubt that, in principle, there is still

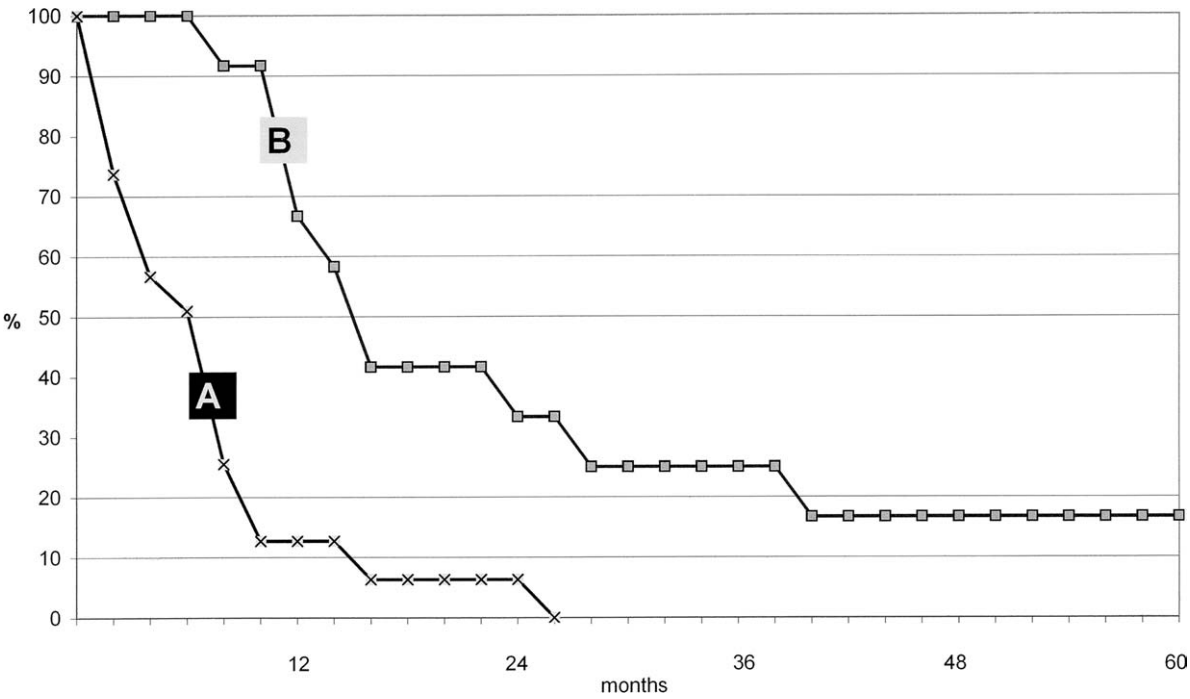

Fig. 2. Survival rates in patients who had surgical palliation (**A**) and patients with incidentally detected T2 carcinoma (cholecystectomy alone before 1995) (**B**).

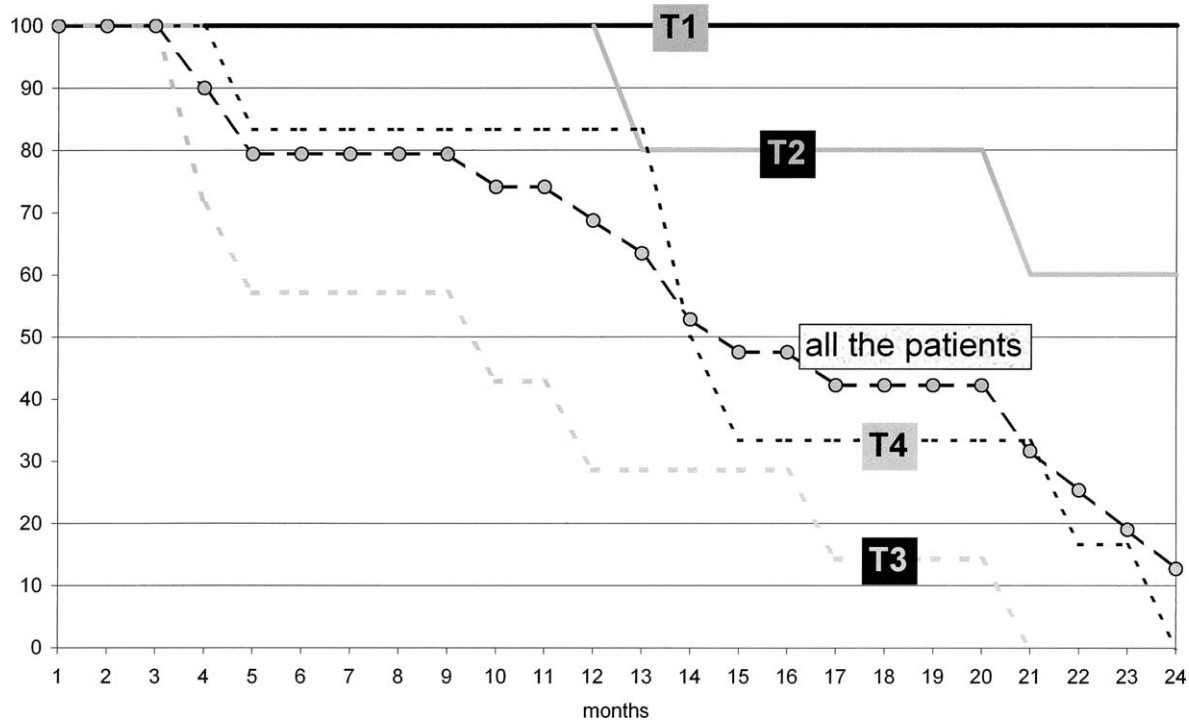

Fig. 3. Survival rate by local extent (*T*) in the 20 patients undergoing radical resection.

no adequate justification for more extended resections, with their higher morbidity and mortality rates, in these tumors. Our experience consists of two cases (see Table 1): the first was an incidental finding after cholecystectomy for gallstones, whereas the second was an intraoperatively detected tumor stemming from the cystic duct, the treatment of which consisted of a cholecystectomy with resection of the common bile duct. In this latter case, despite the final T1N0M0 staging, the patient had a recurrence at 18

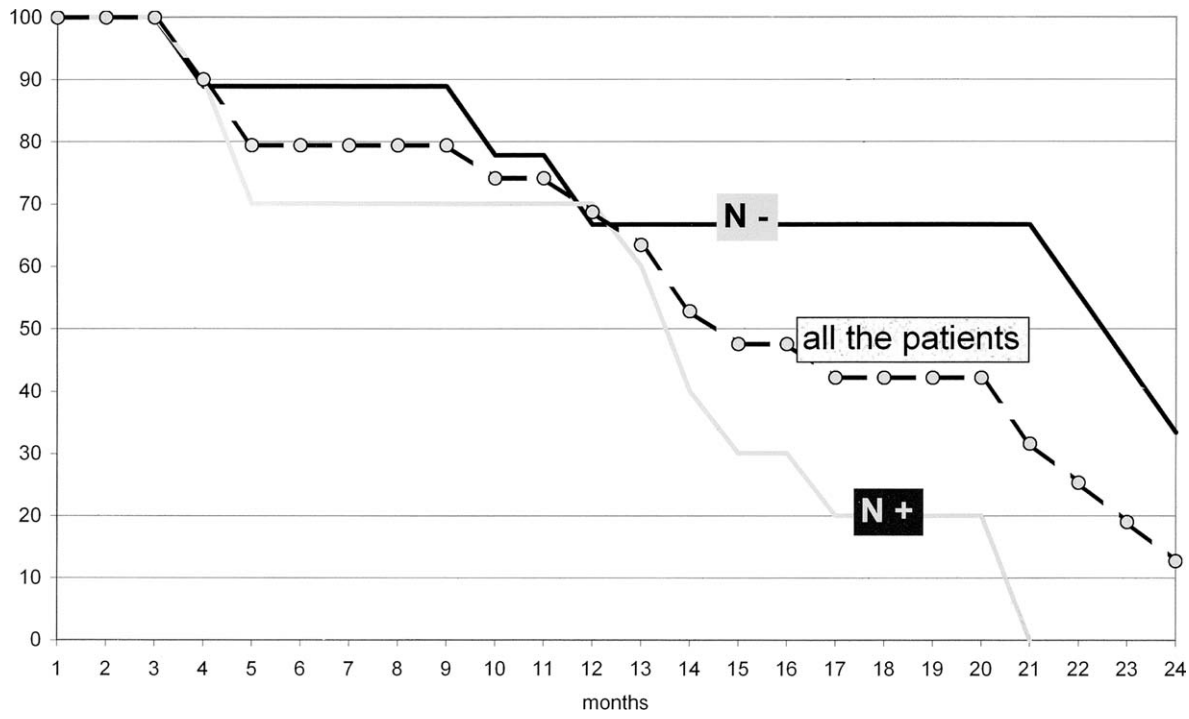

Fig. 4. Survival rate by lymph node involvement (*N*) in the 20 patients undergoing radical resection.

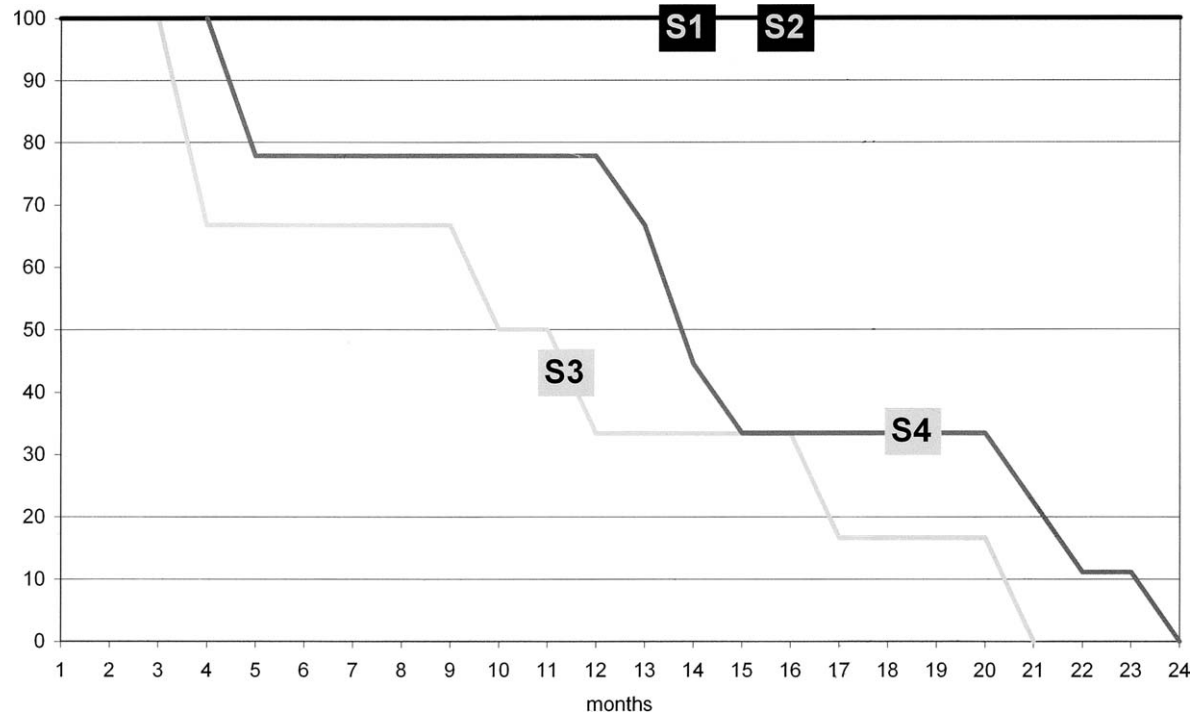

Fig. 5. Survival rate by AJCC stage in the 20 patients undergoing radical resection.

months and the survival period was 23 months; this is a significantly worse outcome than is normally reported for T1 tumors. The most likely explanation for this lies in the fact that carcinomas of the cystic duct are biologically different from cancers of the gallbladder. A recent review of the literature[31] concerning these tumors shows a mean survival of only 18.9 months in 56 patients undergoing radical surgery.

T2 tumors are also often incidental histologic findings after cholecystectomy. Up until the 1980s, the treatment of choice was simple cholecystectomy. In the past decade, however, various studies have shown evidence of neoplastic involvement of the lymph nodes in 50% of these patients[20,21,32,33] and microinfiltration of the serosa in 15%.[34] This has made it necessary to codify an operation characterized by a greater measure of radicality and has led to the establishment of the concept of the extended cholecystectomy, an operation consisting of cholecystectomy, resection of the gallbladder bed (hepatic segments 5 and 4a), lymphadenectomy of the hepatoduodenal ligament and the upper pancreaticoduodenal margin and, in cases of infundibular or cystic duct tumors, resection of the common bile duct.[35–37] Our experience also reflects this change in surgical strategy. Twelve patients with T2 carcinomas treated in the period up to 1995 were operated on by simple cholecystectomy, whereas the next six patients (Table 5) underwent an extended operation in a single session (2 cases) or in two sessions (4 cases with incidental detection of the tumor after cholecystectomy for gallstone disease). In three (50%) of these six patients, the histologic examination enabled us to detect the presence of lymph node metastases and in one case (16.7%) along with microinfiltration of the gallbladder bed (thus passing from T2 to T3). In the light of the strategic changes described, the 12 patients operated on in the period up to 1995 are not considered part of the group of patients undergoing radical surgery but rather part of the group undergoing palliative operations. Although survival rates for

Table 5. New TNM classification after extended cholecistectomy in patients with T2NX gallbladder carcinoma operated on after 1995 (TNM variations in bold)

No.	TNM after simple cholecystectomy	Final TNM	Final stage
1	T2 NX M0	T2 N0 M0	II
2	T2 NX M0	T2 **N2** M0	IV b
3	T2 NX M0	**T3 N1** M0	III
4	T2 NX M0	T2 N0 M0	II
5	T2 NX M0	T2 N0 M0	II
6	T2 NX M0	T2 **N2** M0	IV b

the 12 patients with pT2Nx tumors remained reasonably favorable (66.7% at 1 year and 16.7% at 5 years; see Fig. 2), the actuarial curve shows a distinct increase in 1- and 5-year survival in the five final patients with T2 tumors (see Table 5) who were treated with extended cholecystectomy (100% and 60%, respectively) (Fig. 6).

The attitude toward locally advanced tumors (T3 and T4) is somewhat controversial. Many investigators, emphasizing the good results achieved in terms of survival,[19,22,38–40] favor an aggressive surgical approach with a radical intent. The short-term morbidity and mortality rates for hepatobiliopancreatic surgery have dropped substantially. This has allowed the use of highly extirpative operations,[40–45] such as hepatopancreatoduodenectomy (as defined by Nimura et al.[14] in 1991), in the radical surgical treatment of this type of gallbladder cancer. Our own experience consists of 13 patients, seven with T3 tumors and six with T4 tumors, who were treated radically with major surgery, mainly extended liver resections (see Table 1). All 13 patients (with the exception of the former patient with T2 disease with microinfiltration of the serosa) had their carcinomas diagnosed before surgery; the more advanced state of disease was reflected by the prevalence of jaundice as a symptom (40%) over pain (6%), which in contrast was more frequent (83%) in patients with T1-T2 tumors. The results of this retrospective analysis showed that in the absence of mortality and major surgical complications, 8 (61.5%) of 13 patients achieved better survival at 12 months (1-year actuarial survival rate 53.8%) (Fig. 7).

Before analysis of the N parameter is addressed, it should be recalled that in 1997 the AJCC[46] formulated a subdivision of gallbladder cancers into disease stages based on the TNM (tumor node metastases) classification (see Table 3). Beginning with an analysis of survival results in large case series reported in the literature, the AJCC classification furnishes stage-related prognostic indications; the patients are then subdivided into two groups, those with stage I or II disease, defined as "localized disease," and those with stage III or IV disease, defined as "unresectable disease." In the first group, the cancer is confined to the gallbladder (T1-T2, N0) and is amenable to radical removal; in the second group, comprising a majority of the patients, the development of regional (N1) or remote (N2) lymph node metastases and/or direct local infiltration (T3-T4) indicate spread of the disease such that surgery with radical intent can be no more than a form of palliation.

On the basis of the AJCC staging,[46] our series of 20 patients takes on a different aspect; six patients (25%) were treated by radical surgery, whereas the other 15 underwent palliative resection (see Table 1). Analysis of survival confirms the reasonableness of the AJCC staging system from the formal point of view, both in our study and in others.[47] The 1- and 5-year survival rates of our stage I-II patients

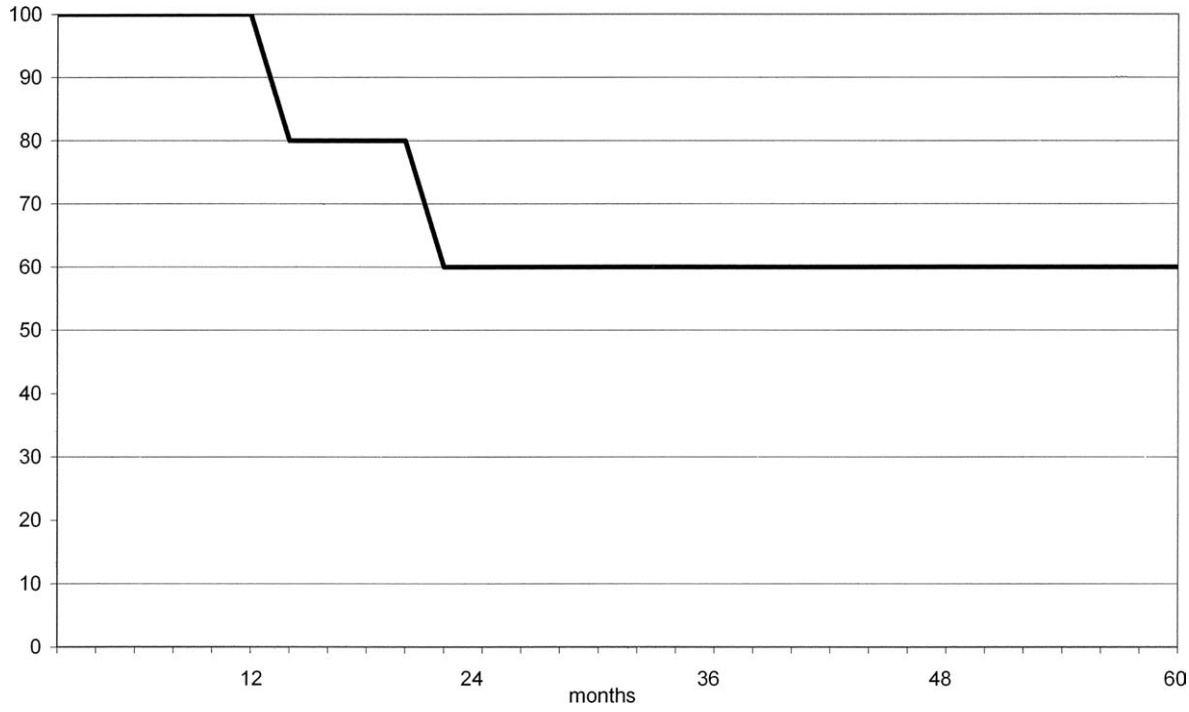

Fig. 6. Survival in the T2 patients operated on by extended cholecystectomy (after 1995).

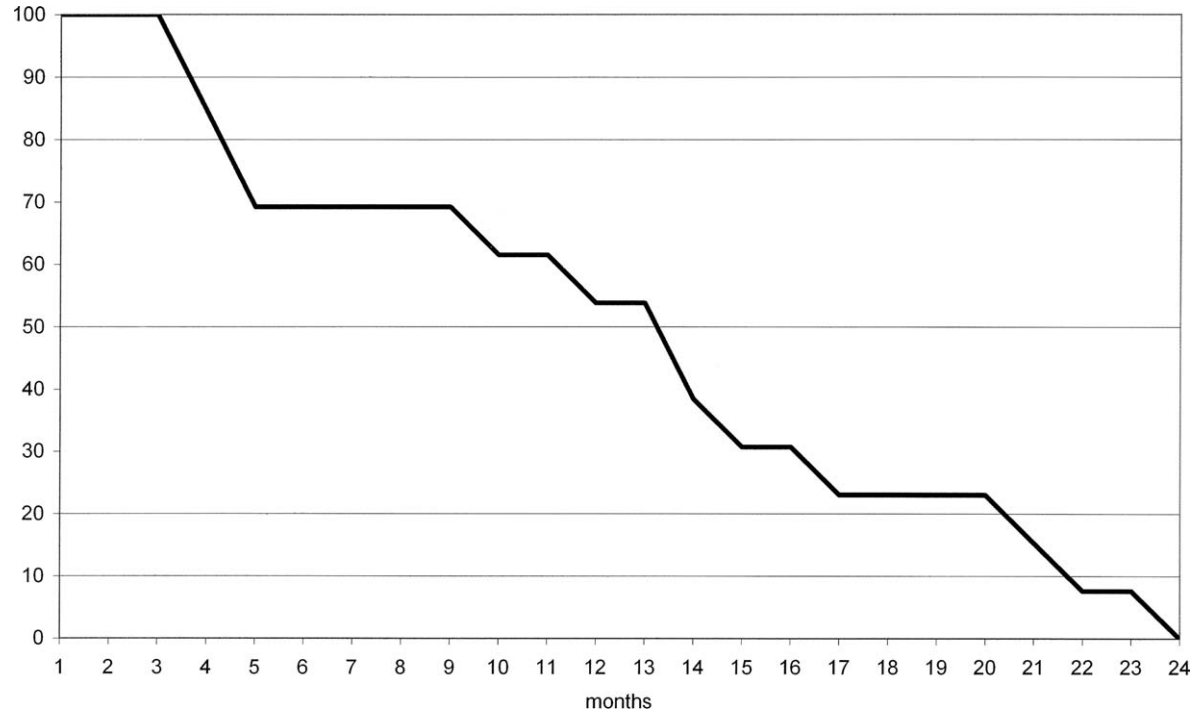

Fig. 7. Survival in the T3-4 patients undergoing radical resection.

were 100% and 75%, respectively, whereas survival rates of the stage III-IV patients were 59.9% and 0%, respectively (Fig. 8). The AJCC staging system therefore clearly shows that, retrospectively, the presence of lymph node involvement makes it possible to stake out a distinct line of demarcation between radical surgery and palliation. Effectively speaking, the actuarial curves furnish evidence of a significant worsening of survival in the presence of positive lymph nodes, even if we compare patients classified

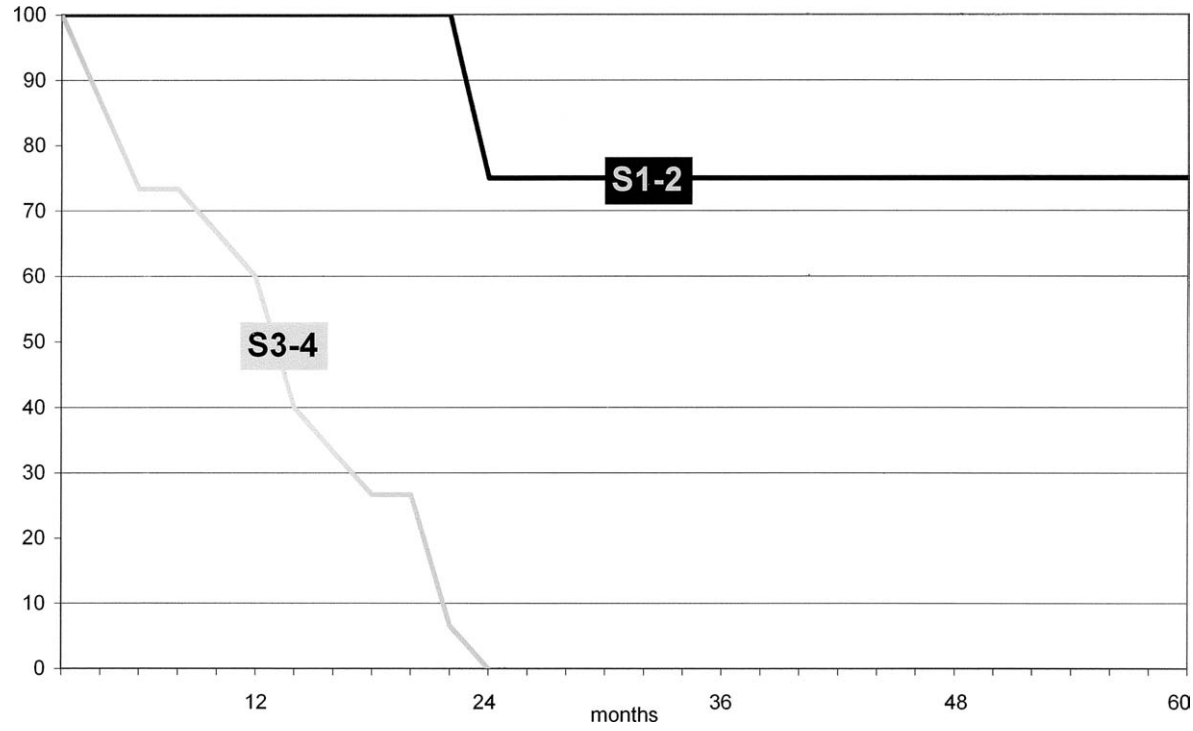

Fig. 8. Five-year survival on the basis of the AJCC staging system.

as N+ and N− irrespective of T status (see Fig. 4). In 1997, the JSBS[48] proposed a new staging system that was based on a more analytical subdivision of the N factor (see Table 5), while at the same time suggesting the advisability of the execution of more extensive lymphadenectomies.[49] The results recently reported by Chijiwa et al.,[50] which were interpreted according to this classification system, show a 28% 5-year survival rate in patients with n1-2 disease and a 1-year survival rate close to zero for patients with n3-4 disease. This shows that a curative resection can be performed even in patients with N1 disease according to the AJCC classification—that is, in patients where the involved lymph nodes are located in the vicinity of the cystic duct, the common bile duct, the portal vein, the common hepatic artery, and the upper pancreaticoduodenal margin. Although our experience cannot be interpreted according to the JSBS staging system for the n3-4 parameters, because the superior mesenteric, celiac, and paraaortal lymph nodes were not removed in all cases, the fundamental finding to emerge is that our data also confirm a longer life expectancy in patients with stage III (T3N1M0) and stage IV (T4N1M0) disease (66.6% 1-year overall) offered resection with a radical intent (Fig. 9). In contrast, the alternative (i.e., simple palliation of symptoms) offers no chance of survival at 1 year. Thus we believe that despite the absolute prognostic validity of the AJCC classification, we cannot exclude N1 patients *a priori* as candidates for surgical resection, and therefore the N factor cannot be regarded as a factor precluding the execution of an extended operation, providing the latter can be performed without exposing the patient to unacceptable risks.

CONCLUSION

We conclude by stating that the local extent of the tumor and the lymph node involvement are the decisive prognostic factors for survival after surgery for cancer of the gallbladder. Simple cholecystectomy is the treatment of choice for T1 tumors, which are characterized in absolute terms by a higher survival rate. Extended cholecystectomy is now the established standard treatment with a radical intent for T2 tumors (the best survival results were achieved in the presence of N0M0 [i.e., in stage 2] disease). In locally advanced cancers, pT3 and pT4, belonging to stages III or IV according to the AJCC classification, with n1-2 lymph node involvement according to the JSBS staging system (N1 according to the AJCC) and M0, surgical resection offers a real chance of long-term survival.

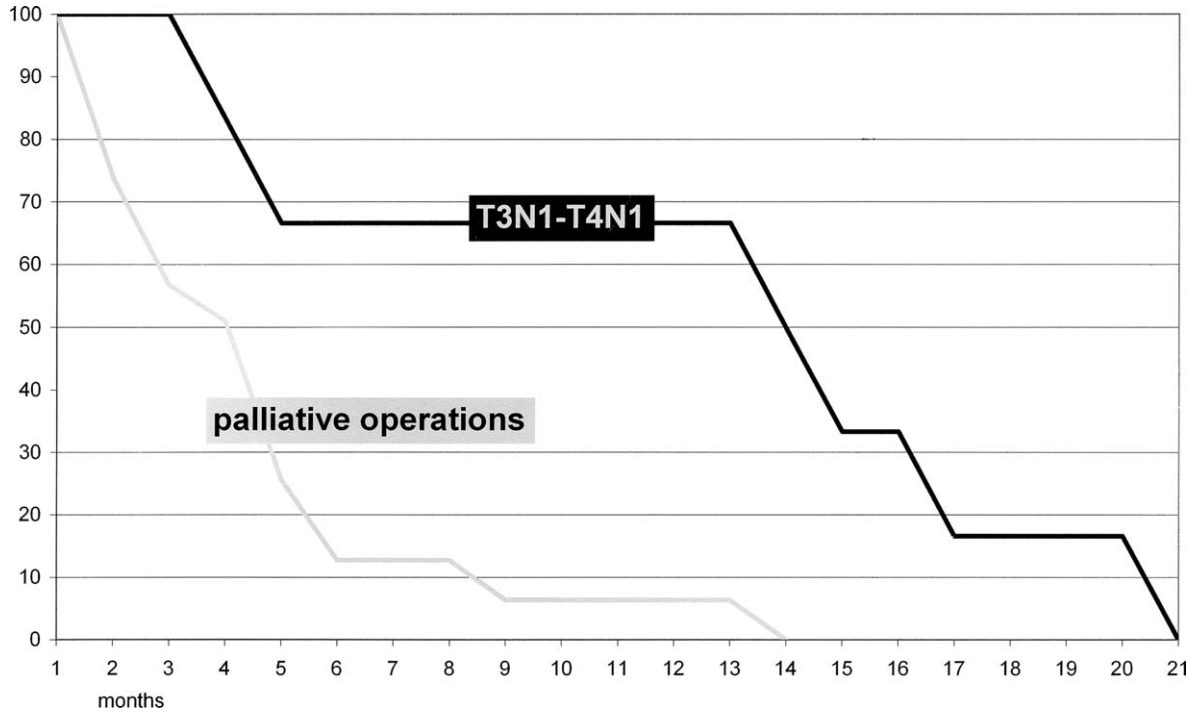

Fig. 9. Survival rates in the group of patients with T3N1–T4N1 stage and in the group of patients with surgical palliation.

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Multiple Focal Nodular Hyperplasia of the Liver in a 21-Year-Old Woman

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Focal nodular hyperplasia (FNH) is a relatively common condition, the diagnosis of which is now regularly made with diagnostic imaging. Cases of multiple FNH (more than four lesions) are rare, however, and the presence of numerous lesions may complicate the workup and diagnosis. We recently treated a young woman with multiple FNH. We report this case to highlight the clinical issues presented by this rare variant of a common benign hepatic disease. (J GASTROINTEST SURG 2004;8:591–595)

KEY WORDS: Multiple focal nodular hyperplasia, benign liver tumor

Focal nodular hyperplasia (FNH) of the liver is among the most common hepatic neoplasms.[1] With current advances in radiologic imaging, it has become an even more frequent diagnosis. The CT appearance is generally that of a small (<5 cm), smooth, or lobular mass with a hypodense central scar.[2] Fifty to ninety percent of cases are diagnosed incidentally during evaluations for nonspecific abdominal complaints.[3,4] FNH typically presents as a single lesion in 70% of patients and with two to four lesions in the remaining 30%.[5] The presence of five or more lesions, defined as multiple FNH, is extremely rare and few reports exist in the literature.[6]

CASE REPORT

A 21-year-old woman was first seen in the office of her primary care physician for a routine physical examination after the birth of her first child 3 months earlier. Her medical history was otherwise unremarkable, and her only medication was an oral contraceptive that she had recently started taking. She denied having any pain, abdominal fullness, or early satiety. On physical examination she did not appear jaundiced. She had no abdominal tenderness; however, she did have a palpable right upper quadrant abdominal mass extending 6 cm below the right costal margin in the midclavicular line.

Blood samples were drawn for serum chemical analysis, which revealed normal transaminases with a minimally elevated alkaline phosphatase level of 205 IU/L. She was subsequently referred for ultrasound examination of the right upper quadrant, which revealed multiple solid masses throughout the liver. The history of any postpartum female using oral contraceptives and with newly diagnosed liver lesions raises suspicion for hepatic adenoma. To better characterize the liver lesions, the patient's primary care physician ordered a CT scan. This study demonstrated an enlarged liver that was nearly completely replaced by innumerable masses containing areas of calcification. There were two dominant exophytic masses projecting inferiorly off segment 4, measuring 10.5×11.5 cm in diameter. There were multiple other ill-defined masses in the remaining liver ranging in size from 1 to 7 cm. No discrete central scar was evident in any of the multiple liver masses (Figs. 1 and 2).

The presence of multiple hepatic masses with calcification is less consistent with hepatic adenoma. The differential diagnosis in a young patient includes the fibrolamellar variant of hepatocellular carcinoma (FHC) as well as FNH. Consequently a CT-guided fine-needle aspiration of a right hepatic lobe mass was performed. The biopsy was suggestive, but not diagnostic, of FNH. Because the diagnosis was uncertain, the patient was referred for surgical evaluation.

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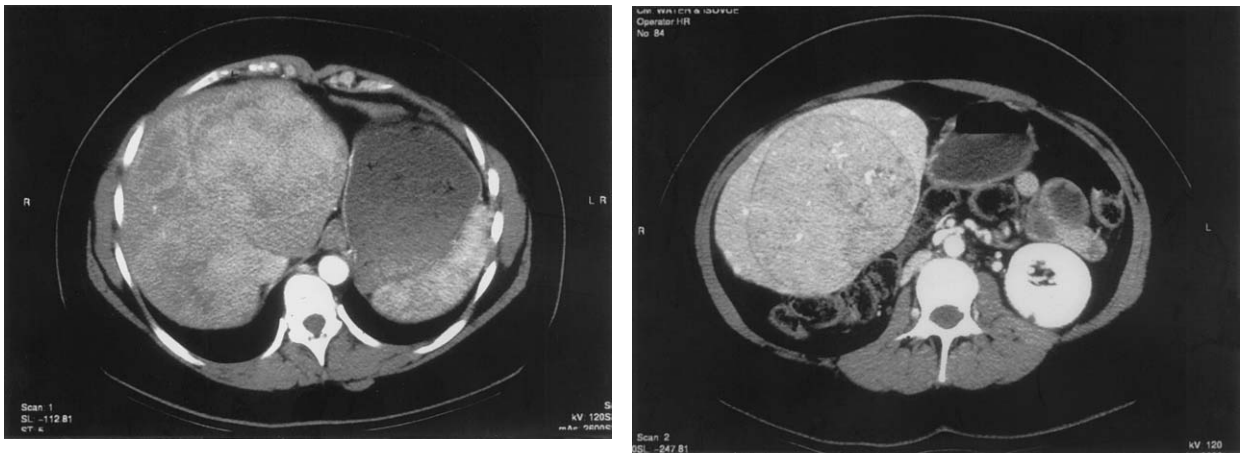

Fig. 1. Arterial phase CT imaging of multiple FNH. Arterial phase images through the superior (**A**) and inferior (**B**) liver. **A**, There is a heterogeneous mass in the left lateral segment that is not hypervascular. The right lobe of the liver is atrophic. **B**, There is an exophytic mass projecting off of the medial segment of the left lobe, which is heterogeneous and contains multiple punctate calcifications.

After the patient's history and results of radiologic imaging studies were reviewed, surgical biopsy was recommended. The rationale for surgical biopsy was to obtain adequate tissue samples to establish a diagnosis with absolute certainty and to allow visual inspection of the multiple areas of involvement.

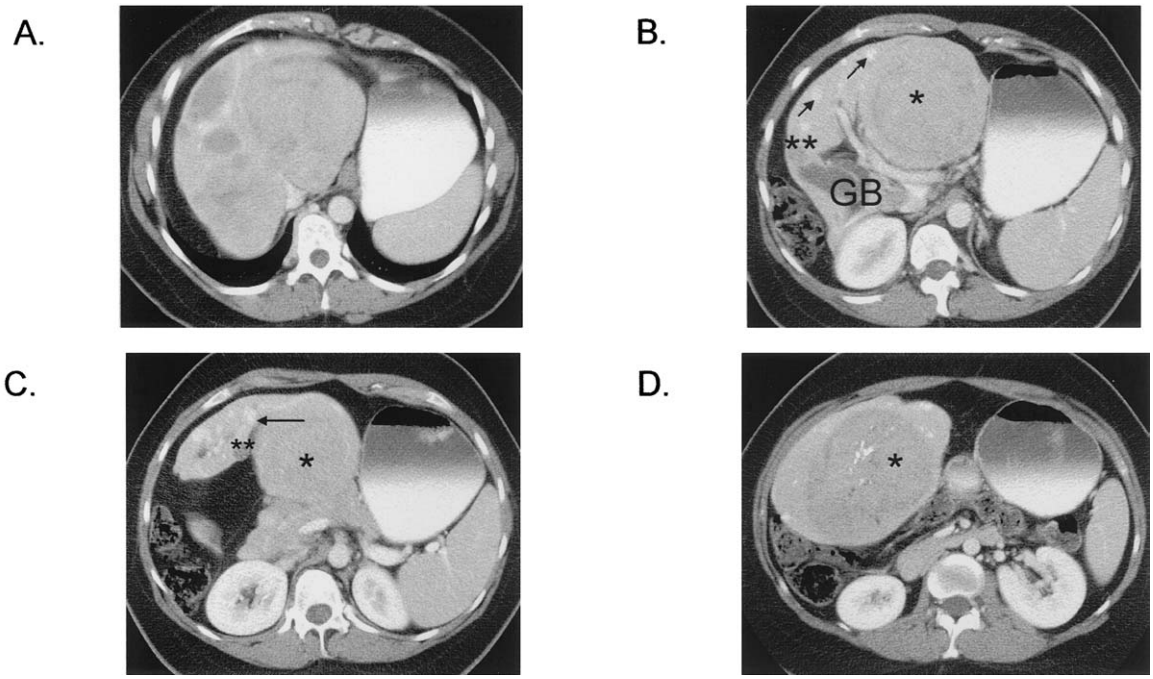

Fig. 2. Portal venous phase CT images of multiple FNH at multiple levels from superior to Inferior. **A**, There is a large heterogeneous mass in the left lateral segment, which is predominantly hypodense to normal liver. The adjacent medial left and right lobes are diffusely heterogeneous, containing multiple hypodense lesions that are difficult to individually discriminate. **B**, Portal venous phase at the same level as in Fig. 1, *A*. The exophytic lateral left segment lesion (*) is again seen, appearing more hypodense to liver. A smaller hypodense lesion (**) is seen next to the gallbladder. Small hyperdense foci (*arrowheads*) represent dilated hepatic veins. **C**, The inferior portion of the exophytic left lateral segment lesion is seen (*). Another small left medial hypodense lesion (**) is evident, as are dilated hepatic veins (*arrowhead*). **D**, The second large exophytic segment IV lesion (*) is evident, appearing more hypodense to liver with unchanged foci of calcification.

An exploratory laparoscopy was performed. Grossly the liver appeared to contain multiple large solid tumors. Visually they appeared discrete but similar in appearance to one another. An area of the left lateral segment was selected for biopsy. A laparoscopic wedge resection was performed with ultrasonic shears (Harmonic Scalpel; Ethicon Endo-Surgery, Cincinnati, OH) and was sent off for frozen-section pathologic analysis. Histologic examination revealed a thin rim of normal liver parenchyma and a nonencapsulated lesion composed of sheets of benign-appearing hepatocytes surrounded by fibrotic bands (Fig. 3). The fibrotic bands contained thin-walled and thick-walled blood vessels and focal bile ductular proliferation located at the interface between fibrotic areas and hepatocytes. However, there were no identifiable interlobular bile ducts. The hepatocytes in the lesion demonstrated severe predominantly macrovesicular steatosis (which was observed in more than 90% of hepatocytes), but no pleomorphism or cytologic atypia. These microscopic features were diagnostic of FNH.

Once the diagnosis of FNH was returned, the operation was concluded. The final pathologic specimen revealed preservation of the reticulin network (as detected by a reticulin stain) and a low mitotic index (<1% by immunohistochemical analysis with MIB-1 antibody), which confirmed the benign origin of this lesion. The patient was discharged on postoperative day 1. In subsequent follow-up, the patient remains asymptomatic. Follow-up CT scanning has revealed no change in the multiple FNH, now at 2 years' follow-up.

DISCUSSION

FNH is a benign tumor-like lesion characterized by a central fibrous scar with irradiating fibrous septa

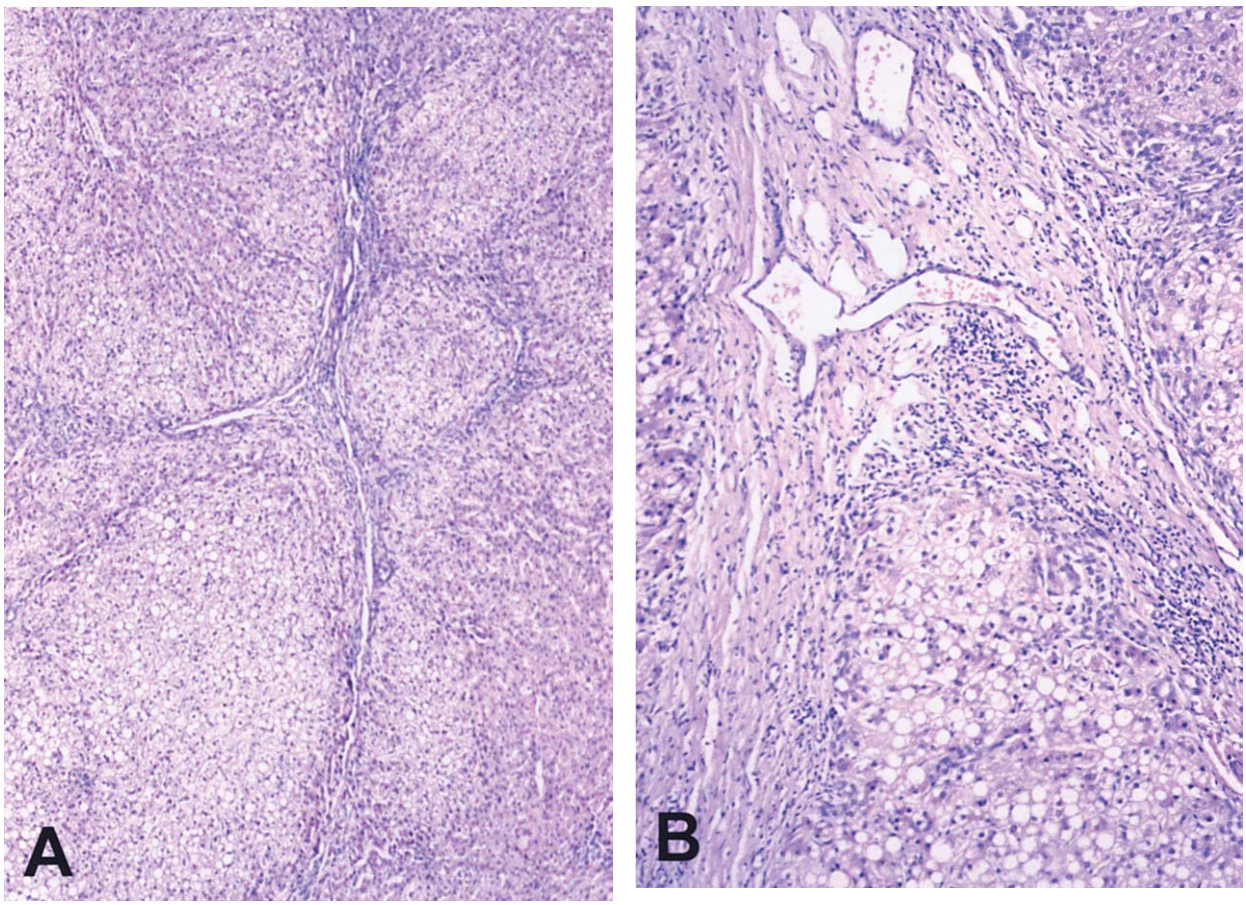

Fig. 3. Microscopic appearance of multiple FNH. Microscopic examination of the surgical specimen revealed features of FNH including nodular appearance on the liver (**A**) and multiple fibrotic bands containing malformed blood vessels and focal chronic inflammation but no interlobular bile ducts (**B**). An unusual microscopic feature in this case was an extensive predominant macrovesicular steatosis involving hepatocytes in the lesion.

that surround hyperplastic parenchymal nodules. The central scar contains an anomalous feeding artery.[7,8] The hepatocytes in the lesion are normal, and bile duct proliferation is usually prominent.[9,10] It is usually a stable lesion that does not enlarge over long periods of time. Rarely, it is complicated by growth, rupture, portal hypertension, hemorrhage, or necrosis.[11]

In this patient, the history and CT images mandated consideration of FNH, FHC, and hepatic adenoma in the differential diagnosis. As compared to FNH, on CT imaging, adenomas tend to be larger, more heterogeneous, may have hemorrhage, and lack a central scar. They generally have less arterial enhancement and may contain fat. Fibrolamellar hepatocellular carcinoma tends to be large, have calcification, and be heterogeneous. It is also prone to hemorrhage and to have areas of necrosis. The lesions in this patient were large, heterogeneous, had little enhancement, and lacked a scar. Thus, on the basis of imaging characteristics, the lesions in this patient were more consistent with adenoma or fibrolamellar hepatocellular carcinoma. As such, definitive biopsy was indicated.

Histologically, adenoma and FHC can have similar characteristics to FNH. Adenoma is often composed of sheets of normal-appearing hepatocytes without features of malignancy. There are few or no portal tracts or central veins, and bile ducts are absent.[12,13] These features distinguish adenoma from FNH. FHC may similarly be composed of sheets of hepatocytes. However, these cells are distinctively plump and deeply eosinophilic. Pale or hyaline bodies in the cytoplasm, prominent nucleoli, and rare mitoses are characteristic of FHC.[14]

The pathogenesis of FNH is unclear, but two predominant theories exist. FNH may be a response to a preexisting vascular abnormality.[8,15] The artery associated with the central scar is larger than normal and causes hyperperfusion in this region and/or arterialization of sinusoids, with resulting hyperplasia of the surrounding parenchyma. Growth of surrounding hepatocytes stops when the sinusoids are compressed and vascular resistance increases with slowing of the blood flow.[8] The second theory relates to the use of oral contraceptives. In contrast to adenoma, the origin of FNH has not been definitively linked to estrogen, but based on isolated reports, it is still thought that estrogen may act as a growth factor and can increase the size and vascularity of the nodules.[8,16–18] Therefore, in any patient with FNH, the use of oral contraceptives should be strongly discouraged.

Another important finding among patients with multiple FNH is an identified association with other vascular malformations and/or neoplasia.[19] The most frequent associations include arterial dysplasia, portal vein atresia, berry aneurysm of the brain, and pulmonary arterial hypertension.[16,19–21] There are additional associations with meningioma, astrocytoma, liver hemangioma, and Klippel-Trenaunay and von Recklinghausen syndromes.[16,19,20,22] As such, patients with multiple FNH are advised to undergo CT or MRI of the brain to detect treatable aneurysmal lesions. Despite such associated pathologic conditions, multiple FNH appears to have a good prognosis. Once the diagnosis of multiple FNH was secured, our patient underwent MRI of the brain. This revealed no evidence of vascular malformations.

Our patient's presentation highlights the difficulty in making the diagnosis of multiple FNH. The historical attributes of youth, postpartum status, female sex, and particularly oral contraceptive use raise suspicion for adenoma. The physical examination finding of a mass in her right upper quadrant was nondiagnostic but is, nevertheless, a most common feature of multiple FNH.[6,16,19,23] Radiographic evaluation by CT exhibited features more consistent with fibrolamellar hepatocellular carcinoma or adenoma, as opposed to FNH. MRI, which we often use to clarify equivocal CT findings, was not used in this case. Because the features of this lesion gave us sufficient cause to suspect malignancy, we did not think that further imaging of any kind would be sufficiently definitive to

Table 1. Clinicopathologic distinction between focal nodular hyperplasia, hepatic adenoma, and fibrolamellar hepatocellular carcinoma

Typical features	FNH	HA	FHC
Physical examination	Asymptomatic, RUQ pain	Asymptomatic, RUQ pain	Asymptomatic, RUQ pain
CT examination	Central scar, feeding artery	Lesional hemorrhage, hematoma, necrosis	Calcifications, central scar
Histologic findings	Central fibrous scar, sheets of hepatocytes, bile duct proliferation	Sheets of hepatocytes, eosinophilic inclusions, absence of bile ducts	Sheets of hepatocytes, abundant fibrous stroma, prominent nucleoli, mitoses

FNH = focal nodular hyperplasia; HA = hepatic adenoma; FHC = fibrolamellar hepatocellular carcinoma; RUQ = right upper quadrant; CT = computed tomography.

negate the need for tissue diagnosis. Certainly MRI could be considered in cases with less concerning radiologic findings.[24] The clinicopathologic distinctions between these three lesions are presented in Table 1.

Although our patient underwent surgical exploration to rule out malignancy, surgery is not indicated for multiple FNH except in cases of diagnostic uncertainty or to palliate symptoms (e.g., pain or early satiety). There have been reports of recurrence and progression after surgery for multiple FNH, thereby mandating long-term follow-up.[15,23] Following physician recommendation, our patient has discontinued using oral contraceptives and remains symptom-free and in good health. Because this patient is only in her twenties, she will require follow-up to document stability of these lesions.

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Hepatic Resections Using a Water-Cooled, High-Density, Monopolar Device: A New Technology for Safer Surgery

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Several techniques and devices have recently been developed in an effort to allow safer liver resections and avoid intraoperative blood loss. The aim of this study was to analyze our initial experience with hepatic resections using a new water-cooled, high-density, monopolar device—the Tissuelink Monopolar Floating Ball (Tissuelink Medical, Inc., Dover, NH)—in order to avoid bleeding during hepatic surgery. We analyzed patients who underwent hepatic surgery between January and June 2003. Sex, age, type of disease, and type of surgical procedure, in association with the duration of the surgical procedure, blood loss, use of vascular clamping of the liver, length of hospital stay, morbidity, and mortality were analyzed. Seven minor liver resections, two major liver resections, and one total cystopericystectomy were performed with the use of this new device. Average blood loss was 150 ml (range 50 to 300 ml). No vascular clamping was used with the exception of one patient. No deaths were recorded. Morbidity included ascites in one case and pleural effusion in another. In conclusion, the Tissuelink Monopolar Floating Ball permitted excellent coagulation of the cut liver surface, thus avoiding bleeding and vascular clamping. As a result, postoperative morbidity and mortality were low. (J GASTROINTEST SURG 2004;8:596–600)

KEY WORDS: Hepatic resection, hepatic technologies, coagulating devices

Surgery represents the best method for treating primary and metastatic liver tumors.[1,2] In previous years, many efforts were made to improve the results of liver resection, limiting its complications as much as possible. Several techniques and devices have been developed recently with the aim of allowing safer liver resections and avoiding intraoperative blood loss, which represents the most important cause of morbidity and mortality associated with this type of surgery.[3]

The aim of this study was to analyze our initial experience with hepatic resections using a new water-cooled, high-density, monopolar device—the Tissuelink Monopolar Floating Ball (TMFB; Tissuelink Medical, Inc., Dover, NH)—in order to avoid bleeding during hepatic surgery.

MATERIAL AND METHODS

Between January and June 2003, we performed liver resections in nine patients. There were three females and six males whose median age was 61.3 years (range 32 to 79 years). Five patients had cirrhosis and hepatocellular carcinoma (HCC), one patient had liver metastasis from an adrenocortical carcinoma, one patient had metastasis from colon cancer, one patient had a Klatskin tumor, and one patient had a hydatid cyst of the liver. Transection of the liver parenchyma was performed in six cases by means of a crushing clamp and the Cavitron Ultrasonic Surgical Aspirator (Valleylab, Tyco Healthcare, Boulder, CO) in one cirrhotic patient who also had HCC. The TMFB was used in all but one of the patients as a preventive treatment for the cut liver surface; the exception was the patient with the hydatid cyst in whom the device was used only for hemostasis of the cut liver surface after total cystopericystectomy. Duration of the surgical procedure, blood loss, use of vascular clamping of the liver, length of hospital stay, morbidity, and mortality were analyzed.

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RESULTS

Seven minor liver resections, two major liver resections, and one total cystopericystectomy (Table 1) have been performed using this new device. In one patient who underwent minor hepatic resection, a simultaneous left hepatic lobectomy (segment II and III according to the Couinaud classification)[4] and a limited resection of segment IV were also performed. In this patient, two spiculated nodules of HCC located at the tips of segments III and IV (Fig. 1) were detected. This double resection was performed in place of a left hepatectomy (segments II, III, and IV), because the indocyanine green clearance[15] value was 18%, and according to the Makuuchi algorithm[5] only two segments should be resected. In the patient with metastases of colon cancer located in segment I (Fig. 2), because of the absence of a safe margin (Fig. 3), the TMFB was also used to treat the liver parenchyma to prevent local recurrence.

The average time needed for liver resections was 20 minutes (range 10 to 55 minutes), and the average blood loss was 150 ml (range 50 to 300 ml). No vessel clamping was performed except in the patient with HCC in segment VI, in whom a Pringle maneuver was established for 5 minutes to allow intravenous infusion, which was needed to expand a volume deficit created by anesthesia. The length of hospital stay for these patients ranged from 5 to 25 days with a mean value of 8 days. No patient died during surgery or during the postoperative follow-up period. Procedure-related complications included ascites in one patient, which regressed after 10 days with medical treatment, and a right pleural effusion, which required two paracenteses in another patient. Both patients were diabetic and were being treated with insulin. The remaining patients had no postoperative complications.

DISCUSSION

Bleeding is the most important intraoperative and postoperative complication in patients requiring hepatic resection for liver tumors. Since the first application of the Pringle maneuver, many methods of vascular occlusion of the vessels of the liver have been developed.[6–8] Recently hypotensive anesthetic agents[9] have been used to reduce intraoperative bleeding.

Despite the development of many techniques of vascular occlusion and new drugs, the Pringle maneuver represents the method most widely used by hepatic surgeons to control intraoperative bleeding. Furthermore, during the past few years it has become clear to all that although the Pringle maneuver certainly reduces intraoperative bleeding and the complications related to it, by limiting the inflow of blood to the liver during the resection, it always produces unavoidable hepatic ischemia, which may on some occasions be the cause of damage to liver tissue and subsequent postoperative liver failure.[10]

For these reasons, efforts are currently being made to prevent the intraoperative blood loss so as to avoid ischemic damage of the parenchyma due to the vascular occlusion.

During liver resection there are many possible ways to perform division of the parenchyma; it can be done using the fingers or by crushing the tissue with a clamp, but all of these usually require that concomitant vascular occlusion procedures be performed.

The TMFB and several other sophisticated devices developed recently allow the surgeon to perform the resection without any inflow occlusion, thus limiting, if not avoiding altogether, the blood loss during the procedure itself.

The TMFB device uses radiofrequency energy focused near the tip. Electrical energy is conducted through continuous low-volume saline irrigation and then into tissue where it is converted into heat by ohmic heating of the tissue. The saline facilitates energy transfer between the device-tissue interface, maintaining contact with the hepatic tissue and dispersing thermal energy. The saline solution also provides surface cooling to prevent the tissue from becoming hotter than 100C.[11] Maintaining the temperature of the tissue at or below 100C also avoids the formation of eschar. Hepatic tissue coagulated without char is softer, more friable, and easier to dissect through tissue that has been charred at a high temperature. The device seals vascular and biliary structures up to 3 mm in diameter by collagen fusion[11] and allows the surgeon to perform hepatic resection without vascular occlusion, thus decreasing the morbidity, especially in patients with low hepatic functional reserve.

The energy source for the TMFB device is radiofrequency electrical energy. In contrast to other available radiofrequency devices, the TMFB device does not require specialty generators and its plug is compatible with most electrosurgical generators currently available.

Table 1. Hepatic resections performed with Tissuelink Monopolar Floating Ball

Type of resection	Hepatic segment	No. of patients
Segmentectomy	VI	2
Segmentectomy	I	1
Subsegmentectomy	IV	1
Left lobectomy	II–III	2
Limited resection		1
Right hepatectomy	V–VI–VII–VIII	2
Total cystopericystectomy		1

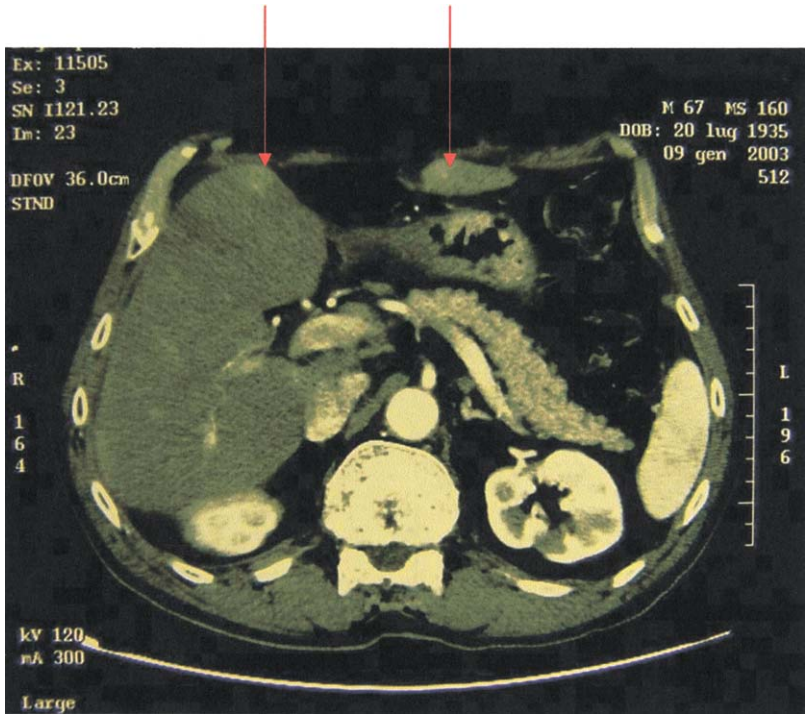

Fig. 1. CT image of the liver. *Arrows* indicate two separate hepatocellular carcinomas, one in segment III and one in segment IV of the liver.

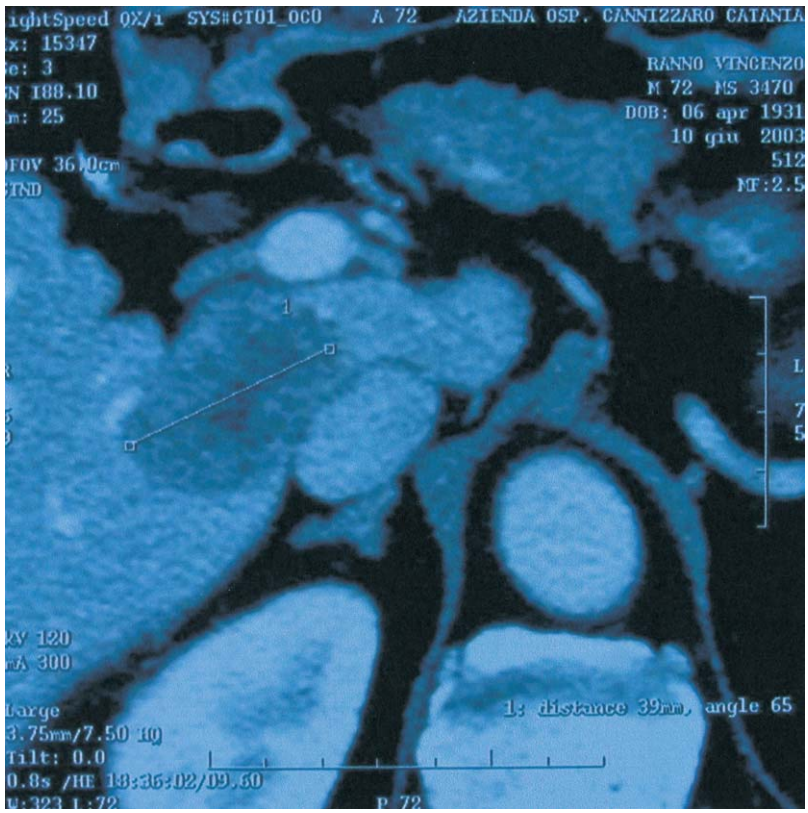

Fig. 2. Spiral CT image of the liver showing a colonic metastasis in segment I.

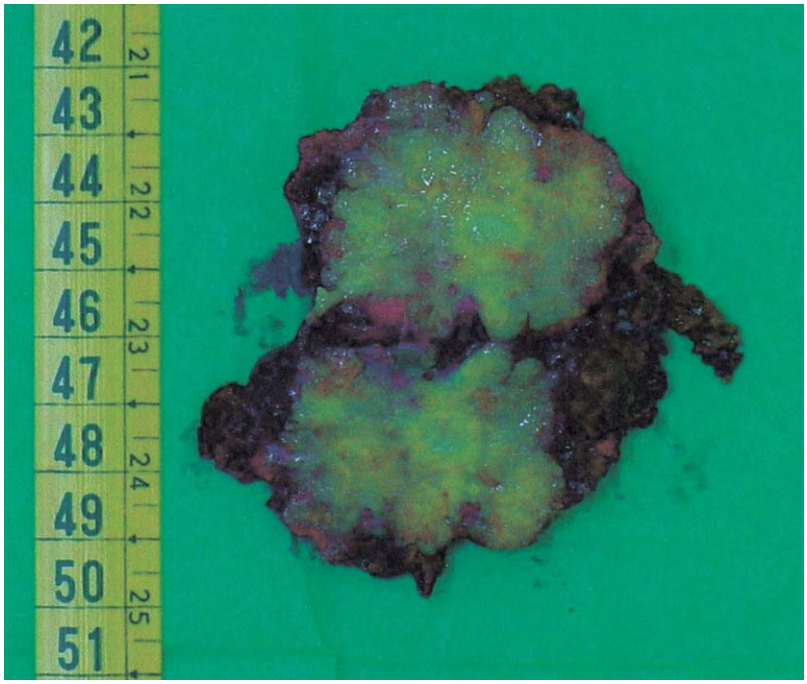

Fig. 3. Photograph of a resected specimen of the liver containing the metastatic nodule of colon cancer with disease-free margins. In this patient, the Tissuelink Monopolar Floating Ball was used to destroy residual tumor remaining at the site of resection.

The TMFB is a device that provides excellent coagulation and, in our experience, limits the bleeding. In fact, the preventive coagulation of the liver surface lessens the blood loss with a double action: the coagulation itself and fusion of vessels up to 3 mm in diameter, which usually are difficult to close with sutures or clips.

Therefore use of this device can be recommended for cirrhotic patients who also have HCC, in whom there is a high risk of complications from hepatic resection because of the diseased hepatic parenchyma.

Although we have no experience in this area, the excellent coagulation produced by the TMFB might be useful, especially in the living donor liver transplantation, in whom preservation of the remaining liver and minimal blood loss are mandatory.

Total cystopericystectomy represents the treatment of choice for patients who have a hydatid cyst.[12] This technique removes the entire cyst with no spillage of the internal fluid, thereby curing the patient and avoiding any complications. In this instance, the TMFB cannot be used to separate the cyst from the liver parenchyma. The action of the device might cause a perforation of the cyst and subsequent complications. The device is, however, useful at the end of total cystopericystectomy to achieve hemostasis of the cut liver surface.

Last but not least, the coagulation of the cut liver surface with this device may provide additional tumor destruction at the margin of resection where additional tumor may have been left behind.

Many other new devices are currently available to perform hepatic resection. All of them have been studied to give surgeons the opportunity to avoid performing vascular occlusion during liver resection, but most of them still have many limitations such as the high cost of the devices themselves or the length of the procedure.[13]

Among these devices, the Cavitron Ultrasonic Surgical Aspirator has certainly already proved its usefulness in liver resection. Very good results have been achieved using the Cavitron Ultrasonic Surgical Aspirator and bipolar cautery water irrigation system.[14] This method decreases the load to the remnant liver during the resection, contributing to the safety of the procedure. Unfortunately, it is a very expensive device so its use is still limited to only a few centers. In contrast, the less expensive TMFB can be used with a normal electrocautery, and thus it can be used nearly everywhere.

Recently a very interesting use of radiofrequency energy to coagulate the liver resection margins has been reported.[15] This innovative and relatively simple technique permits the resection to be performed if not in a short period at least within a reasonable period of time (range 95 to 300 minutes) without any vascular clamping, with very good results, and with no need for blood transfusion.[14] Its use is still limited

to minor liver resections and, in addition, it uses very expensive throwaway needles. Moreover, it cannot be applied too close to the hilus of the liver or the vena cava because of fear of damaging these structures. Moreover, radiofrequency devices sacrifice the parenchymal tissue that is usually spared when other resectional techniques are used.[15]

Another interesting device is the high frequency–supported jet cutting device (HF jet), which allows rapid resections with no blood loss or electrolyte disturbances.[16] However, it is still undergoing experimental studies. It is not clear yet whether it needs inflow occlusion to be performed. No clinical studies have been reported in the literature with the use of this support.

CONCLUSION

The TMFB permits excellent coagulation of the cut liver surface during hepatic resection, thus avoiding bleeding and vascular clamping. In this way, it reduces the morbidity and mortality associated with the operation. Prospective randomized studies are needed in order to determine its absolute beneficial effects.

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Ciliated Hepatic Foregut Cyst of the Left Hepatic Vein

Takki A. Momin, B.S., Ross Milner, M.D., Juan M. Sarmiento, M.D.

Ciliated hepatic foregut cyst is an extremely rare condition observed most frequently in the left hepatic lobe of young men. This report describes an unusual case of ciliated hepatic foregut cyst with involvement of the left hepatic vein in a 68-year-old woman. Preoperative imaging studies demonstrated characteristics of a solid tumor that were suggestive of a leiomyosarcoma of the inferior vena cava. Magnetic resonance venography confirmed a mass in the anterolateral wall of the inferior vena cava or in the left hepatic vein. This report confirms the unusual occurrence of this tumor and the confusing factors related to the diagnostic workup. (J GASTROINTEST SURG 2004;8:601–603)

KEY WORDS: Hepatic cyst, hepatic veins, IVC

Although the term "ciliated hepatic foregut cyst" (CHFC) was not introduced until 1984, Friedreich first described the lesion as a congential malformation in 1857.[1] This was followed by another case description in 1866 by Eberth.[1] Wheeler and Edmondson presented the first histologically proved case of CHFC in 1984.[2]

The differential diagnostic possibilities that must be considered in addition to CHFC, discovery of a cyst in the right upper quadrant, include cholangiogenic cyst, simple cyst, parasitic cyst, and biliary cystadenoma. Anatomic location of the cyst determined by radiographic studies is the most important diagnostic criteria, because CHFCs are usually situated in a subcapsular location on the anterior aspect of the liver.[3] This report describes a case of a solid-appearing CHFC of the left hepatic vein as identified on preoperative abdominal ultrasound imaging and magnetic resonance venography (MRV) of the hepatic veins.

CASE REPORT

A 68-year-old woman, who had recently undergone laparoscopic cholecystectomy for symptomatic cholelithiasis, was referred to our institution for the incidental finding of a hemangioma of the liver on abdominal ultrasound imaging. The mass was described as intrahepatic but appeared to be originating from the superior portion of the inferior vena cava (IVC). MRV of the hepatic veins and IVC revealed a mass in the course of the intrahepatic IVC with narrowing of the inflow of the hepatic veins (Figs. 1 and 2). CT of the chest was negative for metastatic lesions and abnormalities.

With a presumptive diagnosis of IVC leiomyosarcoma, the patient underwent surgical exploration of the abdomen via an upper midline incision. No signs of metastasis were identified. Intraoperative ultrasound imaging indicated that the tumor was located exactly between the left and middle hepatic veins, as suggested by MRV. On gross inspection, the mass appeared to be originating from the superior medial aspect of the IVC, thereby requiring median sternotomy for better exposure and adequate segmental resection. Complete visualization of the anterior IVC by dividing segments 2 and 3 from segment 4 showed that the mass did not involve the IVC, but that it arose from the common trunk of the left and middle hepatic veins (Fig. 3). The mass was resected en bloc along with the common trunk of the left and middle hepatic veins, the corresponding lateral portion of the IVC, and segments II and III of the

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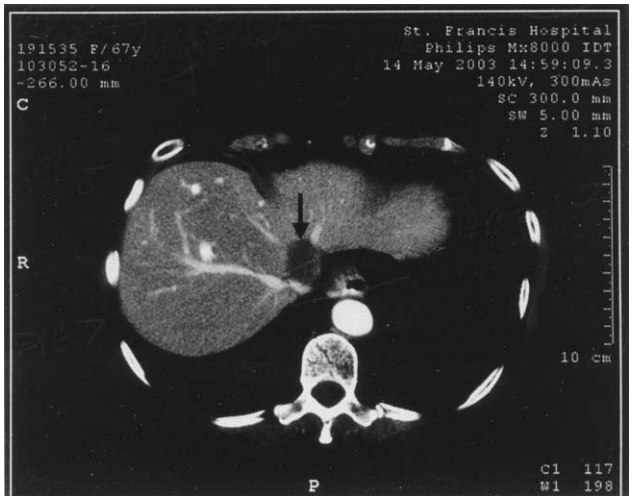

Fig. 1. Magnetic resonance venography of the hepatic veins and inferior vena cava. Note the mass in between the middle and left hepatic veins (*arrow*).

liver. The defect at the origin of these vessels was directly repaired.

Pathologic examination identified a $3.8 \times 3.4 \times 2.3$ cm well-circumscribed mass (Fig. 4) located in the hepatic side of the junction of the left and middle hepatic veins. The mass consisted of a unilocular cyst with a lining of columnar ciliated epithelium and

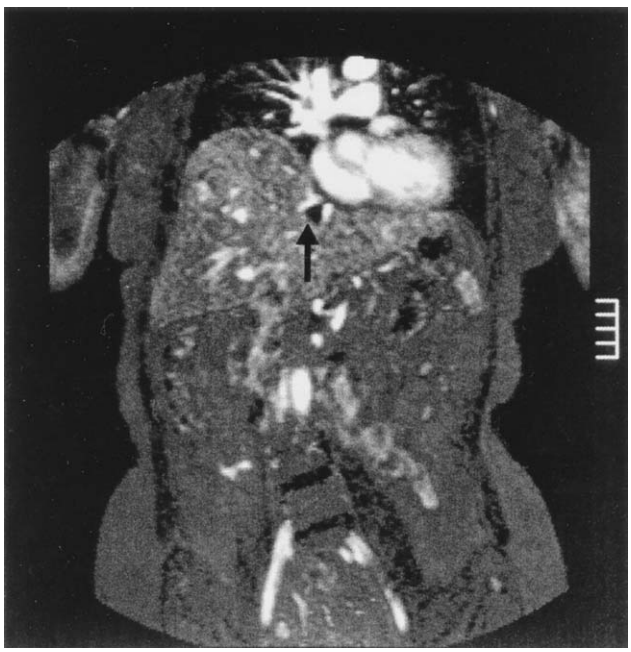

Fig. 2. CT scan of the abdomen. The mass (*arrow*) is occupying the proximal portion of the left and middle hepatic veins and compressing the inferior vena cava. There is no involvement of the right hepatic vein.

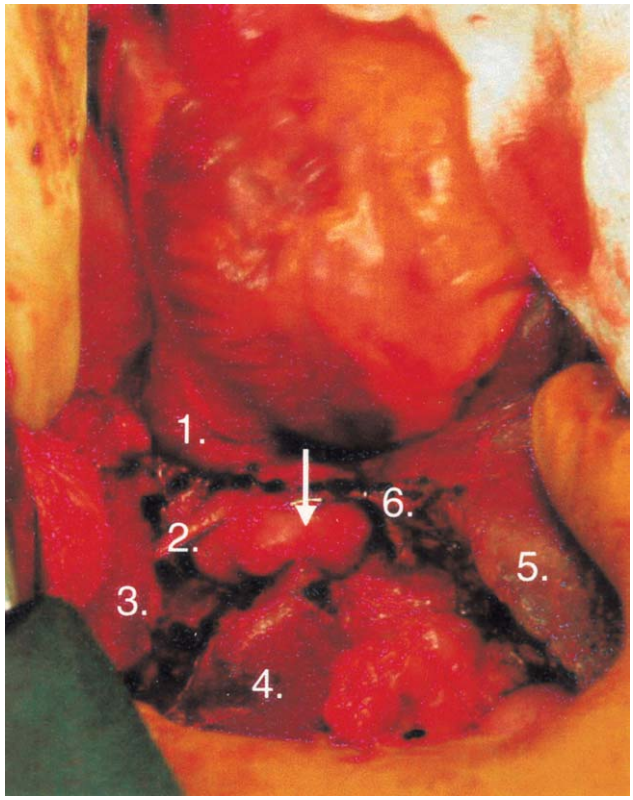

Fig. 3. Intraoperative photograph of the mass. The mass (*arrow*) is located at the confluence of the left hepatic vein (*6*) and the middle hepatic vein (*2*). Note the solid appearance of the mass.

smooth muscle in its wall. Approximately 4 to 5 cm^3 of mucopurulent fluid was discovered within the cyst on serial sectioning. These findings indicated that the mass was a CHFC.

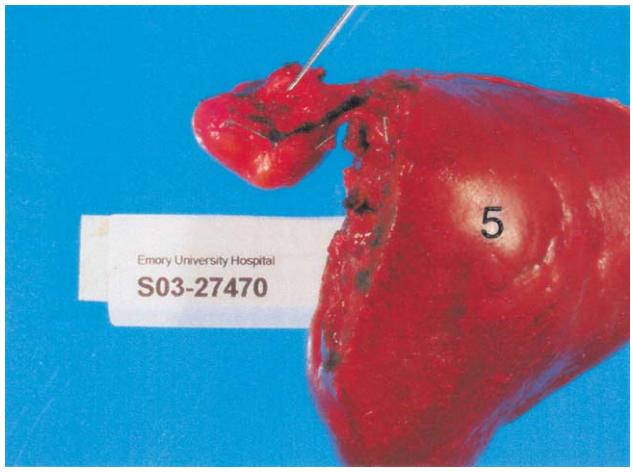

Fig. 4. Surgical specimen. En bloc resection of the left lateral segments of the liver (*5*) with the left hepatic vein connected to the mass. The small stump of the middle hepatic vein has been clipped. The venous stump that was attached to the inferior vena cava is shown with the instrument.

DISCUSSION

CHFC is an extremely rare condition that is observed most frequently in the left hepatic lobe of young men. The pathogenesis of CHFC is unknown, but it is thought to represent a developmental anomaly of the anterior foregut, leading to a detached outpouching of the hepatic diverticulum or adjacent enteric foregut.[4] This assertion is supported by common histologic features characteristic of CHFCs, esophageal cysts, and bronchial cysts, all three originating from anterior foregut derivatives. CHFCs are typically small lesions that range in size from 1 to 4 cm and contain viscous fluid. They are most often solitary and unilocular with a wall composed of ciliated pseudostratified columnar epithelium, scattered mucous cells, loose subepithelial connective tissue, one to three muscle layers, and a fibrous external capsule.[3,5] The morphologic hallmark of CHFC is the presence of pseudostratified, ciliated, mucinsecreting, columnar epithelium associated with bundles of smooth muscle in the cyst wall.[5]

The vast majority of cases of CHFC correspond to benign lesions discovered incidentally during imaging studies, surgical exploration, or at autopsy. There are, however, two reported cases of invasive squamous cell carcinoma arising from a CHFC.[5] It is unclear whether this is secondary to a sparse prevalence or the result of an inherently low malignant potential of CHFC. Surgical excision is recommended in most cases, particularly those in which imaging studies show abnormalities in the cystic wall.[5]

The exact prevalence of CHFC is unknown because of its asymptomatic nature, as was the case with this patient. The number of identified cases is extremely rare, with only 56 reported up until 1999.[1] Most identified cases of CHFC demonstrate typical cystic features on ultrasound imaging. These features include round shape, smooth wall, absence of internal echoes, and the presence of posterior echo enhancement.[4] Failure to observe any one of these characteristics, which are typical of all cysts, makes the diagnostic confidence uncertain. The case described herein represents a case of CHFC of the left hepatic vein that appeared to represent a solid tumor on ultrasound imaging and on MRV of the hepatic veins.

The inability to distinguish CHFCs from neoplastic cysts both radiographically and clinically has been widely described in the literature.[6] There are no known previous cases, however, of CHFC involvement of the left hepatic vein presenting as a solid tumor on ultrasound and MRV. This location of the mass coupled with findings on preoperative imaging studies led to the presumptive diagnosis of leiomyosarcoma of the IVC in our patient.

This case illustrates how CHFCs may easily be mistaken for malignant solid tumors on preoperative imaging studies and MRV. Hence the differential diagnosis of an incidentally identified mass of the right upper quadrant must be expanded to include CHFC regardless of radiographic studies and location of the mass that suggest otherwise.

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A New Free Radical Scavenger, Edaravone, Ameliorates Oxidative Liver Damage Due to Ischemia-Reperfusion In Vitro and In Vivo

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Ischemia-reperfusion injury causes oxidative stress producing reactive oxygen species, which is a serious problem linked to morbidity and mortality in liver surgery. We investigated the effects of edaravone, a new free radical scavenger, on liver oxidative stress in vitro and in vivo. We employed a hypoxia-reoxygenation model of primary cultured hepatocytes using an AnaeroPack (Mitsubishi Gas Chemical Co., Tokyo, Japan). Hepatocytes were exposed to 3 or 4 hours of hypoxia and then returned to oxygenation. We analyzed the time course changes of aspartate aminotransferase (AST), phosphatidylcholine hydroperoxide (PCOOH), and adenosine triphosphate (ATP) content in hepatocytes of edaravone-treated groups or nontreated groups after reoxygenation. Edaravone significantly attenuated the elevation of the AST level of the medium and hepatocellular PCOOH and preserved the hepatocellular ATP level. In vivo, male Sprague–Dawley rats were subjected to 45 minutes of hepatic ischemia and 120 minutes of reperfusion. The rats were intravenously injected with vehicle or edaravone (3 mg/kg or 10 mg/kg) before reperfusion and 1 hour after reperfusion. Serum AST levels and hepatic PCOOH and energy charge were significantly improved in both edaravone groups compared with control. In conclusion, edaravone has the ability to eliminate intra-hepatocellular superoxide species and attenuate oxidative liver damage in liver surgery. (J GASTROINTEST SURG 2004;8:604–615)

KEY WORDS: Edaravone, hepatic ischemia-reperfusion injury, oxidative stress, lipid peroxidization, phosphatidylcholine hydroperoxide

INTRODUCTION

In liver surgery, hepatic inflow vascular clamping such as the Pringle maneuver is frequently performed to control bleeding from the hepatic parenchyma. However, prolonged hepatic ischemia sometimes causes severe hepatic ischemia-reperfusion (I/R) injury. Moreover, in cases of liver transplantation and hemorrhagic shock, hepatic I/R injury cannot be avoided. I/R injury of the liver causes hepatocellular damage that may delay hepatic regeneration and lead to hepatic failure.[1] Therefore, it is important to attenuate the liver damage caused by I/R injury during liver surgery. However, although endogenous antioxidant substances, such as superoxide dismutase, catalase, glutathione, alpha-tocopherol, and beta-carotene, may reduce the effects of radical oxygen species (ROS), these antioxidants do not prevent I/R injury clinically because the ROS scavenging system can quickly become overwhelmed by the large quantities of ROS.[2] Therefore, we attempted to find an effective free radical scavenger.

A new free radical scavenger, edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one), was developed in 1984 and is widely used clinically in Japan for acute cerebral infarction to prevent ischemia-reperfusion injury. Edaravone exerts beneficial free radical scavenging effects especially against hydroxyl

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radical[3,4] and shows antioxidant characteristics in vitro.[5–7] Its protective effects have been demonstrated not only in a cerebral I/R model but also in a myocardial I/R model in vivo.[8,9] Furthermore, edaravone may improve the regional blood flow after cerebral infarction by attenuating the brain edema.[10] It is possible that edaravone is a more effective antioxidant than the others currently used and could attenuate hepatic I/R injury as well as that which occurs in cerebral infarction.

There are three possible mechanisms that generate ROS and play an important role in the hepatic I/R injury: the first is extracellular ROS produced from the NADPH oxidase system located on the cellular membrane of phagocytic cells, such as Kupffer cells and neutrophils in the liver[11–16]; the second is intracellular ROS from xanthine oxidase; and the third is intracellular ROS from mitochondria.

Previously, we reported that phosphatidylcholine hydroperoxide (PCOOH) in serum and liver tissue measured by high-performance liquid chromatography-chemiluminescence method (HPLC-CL) is a sensitive parameter for hepatic I/R injury both in vivo and in vitro. We demonstrated that intracellular superoxide production from the xanthine oxidase system is involved in the mechanism of hepatic I/R injury using Cu–Zn superoxide dismutase (SOD) transgenic mice.[17] We also showed that hepatocytes from Cu-Zn SOD transgenic mice are protected from I/R injury by an anaerobic system.[18]

Recently, some studies reported that edaravone also had beneficial effects on liver I/R damage,[19,20] but the precise mechanism is not well known. In this study, we examine whether edaravone is effective in a liver I/R model in vivo and how edaravone scavenges ROS in hepatocytes using primary cultured hepatocytes. In addition, we show that edaravone ameliorates the hepatocellular dysfunction in protein synthesis and prevents cell death.

MATERIALS AND METHODS

Materials

Edaravone was obtained from Mitsubishi-Tokyo Pharmaceuticals (Mitsubishi Tokyo Pharmaceuticals Corp., Tokyo, Japan). Collagenase (Type I) and Triton X100 was obtained from Wako Pure Chemical Industries (Wako Pure Chemical Industries Ltd., Osaka, Japan). AnaeroPack and its exclusive anaerobic jar were purchased from Mitsubishi Gas Chemical Co. (Mitsubishi Gas Chemical Co., Inc., Tokyo, Japan). L-[4,5-^{3}H]-Leucine (1 mCi/ml) was purchased from Amersham Biosciences (Amersham Biosciences Ltd., Little Chalfont, UK). The ATP assay kit was obtained from TOYO B-Net Co. (TOYO B-Net Co., Ltd., Tokyo, Japan). The DNA reagent kit was from Becton Dickinson (Becton Dickinson Ltd., Oxford, UK). Cell culture media and all the other chemicals were purchased from Sigma-Aldrich Co. (Sigma-Aldrich Co., St. Louis, MO).

Conditions for Animal Experiments

Two-month-old male Sprague–Dawley rats (240–300 g) were used for the in vivo I/R model. The rats were kept in a temperature-controlled room with a 12-hour light–dark cycle. All animals had free access to water and standard laboratory diet. Before I/R the rats were fasted overnight. Surgery was performed under spontaneous ether inhalation. Seventy percent partial liver ischemia was induced by selective clamping of the portal vein and hepatic artery for 45 minutes. Reperfusion was initiated by removal of the microclips and 120 minutes later, after taking blood samples, all rats were sacrificed and liver tissue was put into liquid nitrogen as soon as possible and stored at −80°C. The rats were randomly divided into three groups. In the control groups, saline was administered intravenously just before reperfusion and 1 hour after reperfusion. Edaravone was freshly dissolved in 1.0 N NaOH, the pH being adjusted to almost neutral with 1.0 N HCl. The edaravone groups (EDA) were subdivided into two groups according to the volume of the drug (3 mg/kg or 10 mg/kg intravenously [i.v.]); the drugs were administered at the same time as above.

Hepatocyte Isolation and Treatment

Hepatocytes were isolated from male Sprague–Dawley rats (150–200 g) according to the method described by Seglen.[21] Cell viability, estimated at the beginning of the experiments, was greater than 90% as determined by trypan blue exclusion. Hepatocytes were resuspended into RPMI-1640 containing 10% fetal bovine serum, 10-8M insulin, and 10-8M dexamethasone. For measurement of the adenosine triphosphate (ATP) and aspartate aminotransferase (AST) levels, hepatocytes were plated (2.5×10^5/ml) on collagen-coated 6-well dishes. For the measurement of protein synthesis, the cells were plated on 12-well dishes. For the measurement of the PCOOH level the cells were plated on 100 mm dishes. The cells were maintained in an incubator at 37°C for 3 hours to allow cell attachment and equilibration. The dead cells were then removed and the medium was changed to a serum free medium. Cells were incubated for 21 hours and used for various experiments. The dishes were randomly divided in two, the control and edaravone groups. In the control group, after incubation for 24 hours, vehicle only (0.05% ethanol)

was added to the medium and in the edaravone group, edaravone at 10 μM (0.05% ethanol) was added. To test the dose dependency, edaravone was added at 0.1, 1, 10, and 50 μM. The dishes were incubated anaerobically for 3 or 4 hours using an anaerobic box devised by Kamiya and associates,[22] then aerobic incubation was performed for 24 hours. That is, a hypoxic condition was created by placing a cell culture dish with one pouch of AnaeroPack into an airtight jar and the reoxygenated condition was created by removing the dish from the jar.

From the control and EDA groups, the hepatocytes and medium were sampled immediately before the anaerobic incubation (pre), immediately after the anaerobic incubation (0 hours), and immediately after 2, 4, 6, 12, and 24 hours of reoxygenation. For the DNA content analysis, after 4 hours of hypoxia and 24 hours of reoxygenation, 5×10^5 cells were collected, pelleted, and washed with phosphate-buffered saline (PBS). Then the cells were treated with propidium iodide and ribonuclease A using a DNA reagent kit. Ten thousand fixed cells were examined per experimental condition by flow cytometry and the percentage of degraded DNA was determined by the number of cells displaying subdiploid (sub-G1) DNA divided by the total number of cells examined.

For the measurement of protein synthesis, 5 μl of [^{3}H]-Leucine was added to the medium after 24 hours of reoxygenation. After pulse labeling for 4 hours, the medium was removed and the hepatocytes were washed by PBS three times. The cells were lysed in situ by the addition of 0.1 ml of 0.5 M NaOH containing 0.05% Triton X100. The protein was denatured by adding 10% trichloroacetic acid and harvested with a multichannel cell harvestor onto glass filters. The filters were dried and [3H]-Leucine incorporated into protein was assessed by liquid scintillation counting. For in vitro experiments, 4–6 hepatocyte preparations were used as indicated in the figure legends. In each hepatocyte preparation we measured 3–6 wells at each time and in each group.

Measurement of the Parameters

AST was measured using a spotchem (Kyoto Daiichi-kagaku Co., Ltd., Kyoto, Japan) according to the procedures of the dry chemistry method. Hepatocellular ATP was determined using an ATP assay kit and the levels were read on a luminometer (Lumat LB 9507; EG & G Berthold, Bad Wildbad, Germany). Hepatocellular PCOOH was measured by HPLC-CL as described by Miyazawa and associates.[23] Hepatocytes were grown to 2.5×10^6 cells per dish. The medium was removed and replaced with 2.5 ml of PBS and the cells were carefully scraped using a cell scraper. The mixture of scraped cells was collected and stored at −20°C. Two milliliters of 0.002% butylated hydroxytoluene (BHT)-containing 0.15 M NaCl were added to the isolated hepatocytes and the lipid extraction was conducted in triplicate for each specimen. Hepatocyte samples were injected into a mixture of chloroform and methanol (2:1, v/v), shaken well to dissolve the lipid in the chloroform layer, and centrifuged at 3000 revolutions per minute (rpm) for 10 minutes. The chloroform extraction was repeated three times. The collected chloroform layer was concentrated by evaporation and the residue was reconstituted in chloroform (400 μl). Twenty microliters of the specimen was separated by HPLC (column: Finepak SIL NH2-5, Nippon Bunko Co., Ltd., Tokyo, Japan) and tested for chemiluminescence by adding cytochrome C and luminal using a chemiluminescence detector (Tohoku Denshi Sangyo Co., Ltd., Sendai, Japan). The PCOOH level was obtained by calculating the ratio of the area of the sample to that of the reference standard supplied by the Functional Molecular Analysis Group of the Department of Agriculture (Tohoku University, Sendai, Japan).

The PCOOH level in the hepatic tissue was measured as follows. Lipid was extracted according to the following procedures: a homogenate of the liver specimen was prepared by adding a physiological saline solution containing 0.002% BHT to 200 mg of frozen liver. A chloroform/methanol mixture (2:1, v/v) was added to the homogenate and shaken to dissolve the lipid in the chloroform layer. After centrifugation at 3000 rpm for 10 minutes at 4°C, the lower chloroform layer was isolated by three repetitions of the operation. The isolated chloroform layer was concentrated by evaporation and then the pellet was suspended into 100 μl of chloroform to prepare the specimen. Twenty microliters of the specimen was measured the same as above.

Nucleotide measurement of the liver tissue was determined by the following method. The frozen liver samples were weighed on a weighing machine and powdered in a stainless steel mortar using dry ice, immersed in liquid nitrogen, and then mixed with 0.9 N $HClO_4$ for homogenization. Then, the mixture was centrifuged at 3000 rpm for 10 minutes at 4°C. The supernatant was neutralized with cold 3.75 M K_2CO_3 and centrifuged again. The final supernatant was taken to measure the adenine nucleotides by HPLC. The energy charge (EC) was calculated by the following equation proposed by Atkinson[24]: EC = (ATP + 0.5 ADP)/(ATP + ADP + adenosine monophosphate [AMP]).

Statistical Analysis

Each determined value was tested by two-factor analysis of variance (ANOVA) (StatView 5.0; SAS

Institute, Inc., Cary, NC), whereas the Fischer posthoc least significant difference (PLSD) was used as the posthoc test. The results are shown as the mean ± standard error (SEM) and a difference of p less than 0.05 was taken as significant.

RESULTS

In Vitro Experiments

Measurement of AST in Medium. The changes of the AST levels in the medium undergoing 3 hours of hypoxia are shown in Fig. 1, *A*. In the control group, the AST levels at 6, 12, and 24 hours after reperfusion were 25.9 ± 11.5, 39.5 ± 4.4, and 59.0 ± 19.5 IU/l, respectively, indicating that the AST level in the medium had significantly increased. Meanwhile, in the edaravone groups, the AST levels were not increased significantly until 24 hours after the initiation of reoxygenation. The levels at 6, 12, and 24 hours after the initiation of reoxygenation in the EDA groups were 6.6 ± 1.5, 15.5 ± 4.6, and 36.5 ± 11.4 IU/l, respectively. The AST levels in the medium were significantly reduced in the EDA groups compared with the control groups at 6, 12, and 24 hours after the initiation of reoxygenation. The changes in the AST levels undergoing 4 hours of hypoxia showed the same tendency (Fig. 1, *B*). Edaravone significantly inhibited the elevation of the AST levels at 12 and 24 hours after the reoxygenation.

Measurement of Intracellular ATP. The intracellular ATP levels of the hepatocytes were decreased by hypoxic loading in both the control group and the EDA group. As shown in Fig. 2, *A*, the intracellular ATP levels were significantly maintained in the EDA

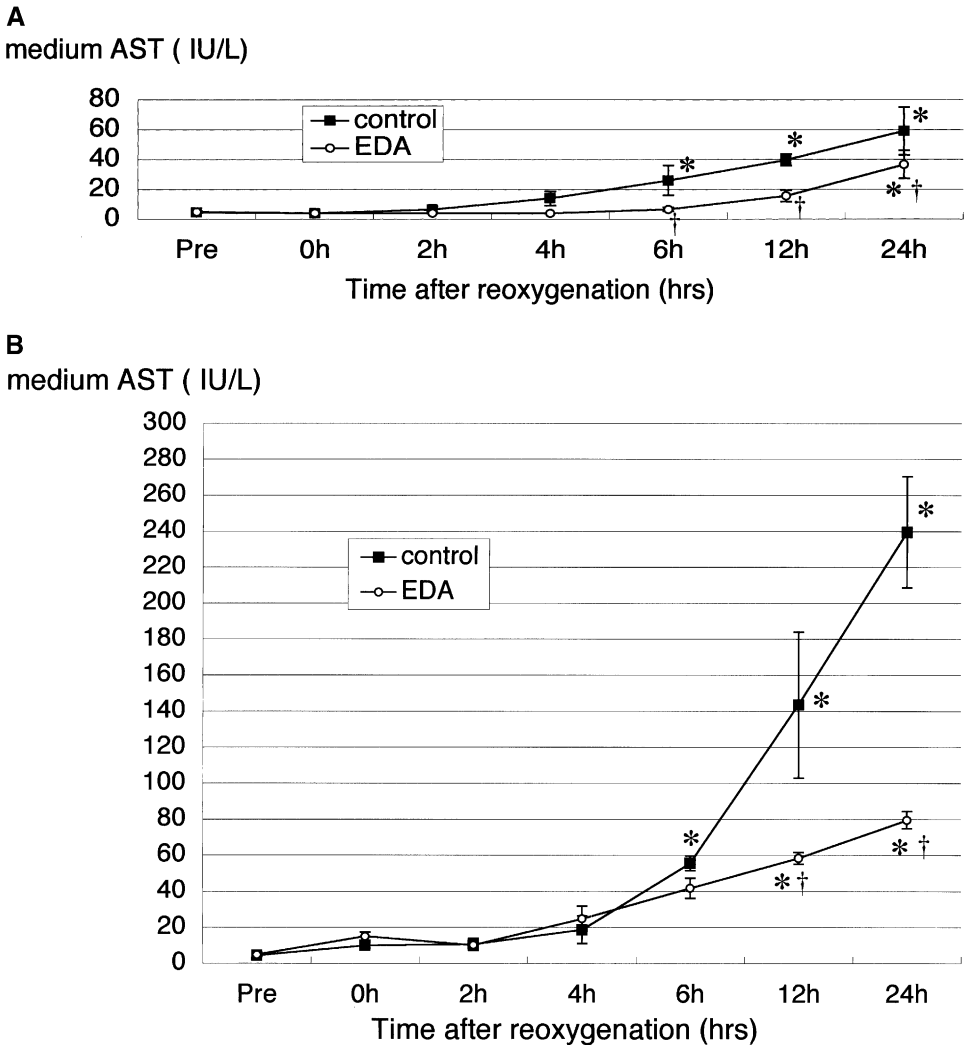

Fig. 1. Changes in the aspartate aminotransferase (AST) level in the medium with 3 hours of hypoxia (**A**) (4–5 hepatocyte preparations) and 4 hours of hypoxia (**B**) (4–5 preparations). $^{*}p < .05$ vs. pre, control group (Fischer PLSD); $^{\dagger}p < .05$ vs. control group at the same time (Fischer PLSD).

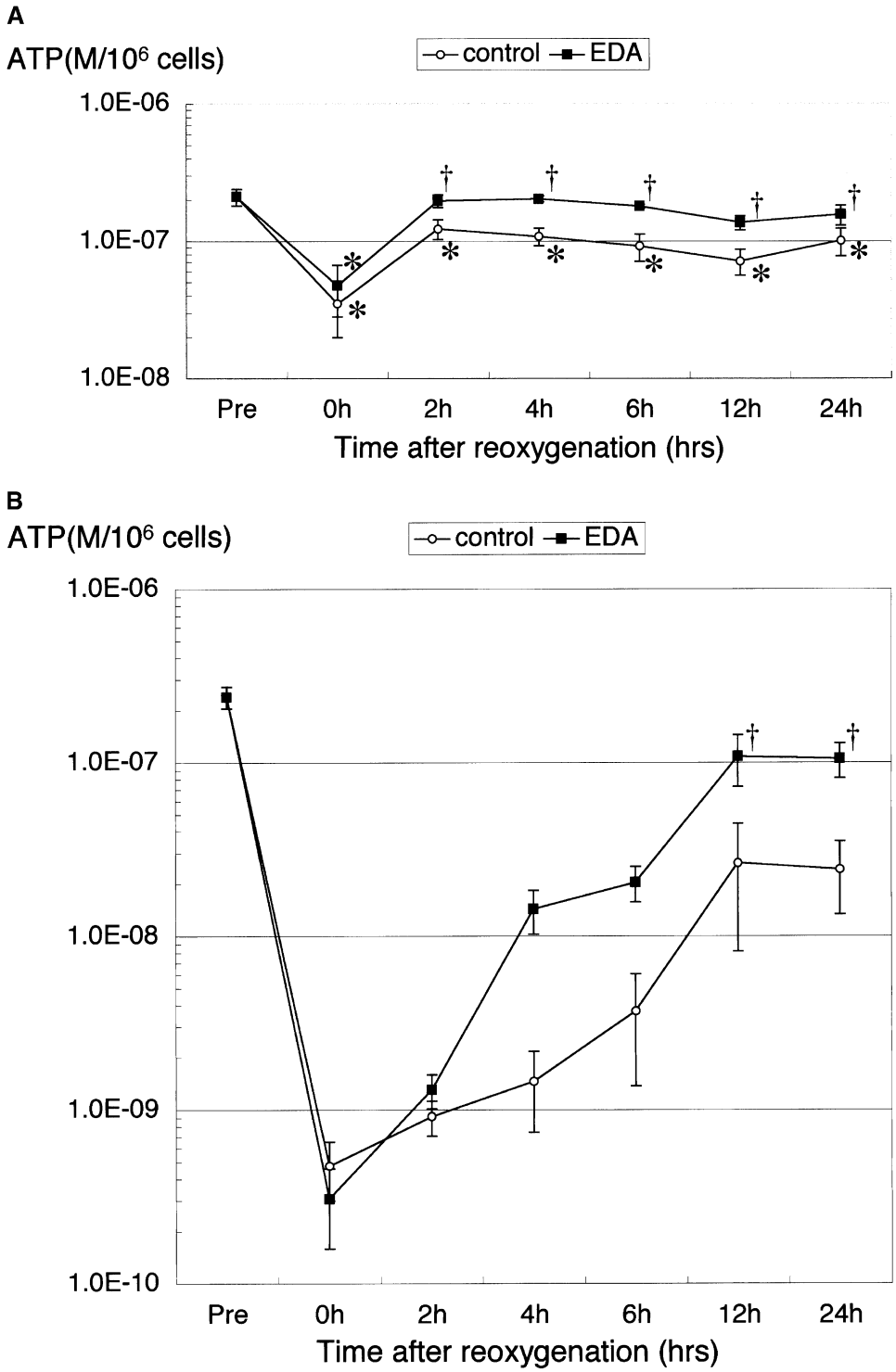

Fig. 2. Changes in the intracellular adenosine triphosphate (ATP) level with 3 hours of hypoxia (**A**) (5 hepatocyte preparations) and 4 hours of hypoxia (**B**) (5–6 preparations). In (**B**), all data were significantly low vs. pre, control group (Fischer post-hoc least significant difference [PLSD]). *$p < .05$ vs. pre, control group (Fischer PLSD); †$p < .05$ vs. control group at the same time (Fischer PLSD).

group at 2–24 hours after the reoxygenation. Similar results were obtained in the 4-hour hypoxia groups (Fig. 2, *B*). Edaravone significantly preserved the hepatocellular ATP at 12 and 24 hours after reoxygenation succeeding 4 hours of hypoxia.

Measurement of Hepatocellular PCOOH. The hepatocellular PCOOH levels in the control group after 3 hours of hypoxia revealed a significant increase at 4, 6, 12, and 24 hours after the initiation of the reoxygenation compared with the previous level.

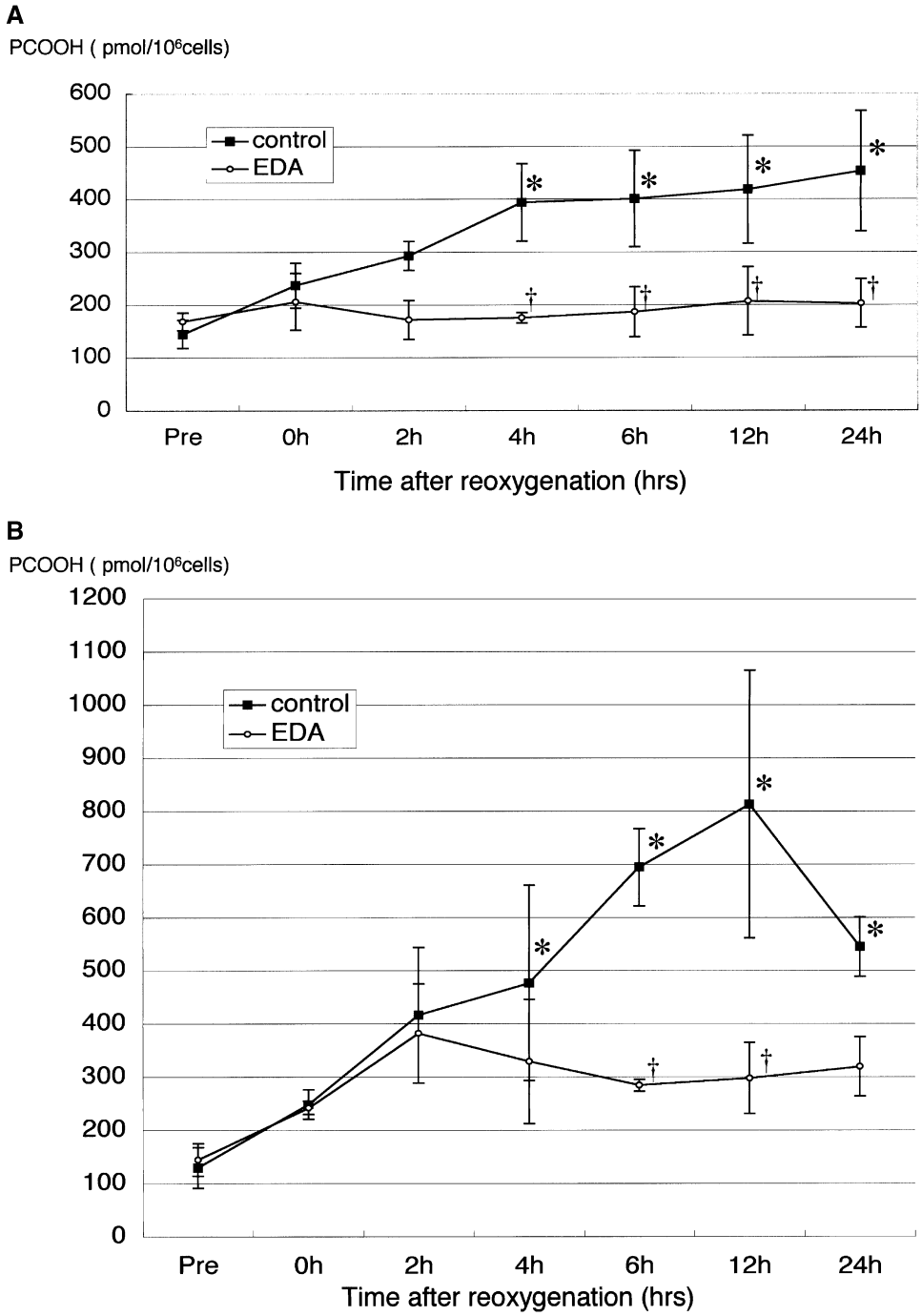

Fig. 3. Changes in the phosphatidylcholine hydroperoxide (PCOOH) concentrations in hepatocytes with 3 hours of hypoxia (**A**) (5 hepatocyte preparations) and 4 hours of hypoxia (**B**) (4–5 preparations). $^{*}p < .05$ vs. pre group (Fischer post-hoc least significant difference [PLSD]); $^{\dagger}p < .05$ vs. control group at the same time (Fischer PLSD). *Open bars* = edaravone (EDA) group; *closed bars* = control group.

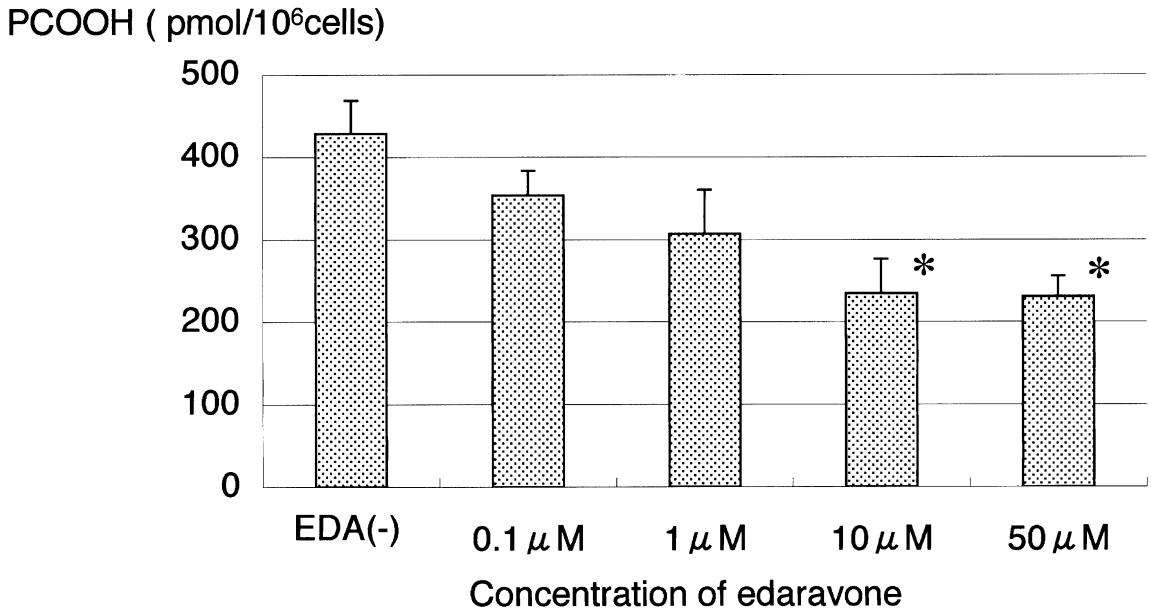

Fig. 4. Inhibitory effect of edaravone (EDA) on phosphatidylcholine hydroperoxide (PCOOH) formation at 4 hours after the initiation of reperfusion (4 hepatocyte preparations). *$p < .05$ vs. EDA (-) group (Fischer post-hoc least significant difference [PLSD]).

The PCOOH levels in the control group at 4, 6, 12, and 24 hours after the reperfusion after 3 hours of hypoxia were 393.9 ± 82.0, 400.9 ± 101.7, 418.3 ± 114.2, and 453.2 ± 127.3 pmol/10^6 cells, respectively, and the levels were significantly lower in the EDA group to 175.6 ± 11.3, 186.8 ± 52.6, 207.0 ± 72.4, and 202.5 ± 51.8 pmol/10^6 cells, respectively. Thus, in the EDA group undergoing 3 hours of hypoxia, there was no increase in the PCOOH level by reoxygenation (Fig. 3, *A*). In the 4-hour hypoxia groups, the PCOOH levels at 6 and 12 hours after the reoxygenation were significantly increased in the control group compared with the EDA groups (Fig. 3, *B*).

Post-hypoxic treatment with edaravone dose dependently inhibited the reperfusion-induced elevation of the hepatocellular PCOOH at 4 hours after the initiation of reperfusion (Fig. 4). The PCOOH levels at 0 (EDA (-)), 0.1, 1, 10, and 50 μM were 428.3 ± 46.9, 353.0 ± 35.2, 306.9 ± 61.2, 234.9 ± 47.8, and 231.0 ± 24.7 pmol/10^6 cells, respectively. The levels were significantly reduced by edaravone at the concentration of 10 and 50 μM.

Protein Synthesis. The effect of edaravone on the [3H]-Leucine incorporation into the protein of the hepatocytes is shown in Table 1. In both the 3- and 4-hour hypoxia groups, there was a significant increase in hepatocyte protein synthesis when edaravone was added.

Flowcytometrical Analysis. Figure 5 shows the flowcytometrical analysis of 4 hours of hypoxia followed by 24 hours of reoxygenation. The percentages of M1 fraction in pre, control, and edaravone groups were 23.6%, 40.4%, and 25.1%, respectively. These results indicated that edaravone could suppress the DNA degradation of hepatocytes caused by hypoxia-reoxygenation injury.

In Vivo Experiments

To investigate the effect of edaravone in vivo, we employed a rat 70% hepatic reperfusion model by partial clamping of the portal vein and hepatic artery. As shown in Fig. 6, the serum AST levels

Table 1. Effect of edaravone on protein synthesis of hepatocytes (4 hepatocyte preparations). Protein synthesis was estimated by incorporation of [3H]-Leucine by liquid scintillation counting (cpm)

Group	Count (cpm)
Pre	102582 ± 1029*
3 h hypoxia	
control	83100 ± 4514
EDA	97715 ± 894†
4 h hypoxia	
control	31641 ± 1986*
EDA	46554 ± 2747*†

cpm = cycles per minute; EDA = edaravone; PLSD = post-hoc least significant difference.
*$p < .05$ vs. pre group (Fischer PLSD).
†$p < .05$ vs. control group at the same duration of hypoxia (Fischer PLSD).

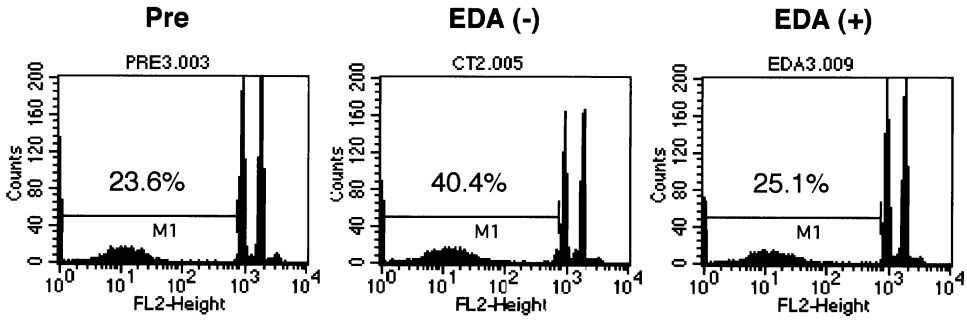

Fig. 5. Fluorescence-activated cell sorter (FACS) analysis of the hepatocytes with 4 hours of hypoxia followed by 24 hours of reoxygenation.

at 2 hours after reperfusion of the vehicle treated (control) group, edaravone 3 mg/kg i.v. treated group, and 10 mg/kg i.v. group were 1657 ± 40, 1140 ± 171, and 978 ± 139 IU/l, respectively, and the AST levels of both edaravone groups were significantly lower than that of the control group.

Figure 7 shows the PCOOH level in the hepatic tissue at 2 hours after the reperfusion. The levels of the control group, edaravone 3 mg/kg i.v. group, and 10 mg/kg i.v. group were 4379 ± 278, 2360 ± 625, and 1760 ± 663 pmol/g liver, respectively. Thus, edaravone significantly reduced the lipid peroxidation.

The EC values of the hepatic tissue of the control, edaravone 3 mg/kg i.v., and 10 mg/kg i.v. groups were 0.488 ± 0.074, 0.573 ± 0.038, and 0.650 ± 0.029, respectively (Fig. 8). The EC values were significantly maintained in the edaravone 10 mg/kg i.v. group compared with the control group.

DISCUSSION

Edaravone is widely used in Japan for the treatment of acute cerebral infarction. Many studies have reported the various effects of edaravone, including scavenging hydroxyl radical[3,4] and peroxyl radical, attenuating vascular endothelial cell and cranial nerve cell injury,[25,26] inhibiting the development of brain edema,[5,6] and improving the energy metabolism of the brain tissue.[7] Probably, these effects are related to each other. In the myocardial field, it has been reported that edaravone reduces myocyte damage.[8,9]

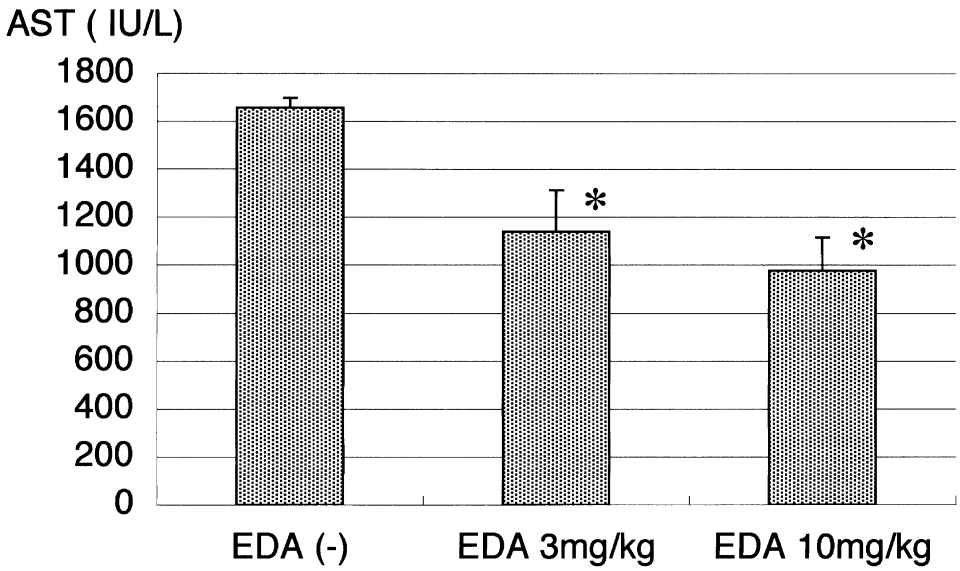

Fig. 6. The serum aspartate aminotransferase (AST) level at 2 hours after the initiation of reperfusion (n = 3). *$p < .05$ vs. control group (Fischer post-hoc least significant difference [PLSD]).

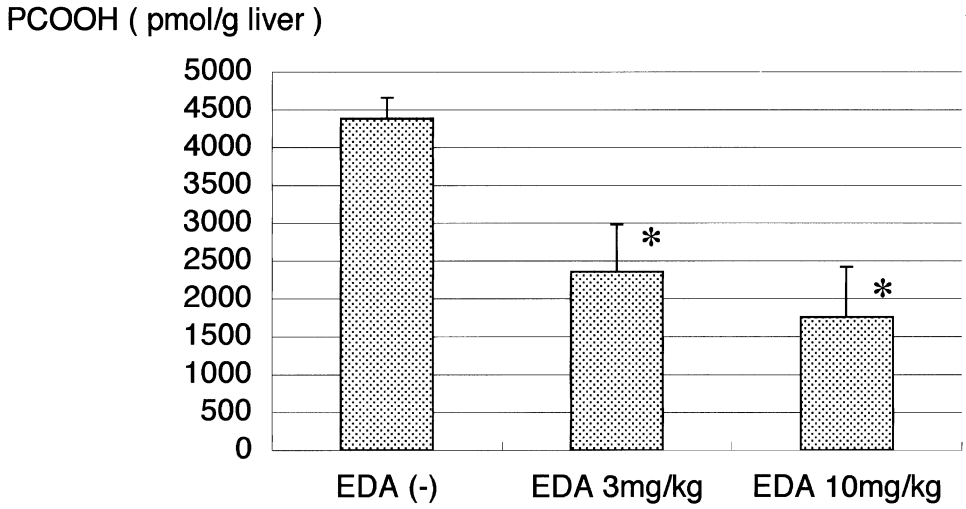

Fig. 7. Phosphatidylcholine hydroperoxide (PCOOH) concentrations in the liver tissue at 2 hours after the initiation of reperfusion (n = 3). *$p < .05$ vs. control group (Fischer post-hoc least significant difference [PLSD]).

Also, some studies have indicated that edaravone has had a beneficial effect on hepatic I/R injury. Okatani and associates reported that edaravone protected against mitochondrial injury in a hepatic I/R model and improved hepatic energy metabolism in vivo.[20] Our results, showing a significant preservation of the hepatocellular ATP level and the EC value of the hepatic tissue by edaravone, support the results of their investigation. In hepatic I/R injury, mitochondrial membrane permeability transition was observed,[27–29] which is associated with oxidant stress-induced cell killing. These results taken together with ours suggest that one of the important effects of edaravone is attenuating the oxidative stress of the mitochondrial membrane by scavenging intracellular ROS derived from mitochondria and the xanthine oxidase system resulting in the preservation of the intracellular ATP concentration and leading to the rescue of the hepatocytes from cell death. Kim and associates reported that the balance between ATP depletion after the

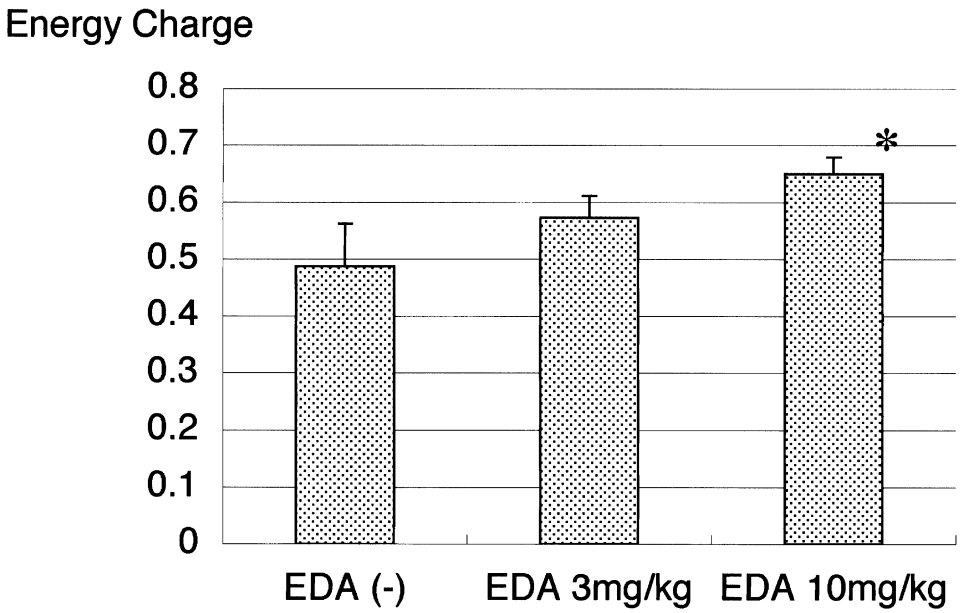

Fig. 8. The energy charge (EC) level of the hepatic tissue at 2 hours after the initiation of reperfusion (n = 4). *$p < .05$ vs. control group (Fischer post-hoc least significant difference [PLSD]).

mitochondrial permeability transition and ATP generation operates a switch that determines whether the death of the cell will be by necrosis or apoptosis.[30] Edaravone may relieve the hepatocytes from both types of cell death by attenuating the oxidative stress of the mitochondrial membrane. Actually, the suppression of the AST elevation in the medium indicates that edaravone prevented the death of the hepatocytes. Furthermore, our flowcytometrical analysis (Fig. 5) clearly indicated that edaravone prevents DNA degradation in vitro. However, in our hypoxia-reoxygenation model in vitro, the form of death seemed to be necrosis because the terminal deoxynucleotidyl transferase mediated (TUNEL) assay of the hepatocytes showed no difference between the control and edaravone groups (data not shown).

We measured the concentrations of PCOOH, a phosphatidylcholine hydroperoxide, as a parameter of reperfusion injury. We previously demonstrated that PCOOH is a sensitive parameter of reperfusion injury.[31–33] The results of our in vitro experiments suggest that edaravone also reduces the lipid peroxidation of the hepatocytes caused by intracellular ROS (Figs. 5 and 6). In our in vitro hypoxia-reoxygenation model, it is not necessary to consider the ROS from nonparenchymal cells. Thus, it follows that the lipid peroxidation of hepatocytes is caused by intracellular ROS produced by xanthine oxidase and mitochondria and that edaravone is able to scavenge the intracellular ROS. It was already reported that edaravone inhibited the oxidation of phosphatidylcholine liposomal membranes initiated by both water- and lipid-soluble initiators.[34] This membrane was artificial, but our results proved that edaravone inhibits the oxidation of phosphatidylcholine in the living membrane of hepatocytes.

We used an anaerobic box for the in vitro experiments and the durations of hypoxia were 3 and 4 hours. According to Kamiya and associates,[22] the oxygen level in the chamber drops to less than 1% in 60 minutes. In a preliminary study, AST was not elevated after 2 hours of hypoxic exposure and the hepatocytes were almost viable even after 3 hours of hypoxic exposure. However, 4 hours of hypoxic exposure was very critical for hepatocytes because the hepatocytes were hardly alive at 24 hours after the initiation of reoxygenation as evaluated morphologically. The AST, ATP, and PCOOH levels of the 4-hour hypoxic exposure group compared with that at 3 hours indicated that the hepatocytes had suffered more severe injury. Even with such severe injury, edaravone could rescue the hepatocytes from death, as we also confirmed morphologically (Fig. 9).

To confirm the beneficial effect of edaravone in vivo, we performed the rat partial hepatic I/R experiments. We demonstrated similar results as in the in

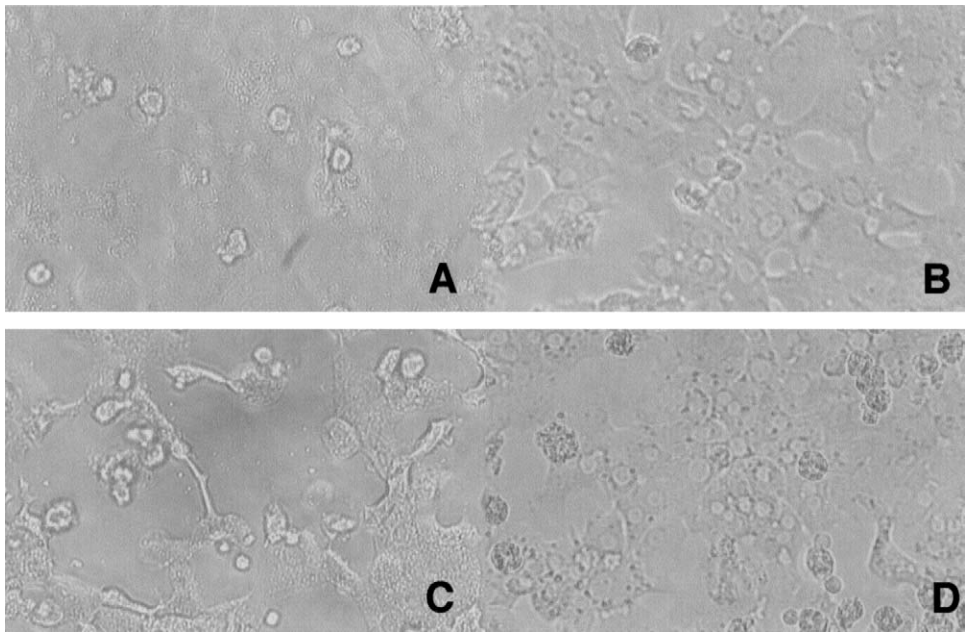

Fig. 9. Morphological changes in hepatocytes with 3 or 4 hours of hypoxia followed by 24 hours of reperfusion. (**A**) Vehicle-treated hepatocytes with 3 hours of hypoxia. (**B**) Edaravone-treated hepatocytes with 3 hours of hypoxia. (**C**) Vehicle-treated hepatocytes (4 hours of hypoxia). (**D**) Edaravone-treated hepatocytes (4 hours of hypoxia). Original magnification is ≅200 å.

vitro studies indicating that edaravone is useful as an antioxidant drug. However, we cannot extrapolate easily from the in vitro results how edaravone works as an antioxidant drug in vivo. A large number of studies about hepatic I/R injury have shown that its pathophysiology is complex and involves a number of contributing factors, such as Kupffer cells, endothelial cells, neutrophils and T-cell activation, cytokines, chemokines, proteases, tumor necrosis factors, complement activation, nitric oxide, microcirculatory disturbances, etc.[35,36] The scavenging of which ROS by edaravone is mainly responsible for the reduced injury is still unknown, because intracellular ROS, extracellular ROS, or both are scavenged by edaravone. Although we demonstrate that edaravone can scavenge intracellular ROS in vitro, it is not clear to what extent this contributes to attenuating the oxidant stress in vivo. Further experiments are necessary to clarify the effects of edaravone in hepatic I/R, using, for example, Kupffer cells, neutrophils, or endothelial cells.

CONCLUSION

Edaravone was able to ameliorate the oxidant stress of hepatocytes induced by intracellular ROS in an in vitro hypoxia-reoxygenation model and its beneficial effect was also observed in an in vivo rat I/R model. These results suggest that edaravone would be useful to protect against liver damage and cell death in liver surgery.

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Surgery for Ileal Mesenteric Lymphangioma During Pregnancy: Case Report and Review of the Literature

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Mesenteric lymphangioma is one of the least frequently encountered types of benign tumor. This case report concerns a 31-year-old pregnant woman with a mesenteric cystic lymphangioma in the ileum. The multiloculated cystic mass was noted near the uterus by CT before the patient became pregnant. After becoming pregnant, she was followed without treatment for the asymptomatic mass. At 25 weeks' gestation, however, she underwent emergency surgical treatment for small bowel obstruction. Concomitant small bowel resection was performed to remove the cyst. Herein we review seven reported cases of mesenteric benign tumor in pregnancy and explore the clinical features. (J GASTROINTEST SURG 2004;8:616–620)

KEY WORDS: Mesenteric lymphangioma, small intestine, pregnancy, surgical treatment

Abdominal lymphangiomas are characteristically found in the first decade of life, and this has been taken as evidence of a congenital etiology thought to reflect developmental abnormalities rather than a true neoplasm.[1,2] An abdominal lymphangioma is more commonly located in the mesentery than in the omentum,[3] probably because of the rich lymphatic network. Nearly two thirds of cases of abdominal lymphangioma were found in the small bowel mesentery.[3–5] On the other hand, abdominal lymphangioma seems to differ significantly from other mesenteric cysts[4] and retroperitoneal cysts,[6] because the disease often behaves in a proliferative and invasive manner and some patients develop acute abdominal symptoms caused by complications of intestinal obstruction.[6,7] In adult patients, moreover, abdominal lymphangioma tends to occur in middle-aged women and to remain asymptomatic,[5,7] often being discovered coincidentally at surgery or autopsy.[8,9]

We encountered a patient with ileal mesenteric lymphangioma who required emergency surgery during pregnancy. The indication for surgery and the timing of the laparotomy in this rare condition are discussed here.

CASE REPORT

A 31-year-old woman, who had undergone an appendectomy at the age of 14 years, was found to have a suspicious ovarian cyst on abdominal ultrasonography at the time of a spontaneous abortion during the second month of pregnancy in May 2001. Subsequent CT examination, including the acquisition of contrast-enhanced images of the abdomen, showed a thin cyst wall and multiloculated cystic lesion ($19 \times 8 \times 5.5$ cm in size) without adipose tissue, calcification, or a solid component at a level 5 to 15 cm below the aortic bifurcation on the medial border (Fig. 1). The ovaries were located in the bilateral adnexal region separated from the cystic mass, and the positional relationship between the mass and small intestine seemed to preclude an omental origin. In September 2001, the patient was in the second month of pregnancy. MRI at 12 weeks' gestation revealed that the tip of the multilocular cyst was displaced at a level 2 cm above the aortic bifurcation in the left lower abdomen; the possibility of retroperitoneal tumor was deemed low on the basis of the topographic relationship between the mass and the large intestine (Fig. 2). Around 24 weeks' gestation, the patient began to have frequent upper abdominal pain. At 25 weeks' gestation, she was admitted to our hospital because of severe abdominal pain and vomiting. Physical examination revealed abdominal distention and left upper abdominal tenderness without muscle

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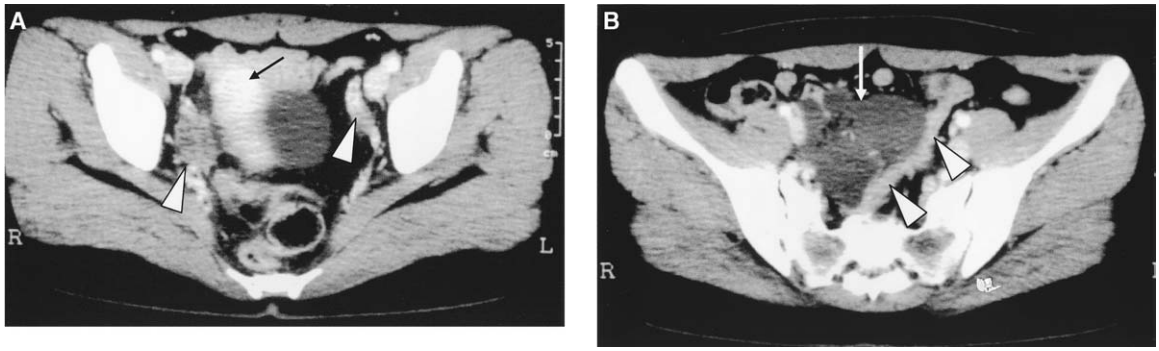

Fig. 1. Contrast-enhanced CT scans. **A**, The cystic mass is adjacent to the uterus (*arrow*), and bilateral ovaries (*white arrow heads*) are evident in the adnexal region separated from the cyst. **B**, The multilocular cyst (*white arrow*) is adjacent to the small intestine (*white arrow heads*).

guarding or rebound tenderness. On admission, her temperature was 36.1° C and pulse 100 beats/min. Laboratory data included the following: white cell count, 7600/mm^3; hemoglobin, 10.5 g/dl; and C-reactive protein, 0.19 mg/dl. The patient was 156 cm tall and weighed 61 kg. Three hours after admission, laparotomy was performed under general anesthesia. An abdominal incision was made in the left upper quadrant after the location of the mass was confirmed by ultrasonographic examination; 100 to 150 ml of chylous fluid and a soft, milky white mass measuring 15 × 10 cm were found. The mass lay in the mesentery in contact with the small intestine and was located 100 cm from the terminal ileum (Fig. 3). The intestine showed passive congestion probably due to stretched mesentery and/or traction on the root of the mesentery. Resection of a 30 cm long portion of the ileum was required to achieve total excision of the cystic mass. Microscopically, multicystic spaces were observed in the submucosal, proprial muscle, subserosal, and mesenteric layers (Fig. 4). The cystic spaces were lined with an attenuated endothelium and filled with proteinaceous fluid. Some of the cystic spaces possessed fascicles of poorly developed smooth muscle. The nuclei of the endothelium showed no atypia or mitosis. These findings supported the diagnosis of

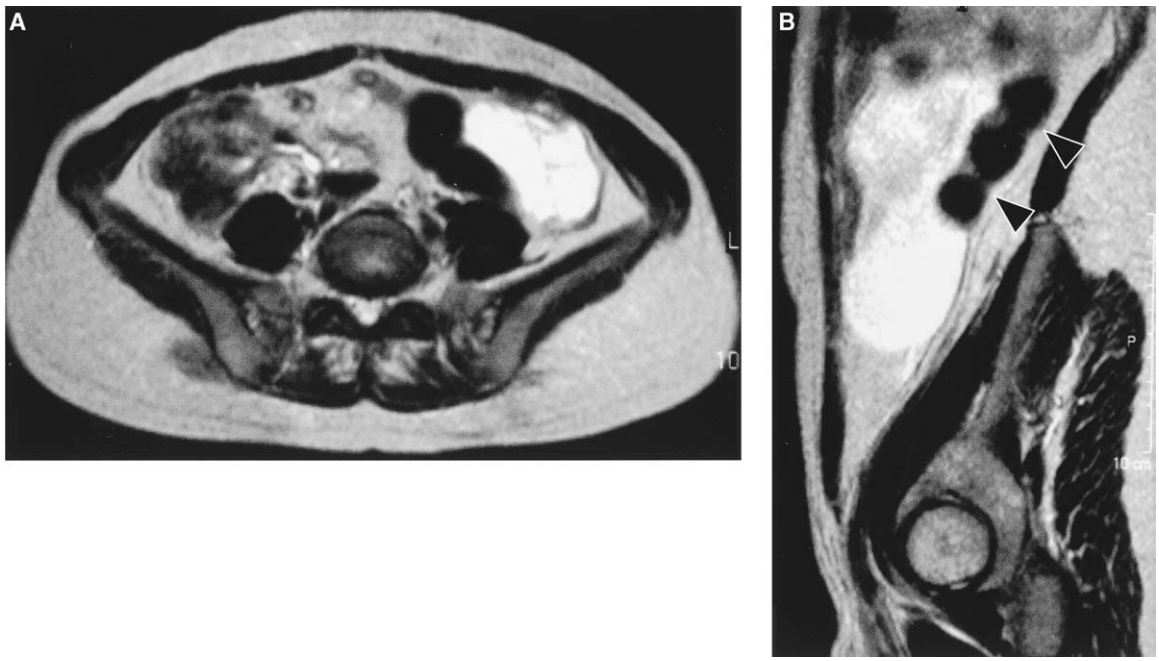

Fig. 2. Magnetic resonance images. **A**, A high-intensity, multilocular cyst is evident in the left lower abdomen on T2 weighted image. **B**, Mass is located in the anterior portion of the descending colon. *Black arrow heads* indicate descending colon.

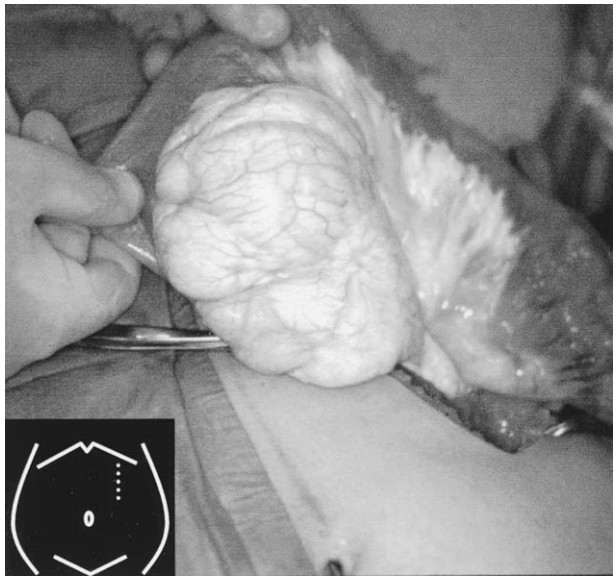

Fig. 3. Operative view of lymphangioma. A soft, milky white mass involves the small bowel mesentery. *Inset* shows the skin incision (*dotted line*).

cystic lymphangioma. Fifteen weeks after surgery, she gave birth to an infant (3690 gm) by spontaneous delivery. At the time of this writing, she is doing well with no evidence of recurrence 18 months after surgery.

DISCUSSION

The early diagnosis of mesenteric lymphangioma is important because this tumor should be regarded as a cause of acute abdomen and because excision is facilitated by its smaller size.[5,7,10] Ultrasonography, CT, and MRI are the most useful tools for evaluating abdominal cysts. Although a precise diagnosis is not always easy, these imaging modalities reveal the size of the tumor, the characteristics of the cyst wall (thin or thick), the internal nature (unilocular or multilocular), the contents (serous, chylous, or hemorrhagic), and the location (mesentery, mesocolon, or omentum). The typical imaging features of abdominal lymphangioma have been described.[3,7,11,12]

The clinical features of abdominal lymphangioma have also been well documented. Our patient was of particular interest because she had an episode of intestinal obstruction in association with an enlargement of the pregnant uterus. Although omental cysts are very mobile in all directions, mesenteric cysts seem to be mobile in a transverse plane rather than the craniocaudal direction.[10] This phenomenon may aggravate symptoms and/or signs for pregnant women. In our patient the ileal mesenteric mass was displaced from the pelvic space toward the left upper quadrant because of compression from the pregnant uterus. It should be noted that a relatively large number of patients with mesenteric lymphangioma require an emergency operation,[6] that bowel resection is more frequently necessary to remove the tumor compared with other types of mesenteric or omental cysts,[3–5] and that surgery in the latter months of pregnancy involves technical difficulties. In view of these facts, surgical excision in pregnant women with mesenteric lymphangioma may be the procedure of choice, even when it is asymptomatic.

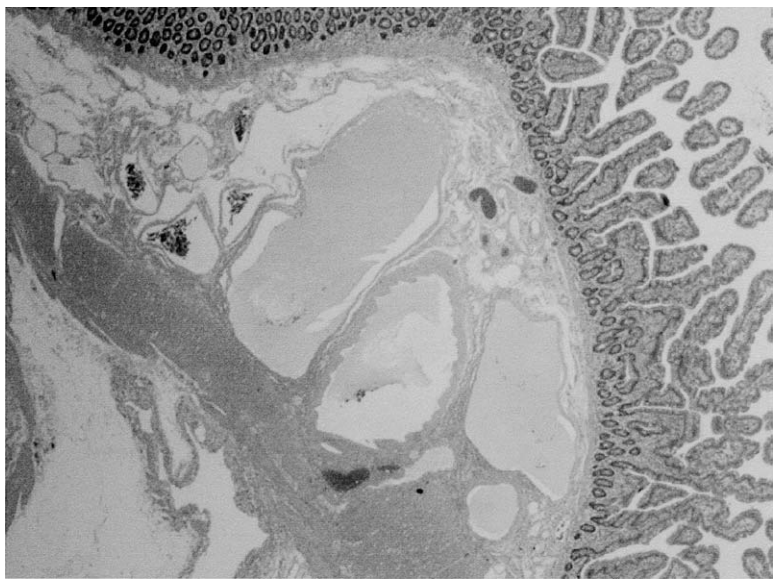

Fig. 4. Microscopic view. Multiple cystic structures are filled with proteinaceous fluid in the submucosa and propria muscle.

Table 1. Cases of mesenteric disease reported during pregnancy

			Laparotomy		Tumor		
Case	Year	Age (yr)	GA (wk)	Surgery	Size	Location	Diagnosis*
1	1967[13]	22	18	Intestinal resection	3300 g	Ileum	Cyst
2	1977[14]	31	8	Tumorectomy	20 cm	ND	Lymphangioma
3	1986[15]	20	27	ND	ND	ND	Cyst
4	1988[16]	36		Tumorectomy (after delivery)	9150 g 40 cm	Ileum	Mucinous cystadenoma
5	1989[17]	24	21	Tumorectomy	21 cm	ND	Cyst
6	2000[18]	34	14	Intestinal resection	7000 ml 35 cm	Ileum	Lymphangioma
7	Present case	31	25	Intestinal resection	15 cm	Ileum	Lymphangioma

GA = gestational age; ND = not defined.
*Pathologic diagnosis.

To the best of our knowledge, seven cases (including ours) of mesenteric benign disease during pregnancy have been reported.[13–18] As summarized in Table 1, laparotomy was undertaken during gestation in all except one patient, and three of the cases required small bowel resection. All patients had a relatively large tumor. The location of the mesenteric mass was the ileum in all four of the patients for whom this information was available. These facts suggest that the tumor size and location are closely associated with acute surgical abdomen in pregnant women. Moreover, laparotomy was performed during the period up to 25 weeks' gestation in patients with mesenteric lymphangioma. These observations indicate that surgical treatment should be considered for prepregnant as well as pregnant women with mesenteric lymphangioma, especially in high-risk women with a large tumor and an ileal abnormality. A less invasive type of surgery will be possible for most of these patients.[19,20]

CONCLUSION

In pregnant women with mesenteric lymphangioma, early diagnosis, including an evaluation of tumor size and location, and surgical treatment during the early months of gestation will bring great benefits. Needless to say, the presence of fetal life should be carefully ascertained particularly in gestations of less than 12 weeks. In the present case, however, because the imaging modalities possibly allowed a diagnosis of mesenteric lymphangioma, the excision of the tumor by laparoscopic surgery might have been preferable before pregnancy.

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A Surgical Rat Model of Human Roux-en-Y Gastric Bypass

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Obesity affects 30% of the United States population and its detrimental effects are obesity-related metabolic diseases. For patients refractory to conventional weight loss therapy, gastric bypass surgery is one of the proven methods for inducing a sustained weight loss and reversing the metabolic sequelae of obesity. To understand the mechanisms of weight loss and the amelioration of related metabolic comorbid conditions, a reproducible animal model is needed. We report our developmental experience with rat models of sequential Roux-en-Y gastric bypass after reproducing the diet-induced obesity that characterizes the hallmarks of human obesity. Four experiments were performed to induce weight reduction through successive modifications: In Experiment 1 a 20% stapled gastric pouch with a 16 cm biliary-pancreatic limb and a 10 cm alimentary limb accomplished sufficient weight loss within 10 days to ameliorate metabolic changes associated with obesity, but the occurrence of gastrogastric fistulas prevented sustained weight loss; in Experiment 2 the model was improved by dividing the stomach to avoid gastrogastric fistula, but again sustained weight loss was not achieved; in Experiment 3 the biliary-pancreatic limb was lengthened from 16 to 30 cm, reducing the common channel to approximately 18 cm. Sustained weight loss was achieved for 28 days. In Experiment 4 the model in Experiment 3 was modified by dividing the stomach between two rows of staples. Sustained weight loss was observed for 67 days. We developed a reproducible rat model of Roux-en-Y gastric bypass. The existence of this model opens a new field of research in which to study the metabolic sequelae of obesity and the mechanisms of weight loss. (J GASTROINTEST SURG 2004;8:621–630)

KEY WORDS: RYGB, rat model, diet-induced obese rat, weight loss

The extensive similarity and homology between human and rodent genomes make animal models a powerful tool to study similar human conditions. Two examples are (1) the diabetic dogs of Banting and Best[1] that were treated with insulin and (2) the demonstration of normal growth in beagle pups administered total parenteral nutrition by Dudrick et al.[2] Conversely, the absence of an animal model to help understand the mechanisms of a pathophysiologic process makes more difficult the development of specific drug therapy. Thus the availability or the development of an animal model of human disease is essential.

Obesity is a metabolic condition the etiology of which is environmental, social, and genetic[3]; obesity has achieved epidemic proportions in the United States.[4–6] An increase in body weight is associated with a significant increase in obesity-related diseases including type 2 diabetes, hyperlipidemia, and cardiovascular diseases.[7,8] The adverse clinical outcomes of these comorbid conditions are such that a 20% increase in body weight above ideal is associated with

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a 20% increase in the mortality rate.[9,10] An additional problem is that morbid obesity is now appearing in children with greater frequency.[11]

The following three main treatment modalities are currently used to induce weight loss: (1) reducing caloric intake via dieting; (2) increasing energy output via exercise, or a combination of the two; and (3) controlling malabsorption through diversion of nutrients from segments of the gastrointestinal tract. Unfortunately, given our current lifestyle, achieving and maintaining such long-lasting weight loss is difficult with only modification of diet and exercise. Currently approved drugs reduce weight by 5% to 10% in 1 year, and most persons regain their weight once therapy is discontinued.[12]

Because it is difficult to achieve sustained weight loss with existing clinical treatment, bariatric operations are becoming one of the most common abdominal surgical procedures performed daily in the United States.[13] Current consensus is that a successful operation has two components: a small gastric pouch to limit the amount of food ingested, inducing early satiety, and an element of subclinical malabsorption, reducing the amount of food that can be absorbed. Of the numerous operations developed during the past decades, the Roux-en-Y gastric bypass (RYGB) is considered among the most successful and safe operations following which morbidly obese patients usually lose an average of 49% to 65% of their initial body weight within 2 to 5 years.[13–15] Besides the robust weight loss, the surgical procedure ameliorates obesity-related diseases (initially identified as syndrome X[7] and now commonly referred to as "metabolic syndrome"), particularly diabetes[15] and hyperlipidemia.[9,16]

Despite the success of bariatric operations, they are associated with recognized perioperative complication rates ranging from 3% to 20% and mortality rates ranging from 0.5% to 2.0%.[17] Furthermore, there is a subset of morbidly obese patients in whom surgery is life-threatening and contraindicated. Because current drug treatments for obesity do not achieve a sustained weight loss, one of the most effective treatments is gastric bypass. To understand the mechanism of weight loss and the amelioration of related metabolic comorbid conditions, a reproducible experimental animal model is needed. We report our developmental experience with sequential RYGB rat models after reproducing the diet-induced obesity that characterizes the nature of human obesity. Our data show that this model ameliorates obesity-related metabolic changes and induces sustained weight loss.

MATERIAL AND METHODS

The Committee for the Humane Use of Animals at the State University of New York Upstate Medical University approved these studies. Animal care was in accordance with National Institutes of Health guidelines.

Common Procedures

Diet-Induced Obesity. The method of Levin et al.[18] was used to produce diet-induced obesity in rats. Three-week-old male Sprague-Dawley pups (Charles River, Wilmington, MA) were housed in wire holding cages and fed a coarsely ground high-energy diet (D12266; Research Diets, New Brunswick, NJ) consisting of 8% corn oil and 44% sweetened condensed milk added to 48% Purina Rat Chow (Rat Chow Diet 5008; Ralston Purina, St. Louis, MO) for 7 to 12 weeks to develop obesity. The high-energy diet provided 4.5 kcal/g, of which 21% of the metabolizable energy was protein, 31% was fat, and 48% was carbohydrate; the latter was 50% sucrose. Ten days before the operation, rats on the high-energy diet were also fed the highly palatable liquid supplement Boost-Plus (Mead Johnson, Evansville, IN), providing 1.52 kcal/ml, of which 16% of the metabolizable energy content was protein, 34.0% was fat, and 50% was carbohydrate, to enhance their weight gain. As a control group, 3-week-old Sprague-Dawley pups were fed a diet of regular chow (Rat Chow Diet 5008; Ralston Purina) for the same period (chow-control).

Study Conditions. Rats were in constant study surroundings consisting of 12-hour light/dark cycles (light on from 5 AM to 7 PM), room temperature of 26 ± 1° C, and 45% relative humidity, and they had free access to their diets and tap water.

Anesthesia and Postoperative Pain Control. For preoperative procedures, rats were deprived of food for 16 to 18 hours and were anesthetized with a mixture of ketamine and xylazine (200 mg:5 mg, 0. 8 ml/kg, intraperitoneally). For euthanasia, decapitation was performed under brief isoflurane anesthesia (Baxter, Chicago, IL). Buprenorphine hydrochloride (Reckitt Benckiser Pharmaceuticals, Richmond, VA), 0.05 mg/kg, was given to the rats postoperatively, twice a day for 3 days.

Surgical Procedures. The rat abdomens were shaved and prepared with Betadine solution (Purdue Pharma, LP, Stamford, CT). For the sham operations a midline incision was made, and the stomach and distal esophagus were exposed; the small bowel was laid out for the same duration required for gastric bypass procedures. The abdomen was closed in layers with 3-0 polyglactin sutures (Ethicon, Cincinnati, OH). For gastric bypass operations, three series of experiments were performed in sequence to develop the RYGB model.

Experiment 1: 20% Stapled Gastric Pouch With a 16 cm Biliary-Pancreatic Limb, a 10 cm Alimentary Limb, and a Common Channel of Approximately 34 cm. The original procedure, which was carried out in obese Zucker rats, was previously described in detail.[19] Thirty Sprague-Dawley pups (starting weight 54.9 ± 1.8 g) were studied: 24 diet-induced obese rats and six chow-fed control rats. Diet-induced obese rats fed for 7 weeks were assigned to one of three operative groups as follows: (1) RYGB; (2) sham-operated obese (SO-obese), or (3) sham-operated pair-fed. In the pair-fed group, food intake was restricted and linked to the daily food intake consumed by the RYGB rats. The remaining six rats on the chow diet served as general control subjects for measuring and assessing the difference in body weight throughout this study. Following anesthesia, two double rows of titanium staple lines (TRH30-4.8; Ethicon) were placed from the lesser curvature, 2 to 3 mm below the gastroesophageal junction, to the greater curvature, constructing a ~20% gastric pouch preserving the vagus nerve and without transecting the stomach (Fig. 1, *A*). The gastric bypass staple line was reinforced with multiple interrupted 5-0 polyglactin sutures. The jejunum was divided 16 cm below the ligament of Treitz, creating a 16 cm biliary-pancreatic limb. A 4 to 5 mm end-to-side gastrojejunostomy was sewn using interrupted 5-0 polyglactin sutures on the anterior surface of the gastric fundus. The stump of proximal jejunum was closed with a running suture. A 7 to 8 mm side-to-side jejunojejunostomy was sewn 10 cm below the gastrojejunostomy. The common channel was approximately 34 cm, as indicated in Fig. 1, *A*. The procedure lasted approximately 50 minutes and the abdomen was closed in layers. Body weight and operative complications were evaluated daily. Rats drank water and Boost-Plus starting 24 hours after the operation and for the first 3 days. This was followed by a solid diet. For the first three postoperative days, rats were hydrated with normal saline solution (20 ml) injected subcutaneously to prevent dehydration. All of the rats started to lose weight. However, failure to continue to lose weight occurred in three rats by day 10 (which represents approximately one human year), at which time all rats were euthanized.

Adipose Tissue and Biochemical Studies. Subcutaneous abdominal fat and mesenteric, retroperitoneal, and epididymal fat pads were dissected out and weighed. Differences in fat weights were calculated. Adipose tissue samples were collected from identical anatomic areas in each rat to ensure sampling consistency. Blood was collected to measure glucose, insulin, lipid profile, and leptin. Blood samples for serum and EDTA-rinsed tubes (plasma) were centrifuged for 10 minutes at 4° C. The plasma and serum samples were stored at −80° C before analysis. Plasma glucose, triglyceride, cholesterol (Sigma, St. Louis, MO), and free fatty acid (WAKO, Richmond, VA) concentrations were measured by means of enzymatic colorimetric kits. Plasma insulin (ALPCO, Windham, NH) and leptin (DSL, Chicago, IL) concentrations were measured using enzyme immunoassay kits.

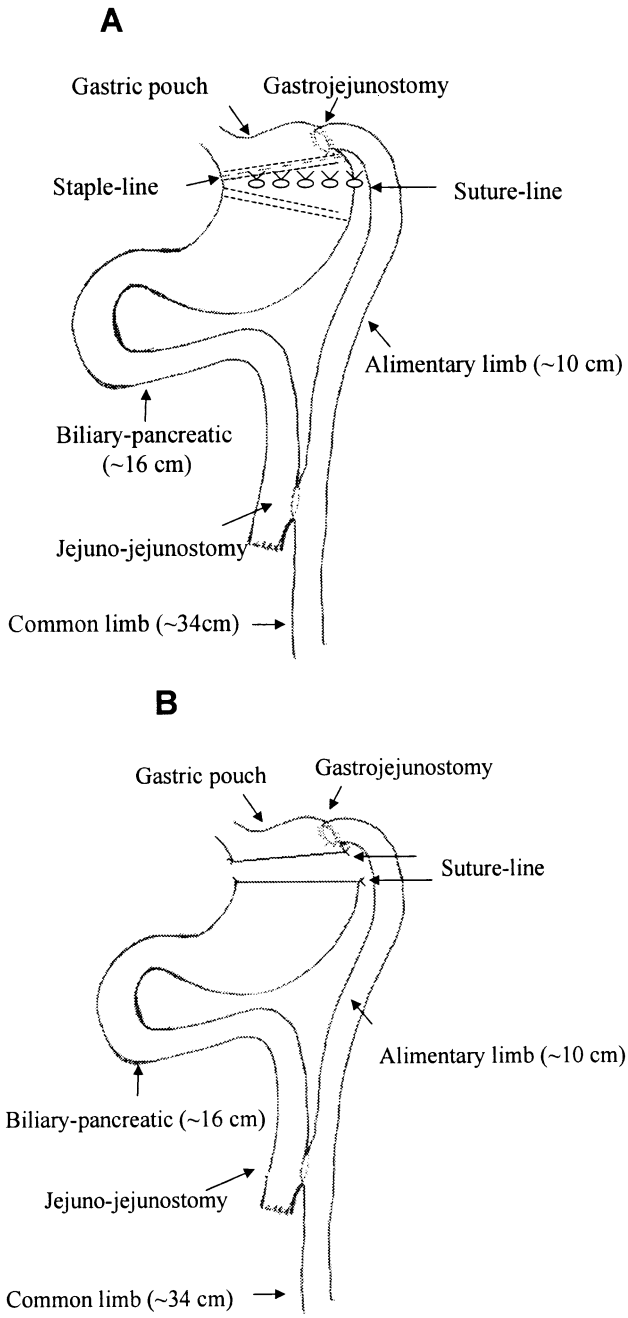

Fig. 1. RYGB. **A**, Two double rows of titanium staple lines were placed without transecting the stomach. **B**, To overcome the occasional problem of gastrogastric fistula, the stomach was divided and both gastric ends were oversewn.

Experiment 2: 20% Divided Gastric Pouch With a 16 cm Biliary-Pancreatic Limb, a 10 cm Alimentary Limb, and a Common Channel of Approximately 34 cm. This pilot study was performed to establish the feasibility of dividing the stomach. Twelve diet-induced Sprague-Dawley rats (449.9 ± 12.4 g) were equally divided into RYGB and control groups. The stomach was divided as shown in Fig. 1, *B*, to overcome the previous gastrogastric fistula. The left gastric vessels and the vagus were preserved as described earlier. Both gastric ends were oversewn using a running 5-0 polyglactin suture, and the suture lines were embrocated. The rest of the procedure was the same as that described for Experiment 1. This procedure extended our operative time to 120 minutes. Rats drank water and Boost-Plus starting 24 hours after operation for 7 days, followed by solid diet. Rats were hydrated with normal saline solution as described earlier. Rats were euthanized 21 days after the surgical procedure when they started to gain weight. Body weight and operative complications were evaluated daily.

Experiment 3: 20% Divided Gastric Pouch, With a 30 cm Biliary-Pancreatic Limb, a 10 cm Alimentary Limb, and a Common Channel of Approximately 18 cm. Thirty-six 3-week-old Sprague-Dawley pups (47.3 ± 0.5g) were fed for 12 weeks to induce obesity. These obese rats were stratified according to body weight and randomly assigned within each stratum to one of three operative groups: (1) RYGB (541.1 ± 6.7 g); (2) SO-obese (545.0 ± 8.0 g); or (3) pair-fed (546.1 ± 7.6 g). A single intramuscular dose of 75 mg/kg of ceftriaxone sodium (Roche, Nutley, NJ) was given as antimicrobial prophylaxis 30 minutes before the surgical procedures. The gastric pouch was created as described in Experiment 2. The biliary-pancreatic limb was lengthened from 16 to 30 cm, and the alimentary limb was established 10 cm below the gastrojejunostomy to induce persistent weight loss. The common channel, between the jejunojejunostomy and the cecum, was approximately 18 cm. Rats drank water and Boost-Plus starting 24 hours after the operation for 7 days, followed by a solid diet. Rats were hydrated with normal saline solution injected subcutaneously as described in Experiment 1. Rats were euthanized 28 days after the surgical procedures. Body weight and operative complications were evaluated daily.

Experiment 4: 20% Gastric Pouch Divided Between Staples, With a 30 cm Biliary-Pancreatic Limb, a 10 cm Alimentary Limb, and a Common Channel of Approximately 18 cm. Experiment 3 was duplicated using 12 obese rats. In 6 a sham operation was performed (SO-obese 746.1 ± 32.6 g). In 6 obese rats the RYGB (730.4 ± 41.3 g) was done by placing a row of titanium staple lines (EZ35B, Ethicon, Cincinnati, OH) between the lesser and greater curvature of the stomach, creating a 20% gastric pouch and transecting the stomach. The staple line was placed 2–3 mm below the gastro-esophageal junction, preserving the vagus nerve. The rest of the operative procedure and postoperative care was as described in Experiment 3.

Statistical Analysis

Changes in body weight, caloric intake, biochemical data, and weight of adipose tissue were analyzed using one-way analysis of variance and multiple comparison tests by controlling the significance level individually as well as jointly at a value equal to P 0.05. When the analysis of variance test rejected the hypothesis of no difference, the Tukey's pairwise multiple comparison was applied to ensure that the family (i.e, SO-obese, RYGB, and pair-fed) error rate was equal to 0.05 jointly. Data are expressed as mean ± standard error. The models were considered separately because of the sequential nature of developing our model over a period of months. The data from the three models were not analyzed jointly or compared to each other simultaneously.

RESULTS

Body Weight Gain During Preoperative High-Energy Diet or Chow Diet Period

Body weight increased continuously from 54.9 ± 1.8 g to 492.5 ± 6.7 g, as shown in Fig. 2. There was no difference in body weight gain among the three preoperative high-energy diet groups. The mean body weight of the chow-control group was 389.7 ± 11.7 g and differed from that in rats fed the high-energy diet ($P < 0.05$).

Experiment 1

Operative complications. Of the 24 obese rats that underwent operation, 21 had a successful outcome. In two rats in the RYGB group, an anastomotic leak occurred on postoperative day 3 and 4, whereas one rat in the pair-fed group died during anesthesia. There were no complications or deaths in the SO-obese group.

Postoperative Body Weight Changes. Body weight decreased during postoperative days 2 to 4, and this was attributed to the effects of anesthesia and the operation. Thereafter body weight began to increase in the SO-obese group, which continued on an ad libitum diet. Body weight increased to 484.4 ± 15.4 g by day 10, similar to preoperative weight (492.1 ± 13.8 g). In the RYGB and pair-fed groups, body weight significantly and continuously decreased after operation. The mean weight loss in the RYGB group was 80 g

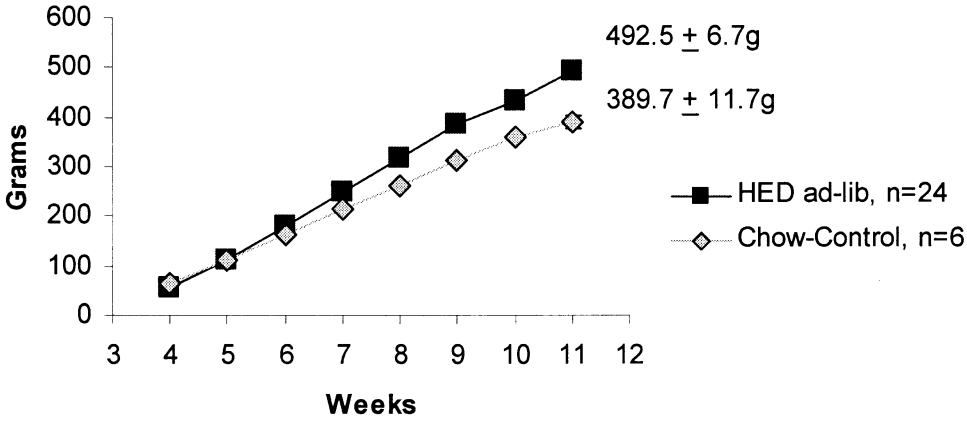

Fig. 2. Effect of diet on body weight gain in the diet-induced obese and chow-control groups after 7 weeks of a high-energy diet (*HED*) or chow-control diet, respectively.

(496.9 ± 16.3 g to 416.9 ± 23.3 g), representing a 16.1% weight loss compared to the preoperative condition. In the pair-fed group, body weight also decreased significantly due to food restriction caused by pair feeding. The mean weight loss was 63.7 g (from 499.8 ± 14.9 g to 436.1 ± 13.9 g) representing 12.7% of the preoperative body weight. A slight increase in body weight was noted in three of the six RYGB rats. A contrast study was obtained that showed a gastrogastric fistula (Fig. 3, *A*).

Caloric Intake. Preoperatively the caloric intake in the SO-obese, RYGB, and pair-fed groups was not statistically different (129.7 ± 5.6 kcal/day, 119.8 ± 10.0 kcal/day, and 120.7 ± 6.2 kcal/day, respectively). By postoperative day 10, caloric intake in the RYGB group decreased 66% compared to the SO-obese rats (31.4 ± 5.8 kcal/day vs. 90.3 ± 5.2 kcal/day; $P < 0.05$).

Weight Changes in Adipose Tissues. Fat content in SO-obese rats was higher than that in chow-control rats ($P < 0.05$): subcutaneous fat (13.1 ± 1.2 g vs. 5.8 ± 0.4 g), retroperitoneal fat (11.5 ± 1.0 g vs. 3.9 ± 0.5 g), mesenteric fat (7.8 ± 0.8 g vs. 2.5 ± 0.2 g), and epididymal fat (8.6 ± 0.8 g vs. 3.5 ± 0.3 g) deposits. In the RYGB rats compared to the SO-obese rats, there was a significant decrease ($P < 0.05$) in subcutaneous abdominal fat (7.3 ± 0.4 g vs. 13.1 ± 1.2 g) and retroperitoneal fat (8.1 ± 1.2 g vs. 11.5 ± 1.0 g). There was no significant change in mesenteric fat between the RYGB and SO-obese groups (5.8 ± 1.1 g vs. 7.8 ± 0.8 g) or in epididymal fat (8.7 ± 1.2 g vs. 8.6 ± 0.8 g). In the pair-fed group compared to SO-obese group, there was no significant difference in subcutaneous (11.2 ± 1.6 g vs.13.1 ± 1.2 g), mesenteric (6.9 ± 1.0 g vs.7.8 ± 0.8 g), retroperitoneal (8.7 ± 1.1 g vs. 11.5 ± 1.0 g), and epididymal fat (7.7 ± 0. 9 g vs. 8.6 ± 0.8 g).

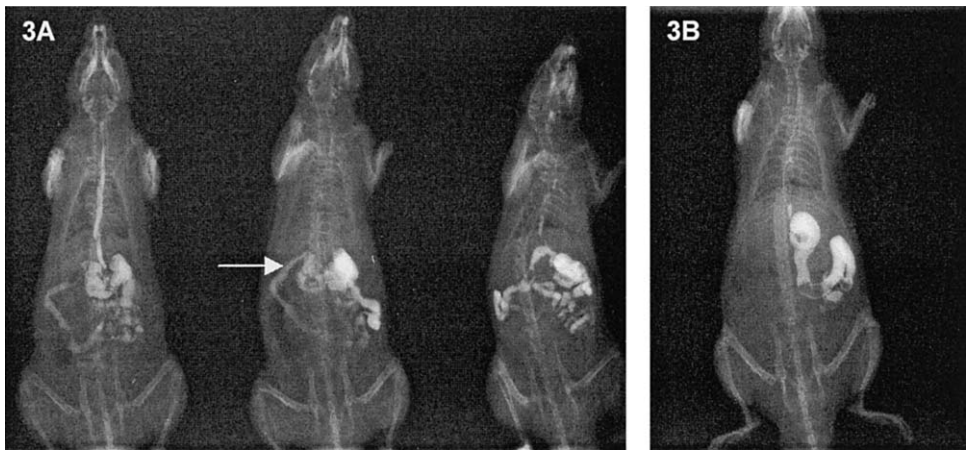

Fig. 3. A, Upper gastrointestinal series confirming a gastrogastric fistula. The arrow shows the defunctionalized stomach and duodenum containing contrast medium. **B**, Radiologic study showing no evidence gastrogastric fistula.

Biochemical Indices. These are summarized in Table 1. The assumption of no difference in three groups (SO-obese, RYGB, and pair-fed) is not rejected for free fatty acid concentrations at $P = 0.05$ by the one-way analysis of variance. For other biochemical indices, the null hypothesis of no difference is rejected at $P = 0.05$; hence Tukey's pairwise test was conducted separately. When comparing pair-fed and SO-obese groups, we found significant decreases based on Tukey's joint tests in plasma glucose, insulin, triglyceride, and leptin concentrations. When comparing RYGB and SO-obese rats, we found that leptin concentrations were significantly lower in the RYGB group based on the joint tests as well. In the case of SO-obese vs. RYGB rats, in plasma glucose and insulin concentrations, significant differences were found in the individual tests; however, this comparison was not significant based on the joint tests.

Experiment 2: A higher than expected mortality rate occurred between postoperative days 1 and 3. Necropsy of the four rats did not reveal major anatomic-surgical problems. We attributed these deaths primarily to the extended anesthesia time and the increased magnitude of the intraoperative trauma. Operative time increased from approximately 50 minutes in Experiment 1 to 120 minutes in Experiment 2.

Postoperative Changes in Body Weight. The pattern of weight loss in 10 days in this experiment was similar to that reported in Experiment 1, although persistent weight loss was not observed. The weight loss curve of the 20% divided gastric pouch, with a 16 cm Y limb and a 10 cm alimentary limb, remained below and ran parallel to the normal weight curve of the control group for the ad libitum diet (Fig. 4, *A*). An upper gastrointestinal series was performed to rule out the presence of gastrogastric fistula. This study confirmed the absence of gastrogastric fistula as shown in Fig. 3, *B*.

The high mortality rate in this experiment suggested that our preoperative, intraoperative, and postoperative management was deficient and not rigorous enough to keep the rats alive for a long period after such a major surgical procedure. This experiment also suggested that the biliary-pancreatic limb should be lengthened to diminish nutrient absorption so that the rats would continue to lose weight.

Experiment 3: Fig. 4, *B* shows weight loss over a 28-day postoperative period. RYGB rats lost 24.3% of their original weight (range 541.1 ± 6.7 g to 409.4 ± 10.6 g), and pair-fed rats lost 16.3% of their original weight (range 546.1 ± 7.6 g to 456.8 ± 9.3 g). It should be noted that the SO-obese rats continued to gain weight from day 7 after surgery to the end of the experiment. The RYGB rats showed sustained weight loss, which was significantly different from the SO-obese and pair-fed rats at the end of the experiment, as shown in Fig. 4, *B*. In comparison to the RYGB group, the weight curve in pair-fed rats showed an initial weight loss but subsequently (from day 14) demonstrated a gradual weight gain.

Of the 36 rats studied in this experiment, three rats in the RYGB group died. All of the rats died of respiratory distress, suggesting bronchoaspiration on postoperative days 1 (two rats) and 4 (one rat). These rats were replaced to ensure consistent numbers among the groups. Of the15 rats that underwent RYGB, 12 had a successful outcome, constituting a 20% mortality rate. There were no deaths in the SO-obese and pair-fed groups.

Experiment 4: Fig. 5 shows a significant weight loss over 67 postoperative days. RYGB rats lost 25.4% of their original weight (730.4 ± 41.3 g to 545.0 ± 43.3 g), while SO-obese continued to gain weight from the seventh day after surgery to the end of the experiment (746.1 ± 32.6 vs. 788.4 ± 33.8 g). Average daily body weight loss per group is summarized in Table 2.

DISCUSSION

Obesity, one of the major health problems confronting this country, has reached epidemic proportion. For the estimated 8 million adults who are morbidly obese and who are refractory to conventional weight loss therapy, a gastric bypass operation is performed to reverse the metabolic sequelae of obesity

Table 1. Biochemical indices (mean ± standard error)

Group	Glucose (mg/dl)	Insulin (ng/ml)	TG (mg/dl)	FFA (mmol/L)	Leptin (pg/ml)
SO-obese (n = 8)	173.1 ± 8.1	0.85 ± 0.17	126.1 ± 31.5	0.40 ± 0.06	944.7 ± 147.3
RYGB (n = 6)	145.4 ± 10.5*	0.46 ± 0.04*	83.1 ± 6.7	0.38 ± 0.03	452.4 ± 133.0†
PF (n = 7)	139.7 ± 5.4‡	0.40 ± 0.12‡	51.9 ± 5.0†‡	0.42 ± 0.06	338.9 ± 61.7†

TG = triglycerides; FFA = free fatty acids.
*$P < 0.05$ vs. SO-obese when analyzed individually.
†$P < 0.05$ vs. SO-obese when analyzed individually and jointly.
‡$P < 0.05$ vs. RYGB when analyzed individually and jointly.

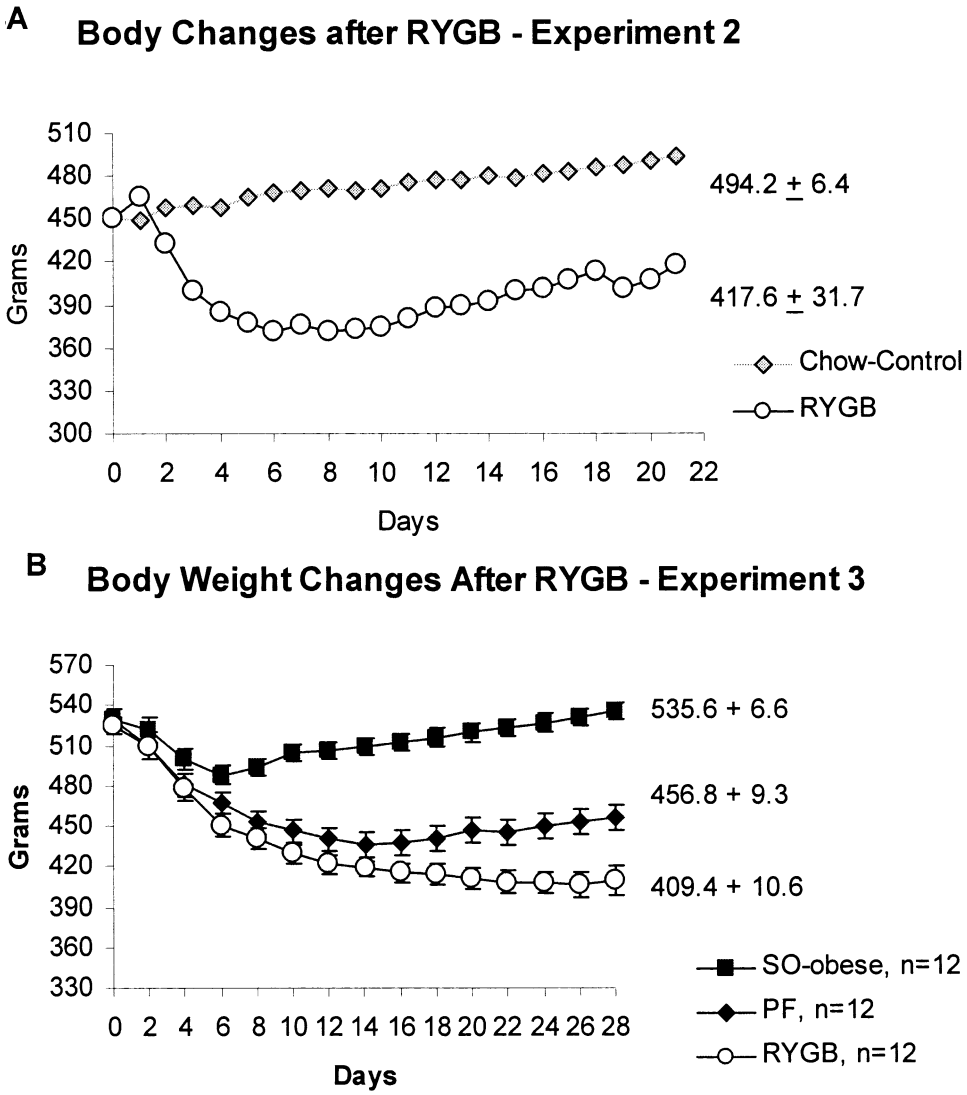

Fig. 4. A, Mean body weight loss at the end of Experiment 2. **B**, Acute and chronic weight loss in Experiment 3. SO-obese = sham-operated obese; RYGB = Roux-en-Y; PF = pair-fed.

and to induce sustained weight loss. The evolution of bariatric procedures that have led to the most currently used operation is based on the following two physiologic principles: (1) restrict food intake via a small gastric pouch and induce satiety; and (2) decrease the amount of nutrients assimilated. The RYGB operation encompasses both principles and has thus emerged as the most common procedure for treating morbidly obese patients at present. In particular, the ability to perform RYGB via minimally invasive laparoscopic surgery has made this operation popular.[13,20,21] Although weight loss certainly occurs, how it occurs and why this operation ameliorates obesity-associated diseases remains unclear and is not well defined. To fully understand and explore the temporal relationship between weight loss and the amelioration or reversal of obesity-related metabolic abnormalities, a robust, well-characterized, and reproducible animal model is needed. To achieve this goal we are reporting our developmental experience with a RYGB rat model.

We initially developed a gastric banding model in Sprague-Dawley rats by suturing a Silastic band around the fundus. No appreciable weight loss occurred because the rats continued to eat in an unrestricted manner. At necropsy we found that the Silastic band was intact but the 20% gastric pouch had ballooned out significantly, increasing the food reservoir. We successfully induced weight loss for 10 days in obese Zucker rats using a RYGB model.[19] Our initial decision to use Zucker rats was based on the following two factors: (1) our previous extensive experience in studying and publishing studies in the Zucker rats[22] and (2) in human obesity, a degree of leptin resistance exists secondary to dietary factors.[23] However, this

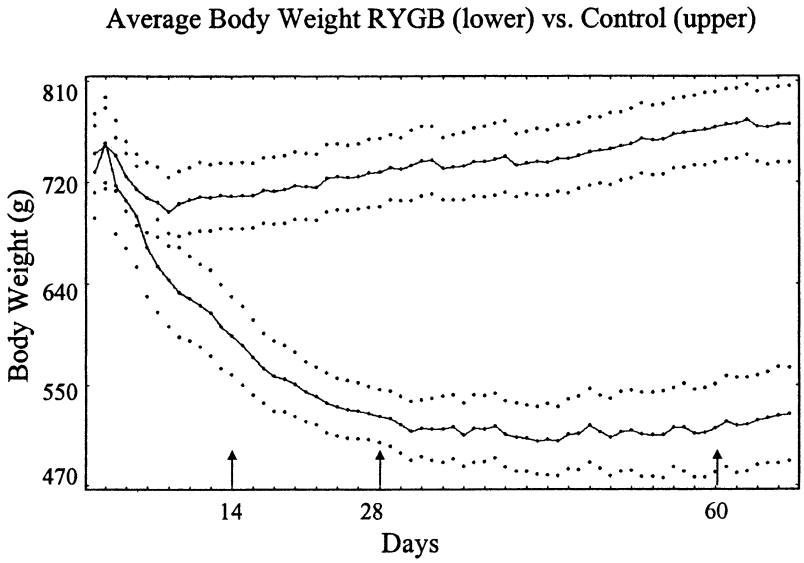

Fig. 5. Body weight after operation in RYGB and SO-obese rats in Experiment 4.

genetic abnormality is a rare and infrequent cause of obesity in humans. In contrast, diet-induced obesity is the most common cause of progressive weight gain in industrialized nations. To study the biochemical and hormonal changes that lead to loss of body weight and amelioration of comorbid conditions after RYGB, a model of diet-induced obesity in rats was necessary.

We induced obesity in Sprague-Dawley rats by mimicking a typical United States diet consisting of a high-fat and high-carbohydrate content. Rats fed a diet of regular chow served as a control group. The weight gain in rats on a high-energy diet was significantly greater compared to chow-fed control rats. After 7 weeks, the obese rats were hyperglycemic, hyperinsulinemic, and had enlarged body fat stores. Previously we reported that these obese rats also had elevated concentrations of corticosteroids and cytokines in mesenteric fat depots.[16] Having characterized the anthropomorphic and metabolic features of the obese rat, we proceeded to perform a series of gastric bypass operations, each building on the experience gained from the previous experimental model.

In Experiment 1, food intake was restricted via a 20% gastric pouch and resulted in a reduction of the food intake by 66% (kcal/day) and a weight loss of 16%. The subcutaneous abdominal fat and retroperitoneal fat in the RYGB rats were significantly decreased compared with the SO-obese group. After RYGB, a decrease in concentrations of glucose and insulin was measured. The decreases in triglycerides and in leptin, plus the decrease in the subcutaneous fat mass, reflect the decreased food intake and the consequent decrease in body weight, because similar values occurred in the pair-fed group. Leptin, an anorectic hormone produced by lipocytes, significantly decreased, as expected, because of the decrease in body weight and body fat content.

The physical limitation of the gastric pouch may not be the only factor leading to weight loss.[24] To test this hypothesis, we included a pair-fed group. When pair-fed rats were provided with the same amount of food consumed by RYGB rats, the weight loss was less compared with the RYGB rats. This difference in weight loss between the RYGB and pair-fed groups indicates

Table 2. Mean daily body weight change

	Day 0–7	Day 8–30	Day 31–67
Mean daily weight change (gm)			
SO-obese	−8.45 (.71)	1.41 (.12)	1.18 (.06)
RYGB	−15.44 (1.38)	−5.51 (.23)	.25 (.11)
Mean initial weight at the beginning of each period (gm)			
SO-obese	762	690	693
RYGB	765	673	504

RYGB = Roux-en-Y.

that the mechanism(s) of weight loss in these two groups of rats may not be similar. We postulate that after RYGB, the small gastric pouch results in early "satiety" signals to the brain via the vagal afferent nerve and plasma ghrelin, terminating meal size and inducing satiation, respectively. In addition, a decrease in food absorption secondary to the 16 cm pancreaticbiliary limb could also contribute to weight loss. However, gastric emptying and small bowel absorption studies currently ongoing should shed further light on the mechanisms of weight loss.

We developed an obese rat model that reproduced the hallmarks of obesity in humans in Experiment 1. Following RYGB, weight loss and amelioration of biochemical indices of obesity were evident after 10 days. Weight loss beyond 10 days did not occur because of the development of suture line fistulas. This led us to modify the model by dividing the stomach. In Experiment 2 we modified the model by completely dividing the stomach to prevent the previous occurrence of gastrogastric fistula. This procedure significantly extended our operative time. The first rats that underwent RYGB with complete division of the stomach died during the first 3 days after surgery. Necropsy did not reveal major anatomic-surgical problems. We attributed these deaths primarily to the longer anesthesia time and the increased magnitude of the intraoperative trauma. However, rats that survived the surgical procedure still did not show a sustained weight loss. We performed an upper gastrointestinal series to determine the presence of a potential gastrogastric fistula. As shown in Fig. 3, *B* and ultimately via necropsy, no fistulas were demonstrated. The success of this modification in creating the gastric pouch by gastric division became our standard RYGB procedure. Nevertheless, persistent weight loss was not observed, motivating us to increase the length of the pancreaticbiliary limb, thereby increasing the length of excluded bowel. However, the most significant contribution of this experiment was relearning the lessons of perioperative care because of the high mortality rate as a result of this lengthy surgical procedure. The following modifications were performed in our model:

- 20 ml of normal saline solution subcutaneously preoperatively to maintain hydration during the surgical procedure
- A single dose of 75 mg of ceftriaxone as antimicrobial prophylaxis
- Intraoperative time was shortened from 120 to 90 minutes
- 40 ml of normal saline solution subcutaneously on completion of every operation
- Heat lamp and hot water bottle to maintain body temperature after surgery
- 20 ml or more of normal saline solution during the 3 first postoperative days, depending on the hydration status of the rat
- Postoperative analgesic, buprenorphine hydrochloride (0.05 mg/kg) twice a day during the first 3 days
- Rats were maintained on the liquid Boost-Plus diet for 7 days instead of 3 days before they were started on the coarsely ground chow diet to facilitate anastomotic healing

These measures decreased mortality. Although time-consuming, when dealing with many rats simultaneously, these techniques were adopted as standard operational practice and were applied in Experiment 3.

In Experiment 3, a 20% divided gastric pouch, with a 30 cm biliary-pancreatic limb, a 10 cm alimentary limb, and a common channel of approximately 18 cm, was successfully created. The initial pattern of weight loss was similar to that reported in the two previous experiments. There was no evidence of a regaining of body weight. Instead, a persistent weight loss was achieved. In contrast, it should be noted that the SO-obese rats continued to gain weight. This is a common phenomenon in rats that tend to slowly gain weight throughout their lifespan. In comparison to the RYGB group, the weight curve in pair-fed rats showed an initial weight loss but subsequently (from day 10) demonstrated a gradual weight gain. This finding suggests that in the presence of the lengthened intestinal bypass, diminished nutrient absorption is a factor contributing to continued and persistent weight loss in RYGB. This clinical impression is supported by our observations that the rats' feces were less formed and wetter, as indicated by the wider staining surrounding the feces on the pan liner under each cage. Pair-fed rats gained weight 10 days after operation, whereas RYGB rats showed persistent weight loss. This suggests that the mechanism(s) of weight loss in the latter is certainly different from that in pair-fed rats, which calls for further studies. Now that we have developed a reproducible model of RYGB such studies are in progress.

However, the value of a sustained weight loss for 28 days was initially questioned in our studies, and a mortality rate of 20% needed to be improved. Hence we embarked on Experiment 4, in which we used an EZ35B stapler to create a 20% gastric pouch to transect the stomach. This decreased the operative trauma of our previous model, in which the pouch was created manually. Our operative time decreased, and the rats awakened faster and were more active during the first postoperative days. Finally, this modification also decreased our mortality rate.

The existence of a robust, reliable, and reproducible rat model of RYGB opens a new field in the research

of obesity. This reliable RYGB permits us to investigate the mechanisms of weight loss after RYGB, as well as the mechanisms of improvement of the diseases related to obesity, including diabetes, heart disease and hypertension, and wound healing.

We thank Boost-Plus Mead Johnson (Evansville, Indiana) for supplying the Boost-Plus used in this study.

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Prognostic Factors in Patients With Submucosal Esophageal Cancer

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The detection rate of early-stage esophageal cancer has increased recently. Various types of treatment including endoscopic mucosal resection, blunt dissection, and esophagectomy with extended lymphadenectomy are employed in patients with submucosal esophageal cancer. The purpose of the present study was to analyze prognostic factors in patients with submucosal esophageal cancer. Univariate analysis showed that lymph node metastasis, subdivision of tumor depth, and lymphatic invasion were correlated with prognosis, whereas sex, age, tumor location, surgical procedure, adjuvant therapy, histologic findings, and venous invasion did not affect prognosis. Multivariate analysis demonstrated lymph node metastasis to be the only significant prognostic factor in submucosal esophageal cancer. Although subdivisions of tumor depth did not reach significance as prognostic factors, lymph node metastasis was strongly related to tumor depth. To select the individualized treatment in patients with submucosal esophageal cancer, accurate diagnosis of lymph node metastasis necessitates a combination of imaging methods such as endoscopic ultrasound–guided fine-needle aspiration, computed tomography, and positron emission tomography. (J GASTROINTEST SURG 2004;8:631–635)

KEY WORDS: Esophageal cancer, submucosal invasion, lymph node metastasis

As a result of the development of imaging technology, superficial esophageal cancer is discovered frequently. Because the incidence of lymph node metastasis is low in carcinoma limited to the lamina propria mucosae, endoscopic mucosal resection has recently been performed.[1] However, once tumor invades the muscularis mucosae or submucosal layer, various treatments such as endoscopic mucosal resection, blunt dissection, esophagectomy with extended lymphadenectomy, or radiation therapy with or without chemotherapy are required. The 5-year survival rate for mucosal esophageal cancer is quoted as 64% to 100%, compared with 33% to 69% for patients with submucosal cancer.[2–8] In contrast, more than 40% of resected gastric carcinomas are early carcinomas with a 5-year survival rate greater than 90% in Japan.[9–11] From the standpoint of histologic and prognostic differences between mucosal and submucosal cancer of the esophagus, or in analogy to early gastric carcinoma, it has been proposed recently that true early esophageal carcinoma be defined as tumor limited to the mucosa.[12–14] Correspondingly, according to the Japanese definition of esophageal cancer,[15] early esophageal cancer represents tumor limited to the mucosa.

In the present study, we examined clinicopathologic factors in submucosal esophageal cancer and analyzed the most important prognostic factors. Herein we discuss the treatment strategy for patients with submucosal esophageal cancer.

MATERIAL AND METHODS

A total of 699 patients with esophageal cancer underwent surgical treatment at Kagoshima University Hospital between 1981 and 2001. Of these patients, 110 exhibited histologic submucosal cancer (with the exception of synchronous tumors in other organs). No patients received preoperative radiation therapy or chemotherapy. Operative strategies were as follows: esophagectomy via the right thoracic approach

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(n = 71), esophagectomy via left thoracotomy (n = 7), blunt dissection (n = 24), and endoscopic mucosal resection (n = 8). Three-field lymphadenectomy was performed in 29 patients. The depth of cancer invasion was histologically subdivided as follows: sm1 = invasion limited to the upper one third of the submucosa; sm2 = invasion to between one third and two thirds of the submucosal depth; and sm3 = invasion into the deepest one third of the submucosa. Histologically, 100 patients were shown to have squamous cell carcinoma and 10 patients had miscellaneous (4 adenosquamous cell carcinoma, 2 adenocystic carcinoma, 2 pseudosarcoma, 1 basaloid carcinoma, and 1 undifferentiated carcinoma). In the present study, 92 patients were enrolled with the exclusion of eight patients who underwent endoscopic mucosal resection and 10 patients with miscellaneous tumor types.

All patients were monitored regularly after discharge by x-ray examination, ultrasonography, and computed tomography. Follow-up data were available for all patients, with a median follow-up period of 65.7 months (range 3 to 249 months). Forty-three patients have died to date: 10 within 1 year, 7 within 2 years, 16 within 5 years, and 10 more than 5 years after surgery. Forty-nine patients are still alive: Twenty-five patients have survived more than 5 years, and 24 patients have survived between 2 and 5 years after surgery. Pathologic data were evaluated in accordance with the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus of the Japanese Esophageal Disease Research Study.[15]

Statistical analysis of group differences was performed with the use of chi-square and *t* tests. The Kaplan-Meier method was used for survival analysis and evaluated by the Wilcoxon test. Prognostic factors were examined by means of univariate and multivariate analyses (proportional hazard regression model). A value of $P < 0.05$ was considered statistically significant.

Table 1. Univariate analysis of various factors

Variables	No. of patients	5-yr survival rates (%)	*P* value
Sex			
Male	83	71	0.2792
Female	9	100	
Age			
⩾65 yr	54	66	0.4199
<65 yr	38	81	
Surgical procedure			
Right thoracotomy	63	80	0.2314
Left thoracotomy	7	40	
Blunt dissection	22	52	
Lymph node dissection			
3-field	26	72	0.3990
Others	66	77	
Adjuvant therapy			
Done	26	74	0.9470
Not done	66	72	
Tumor location			
Upper	18	74	0.3898
Middle	48	80	
Lower	26	64	
Subdivision of tumor depth			
sm1	21	92	0.0059
sm2	28	81	
sm3	43	57	
Lymph node metastasis			
Negative	50	85	<0.0001
Positive	42	58	
Lymphatic invasion			
Negative	41	83	0.0220
Positive	51	64	
Venous invasion			
Negative	67	77	0.1191
Positive	25	63	
Squamous cell carcinoma histology			
Well-differentiated	19	73	0.9824
Moderately differentiated	52	78	
Poorly differentiated	21	63	

RESULTS

Clinicopathologic Features

Patients included 83 men and 9 women who ranged in age from 46 to 81 years (mean age 65.6 years). Table 1 shows the histopathologic findings of esophageal submucosal cancer. Fifteen tumors were located in the upper third, 49 tumors were in the middle third, and 28 tumors were in the lower third of the esophagus. Regarding histologic type, 19 lesions were well-differentiated, 52 were moderately differentiated, and 21 were poorly differentiated squamous cell carcinomas. Lymph node metastasis was found in 42 patients (45.7%). The incidence of lymphatic invasion was 55.4% (51 of 92 patients) and venous invasion was 27.2% (25 of 92 patients). Regarding the subdivision of tumor depth, the number of patients with sm1, 2, and 3 was 21, 28, and 43, respectively. Postoperative chemotherapy and/or radiation therapy was performed in 26 patients (28.3%).

Prognostic Significance of Various Parameters

Univariate analysis demonstrated significant differences in cumulative survival for sex, surgical procedure, lymph node dissection, adjuvant therapy, tumor location, subdivision of tumor depth, lymph node metastasis, lymphatic invasion, venous invasion, and

histologic type. Sex, surgical procedure, lymph node dissection, adjuvant therapy, tumor location, and histologic findings were not related to significant differences in survival (see Table 1). On the other hand, statistically significant differences in 5-year survival were found in factors such as subdivision of tumor depth ($P = 0.0059$) (Fig. 1, *A*), lymph node metastasis ($P < 0.0001$) (Fig. 1, *B*), and lymphatic invasion ($P = 0.022$) (Fig. 1, *C*). Multivariate analysis demonstrated that the presence or absence of lymph node metastasis ($P = 0.0069$) was the only factor independently correlated with prognosis in patients with esophageal carcinoma. The other factors did not reach a statistically significant difference (subdivision of tumor depth; $P = 0.13$ and lymphatic invasion; $P = 0.33$, respectively).

DISCUSSION

Various treatment options exist in submucosal esophageal cancer. Surgery for esophageal cancer is one of the most aggressive treatments among approaches to carcinoma of the gastrointestinal tract. After esophagectomy, postoperative complications include pneumonia due to reflux, recurrent nerve paralysis, and malnutrition.[16–18] When tumor exhibits minimal invasion of the submucosa (sm1), endoscopic mucosal resection or reduction of lymphadenectomy has recently been employed in some cases found not to have lymph node metastasis on preoperative imaging.[1] On the other hand, in patients with deep invasion of the submucosa and positive lymph node metastasis, esophagectomy with extended lymph node dissection has been performed.[19] To select the appropriate treatment for submucosal esophageal cancer, it is necessary to retrospectively analyze factors having a clinical impact on prognosis.

In the present study, we analyzed the various clinicopathologic factors related to prognosis. Lymph node metastasis, subdivision of tumor depth, and lymphatic invasion were significantly correlated with prognosis on univariate analysis. According to the results of multivariate analysis, lymph node metastasis was the sole significant prognostic factor, with subdivision of tumor depth not reaching statistical significance. In this series, when patients exhibiting lymph node metastasis were subdivided according to tumor depth, the proportion of sm1, 2, and 3 tumors showing nodal metastasis was 28.6% (6 of 21), 39.3% (11 of 28), and 58.1% (25 of 43), respectively. Furthermore, of the six patients with sm1 tumors, five patients had only one nodal metastasis. In some patients with sm1 tumors, endoscopic mucosal resection or reduction of lymphadenectomy may therefore be acceptable. In 11 patients with nodal involvement in sm2 disease, metastasis was confined to a single lymph node in six patients and involved two or more nodes in five. Accordingly, less invasive surgery is considered controversial in these patients. On the other hand, two or more nodal metastases were found in 15 of 27 patients with sm3 tumors and curative surgery, including complete lymph node clearance, is recommended for these patients.

It is necessary to diagnose lymph node metastasis as accurately as possible when deciding on the optimal treatment for submucosal esophageal cancer. The accuracy rate of presurgical diagnosis of lymph node metastasis in superficial esophageal cancer ranges from 71% to 96% and depends on the imaging modality used, with the highest rates of detection being achieved with endoscopic ultrasound.[20,21] Endoscopic ultrasound–guided fine-needle aspiration is also useful for preopearive histologic diagnosis in lymph node metastasis, especially in the celiac nodes.[22,23] Recently positron emission tomography has been introduced in diagnosis of preoperative stage. Although positron emission tomography was useful for detecting the distant nodal metastasis and hematogeneous metastasis,[24,25] it was difficult to diagnose early-stage esophageal cancer.[26] Further study is needed to examine the accuracy of diagnosis for early-stage cancer in a large number of patients. In order to diagnose lymph node metastasis more accurately, intraoperative histologic diagnosis by frozen section is essential. Recently the sentinel node concept has been incorporated into the field of gastrointestinal tract cancer.[27,28] If sentinel node navigation surgery was established in submucosal esophageal cancer, the majority of patients would benefit by undergoing less invasive surgery. The presence of lymph node micrometastasis has been reported in esophageal cancer.[29,30] To detect such micrometastatic foci in lymph nodes, rapid immunohistochemical detection of lymph node micrometasasis should be introduced intraoperatively when performing reduction of lymphadenectomy, including sentinel node navigation surgery.[31]

CONCLUSION

The present study found lymph node metastasis to be the sole prognostic factor in patients with submucosal esophageal cancer. However, considering the subdivisions of tumor depth, acceptable establishment of accurate diagnosis of lymph node metastasis using preoperative imaging means such as endoscopic ultrasound, with endoscopic ultrasound–fine-needle aspiration, computed tomography, and positron emission tomography may enable individualized treatment.

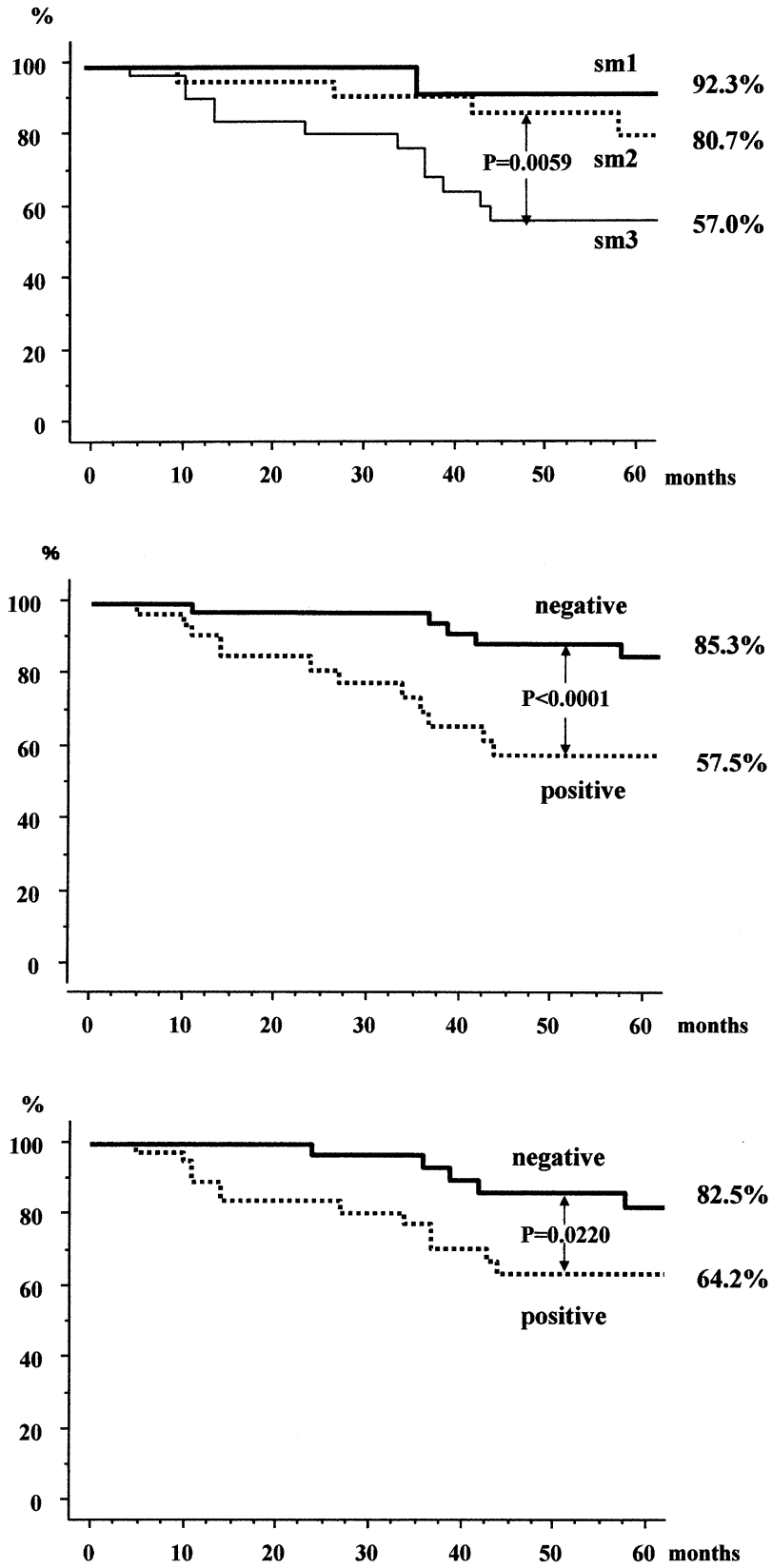

Fig. 1. Five-year survival rate after univariate analysis using the log-rank test. Significant differences were found in subdivision of tumor depth (**A**), lymph node metastasis (**B**), and lymphatic invasion (**C**).

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Laparoscopic Colectomy for Cancer

David W. Larson, M.D., Heidi Nelson, M.D.

Laparoscopic segmental colectomy has been widely accepted as a surgical procedure for benign colonic disease. With improving technology and surgeon experience, more complex procedures have been performed. However, a minimal invasive approach may not be justified for all colonic diseases. The use of laparoscopic surgery for colonic cancer, for example, has been controversial and the results of our national and international trials are yet unknown. We anticipate, given the positive findings of multiple small randomized and nonrandomized trials, that laparoscopic colectomy for cancer may soon prove to be appropriate in this setting. Our aim in this paper is to explore the indications, contraindications, and techniques regarding laparoscopic surgery that we have used in the treatment of colon cancer for patients enrolled in the national trial. (J GASTROINTEST SURG 2004;8:636–642)

KEY WORDS: Laparoscopic colectomy, colon cancer, minimal invasive surgery, techniques

Although it is anticipated that malignant disease will be approached laparoscopically in the near future, it is with benign disease that surgeons are afforded the opportunity to improve their laparoscopic skills. To ensure proper technique, we have used mentorship in combination with video evaluation to develop these skills. In the Clinical Outcomes of Surgical Therapy (COST) trial, surgeons were required to provide proof of at least 20 laparoscopic colon procedures along with an unaltered video. This helped to ensure that proper oncologic resection occurred, preventing possible patient harm. The importance of a proper cancer resection cannot be overestimated. The principles of an open procedure for cancer must be maintained with the laparoscopic approach. The same extent of exploration, margin of resection (5 cm), lymph-node harvest, and vascular ligation (intracorporeal) must be followed. Along with these tenants a commitment to minimal tumor manipulation and port-site protection are necessary adjuncts with regard to this approach. Under proper guidance one can learn this technique after 20–30 resections. This finding has been supported by the literature and is consistent with the recommendations

Table 1. Indications and contraindications

Indications
Colon polyps (not amenable to endoscopic resection)
Crohn's disease
Volvulus
Diverticulitis
Rectal prolapse
Colonic diversion (ileostomy or colostomy creation, unresectable cancer)
Colon carcinoma (on trial)
Contraindications
(i) Absolute
Tumor-related
Tumor infiltration into adjacent structures (T4)
Large phlegmon mass
Acute complications: obstruction, perforation, and ileus
(ii) Relative
Patient-related
Morbid obesity
Multiple previous abdominal surgeries
Extensive abdominal adhesions
Tumor-related
Curable cancer (until trial results available)
Primary tumor with resectable liver metastasis
Carcinomatosis

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of the National Cancer Institute (NCI) 2000 guidelines for laparoscopic surgery.

However, even with proper techniques, contraindications and concerns still exist. Contraindications can be divided into two groups: absolute and relative according to the patient and the tumor-related factors (Table 1). During the COST trial, conversion to open surgery was a requirement if one encountered abdominal adhesions, if the surgeon was unable to mobilize and define the tumor extent, and if there were resectable metastasis. Furthermore, the concern about port-site recurrence made removing a neoplasm larger than 8–10 cm through a small 4–6 cm incision unreasonable. Ultimately, it is the commitment of the surgeon to perform an uncompromised oncologic resection that ensures a successful outcome with regard to the laparoscopic approach.

LAPAROSCOPIC COLON PROCEDURES

Right Hemicolectomy

Regardless of the operation, positioning the patient begins with tucking, padding, and protecting both arms at the sides. Given the multiple changes of position, we commonly use ankle straps if positioned supine, Allen stirrups for the modified lithotomy position, and chest straps to properly secure the patient.

Step One: Exploration. For a right colectomy a five-step procedure is used. The operation commences with the placement of the first port (10/12 mm) using a cut-down method in the supraumbilical position. Through this, a 30-degree optic device is used. The abdomen is insufflated with carbon dioxide to a pressure between 12–14 mm Hg. The second and third trocars are placed under direct vision using a combination of 5- or 10/12-mm trocars depending on the surgical resection planned in the left upper and lower quadrant (Fig. 1).

Step Two: Identification. Exploration of the abdomen in search of signs of metastatic disease is a main component of this step. Of course, a thorough evaluation of the liver is necessary and intraoperative ultrasound can be used to enhance the hepatic evaluation for metastasis. We determine whether adhesions, altered anatomy, or tumor characteristics will require a conversion to open surgery. Furthermore, conversion is accomplished as promptly as possible.

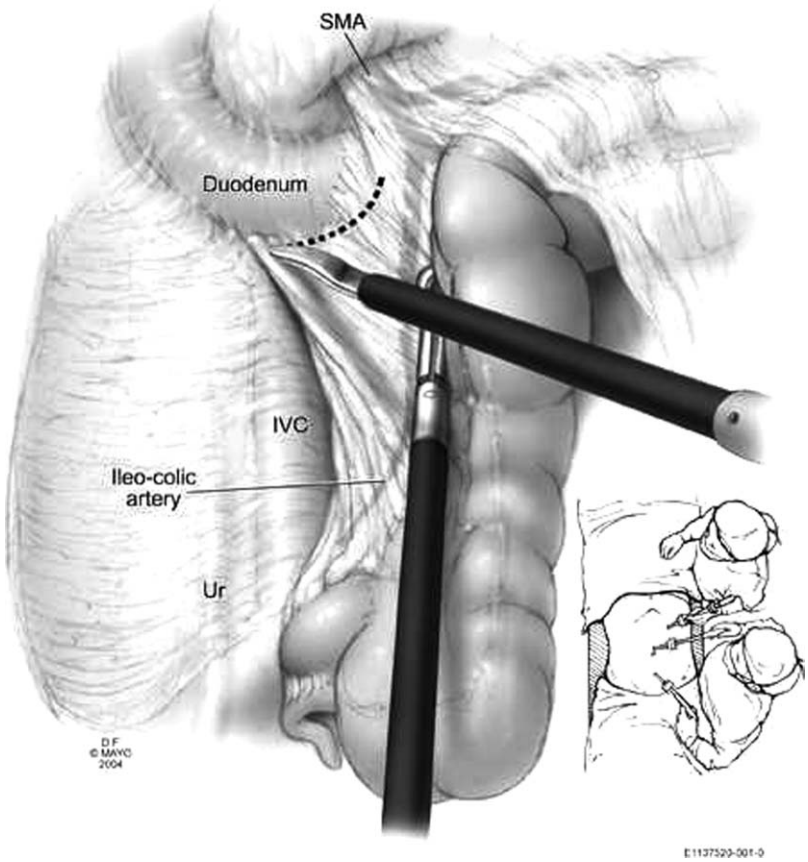

Fig. 1. Mobilization of the right colon and hepatic flexure. Preservation of the ureter (UR) and duodenum. SMA = superior mesenteric artery, IVC = inferior vena cava. Port-site location (insert).

Step Three: Retraction. For cecal mobilization a 30-degree laparoscope is removed from the supraumbilical site and placed through the left upper paramedian cannula. The patient is placed in the Trendelenburg position with the right side tilted up and the surgeon and the assistant stand on the left (Fig. 1). The first step of dissection is ureter identification, which can usually be performed at the level of the pelvic brim. In obese patients one must first score the peritoneum to identify the ureter. Traction and countertraction are the key factors regarding proper anatomic dissection of the large intestine. The surgeon grasps the peritoneum, avoiding direct contact of the bowel for safety, and proceeds with standard mobilization. The right lateral peritoneal reflection is opened and the ascending colon is mobilized medially (Fig. 1). This dissection is continued toward the hepatic flexure along the white line of Toldt. The medial peritoneal attachments of the terminal ileum can be divided up to the level of the duodenum to facilitate extracorporeal mobilization and proper high vascular ligation.

Step Four: Mobilization and Vascular Ligation. For hepatic flexure, mobilization the laparoscope is moved to the lower trocar and the operating surgeon and assistant change positions. The patient is placed in reverse Trendelenburg position with the left side down. Mobilization of the colon at the hepatic flexure should start along the free lateral peritoneal edge. The gastro-colic ligament is grasped near, but not on, the bowel and elevated toward the anterior abdominal wall and feet. This thin ligament can often be separated from the deeper tissues of the colonic mesentery. By identifying and then entering the correct

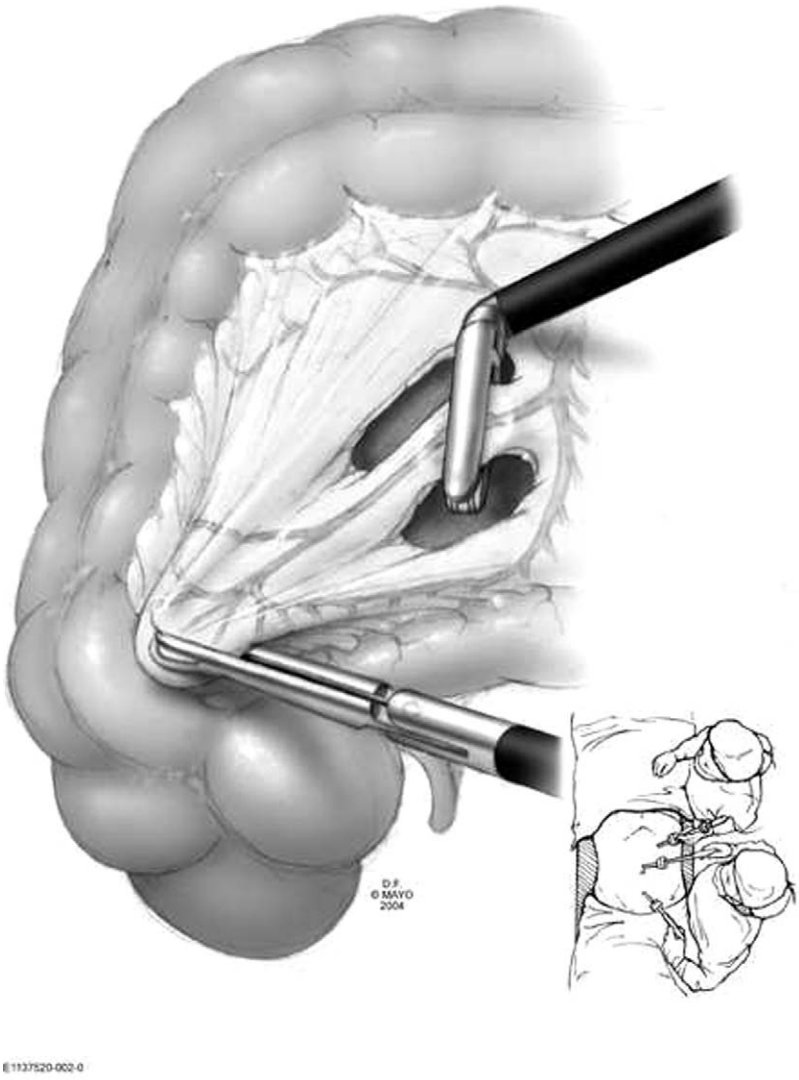

Fig. 2. Intracorporeal vascular ligation. Pedicle ligation of the ileocolic and right colic artery is accomplished with the use of a 30-mm linear vascular stapler. Port-site location (insert).

plane between the gastro-colic ligament and the transverse colon mesentery one can easily mobilize the hepatic flexure. Proper mobilization allows for visualization of the duodenum and ureter, which are protected. Dissection is then continued across the transverse colon medial to the level of the gallbladder. The colon is elevated to expose the superior mesenteric, ileo-colic, right colic, and middle colic vessels. Applying moderate tension on the junction of the ileum and cecum one can readily display the ileocolic vessels facilitating intracorporeal ligation. Mesenteric windows are created within the avascular planes and the vascular pedicle is then secured by using hemoclips, endoloops, or a linear vascular stapler (Fig. 2).

Step Five: Resection and Anastomosis. To exteriorize the right colon, the incision at the supraumbilical port is enlarged around the umbilicus for about 4–6 cm depending on the size of the patient and the specimen. All wounds are protected and the pneumoperitoneum is released through the trocars in a controlled manor. Once exteriorized it is important to maintain mesenteric orientation at all times for a proper anastomosis. The resection and anastomosis is performed in a standard manner, respecting appropriate proximal and distal margins. The mesenteric defect may be closed or left open. The bowel is returned to the peritoneal cavity resuming its normal anatomic position. The abdomen is then irrigated and trocars are removed under direct visualization. After checking for hemostasis, the insufflation is allowed to escape through the camera port and the fascia and skin are closed.

Left Hemicolectomy

Resection of the left colon is essentially the reverse of that for the right colon. The same five-step approach can be applied to the descending colon with the exception of placing the patient in the modified lithotomy position and slight adjustment in the trocar position. Typically, the splenic flexure of the colon needs to be mobilized. For this, the patient is placed in the reverse Trendelenburg position left side up. Often a fourth 5-mm trocar placed in the left lower quadrant will facilitate proper mobilization. The splenic flexure is mobilized with a combination of lateral-to-medial dissection of the descending colon and elevation of the omentum off the distal transverse colon. The first assistant, on the right, applies countertraction to the omentum by elevating it anteriorly, as the surgeon, who stands between the patient's legs, separates it from the colonic border thus entering the lesser sac (Fig. 3). The omentum does not need to be mobilized any more than is necessary to drop the splenic flexure to the level of the umbilicus. This portion of the dissection can be the most difficult part

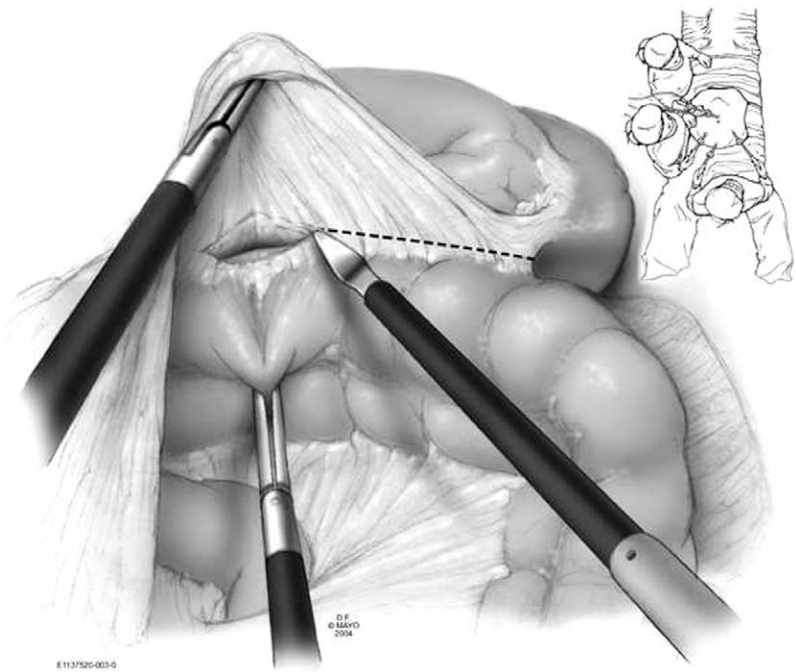

Fig. 3. Taking down the splenic flexure includes lateral-to-medial dissection as well as separation of the omentum from the transverse colon with entry into the lesser sac. Port-site location (insert).

of the procedure. Once mobilized the left colic artery is ligated. Finally, the colon is exteriorized to complete the anastomosis.

Sigmoidectomy

For this resection the patient is placed in a modified lithotomy position (legs up) for simultaneous abdominal and perineal exposure. It is important to keep the thighs level with the abdomen otherwise they will interfere with instrument manipulation.

Step One: Placement of Trocars. Next, the laparoscope is introduced into the supraumbilical port site and the other trocars are inserted under direct visualization. A total of 4 cannulas (two 10–12 mm and two 5 mm) are placed (i) supraumbilical, (ii) supra pubic, (iii) right lower quadrant, and (iv) left lower quadrant.

Step Two: Mobilization. The patient is placed in a steep Trendelenburg right side down position to displace the abdominal contents out of the pelvis and away from the sigmoid colon. The plane of the dissection is immediately medial to the white line of Toldt to avoid undermining the kidney (Fig. 4). The assistant, on the right, operates the laparoscope and the surgeon, on the right, using a grasping instrument

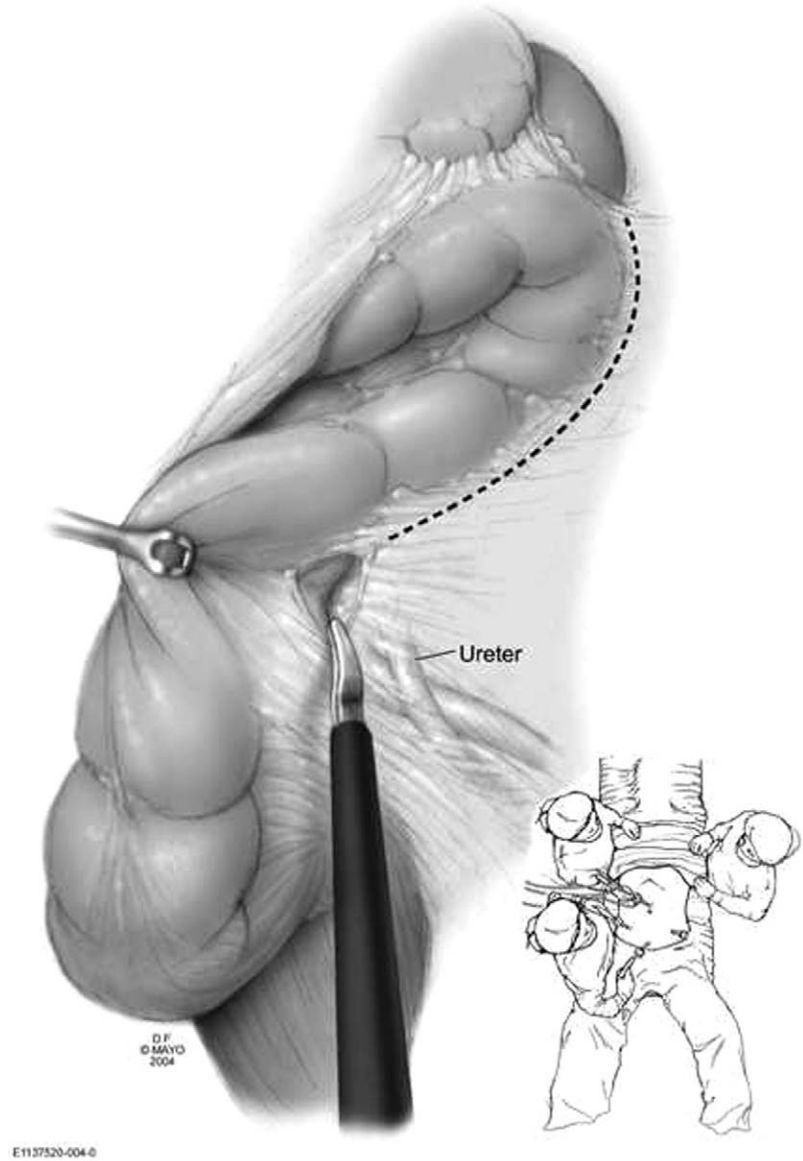

Fig. 4. Sigmoid colon mobilization along the white line of Toldt. Identification of the ureter is key to this dissection. Port-site location (insert).

introduced through the right lower quadrant cannula grasps the pericolic mesentery and retracts it toward the right side of the patient. Through the suprapubic port the electrocautery and scissors are used for dissection. The ureter can usually be identified at the level of the pelvic brim. Lighted stents can be used in difficult diverticular cases especially for those who are less experienced with laparoscopy. Upon completion of the mobilization the ureter should be swept down and away from the mesenteric structures to avoid inadvertent injury during ligation of the vascular pedicle. Once the sigmoid colon is mobilized, the dissection is continued into the proximal pelvis and into the presacral space. With the sigmoid colon retracted cephalad and to the patient's right, the presacral window on the patient's left can be opened. During this procedure the iliac vessels can be easily identified and the presacral space defined. The dissection should continue until the proximal-to-mid rectum is free along the left margin. With the sigmoid retracted in the opposite manner (toward the patient's left side), the presacral window on the right is opened next. The superior hemorrhoidal and sigmoid vessels are then visualized, as the sigmoid colon and proximal rectum are brought under tension by caudal traction.

Step Three: Vascular Ligation. Vascular ligation is achieved by placing the sigmoid colon on tension to expose the mesenteric vessels and the avascular planes on both sides of the vessels. The superior hemorrhoidal vessels and sigmoid arteries are isolated. Vascular pedicle ligation at the level of aortic bifurcation is executed employing vascular staplers, clips, or endoloops. After ligation is achieved, the sigmoid should become more mobile for anastomotic purposes. If necessary, the descending colon can be dissected further cephalad, including the splenic flexure. Dissecting techniques are equivalent to those described for dissection of the splenic flexure during a left colectomy.

Step Four: Division of Rectum. Division of the rectum is achieved by dissecting from side-to-side along the rectal wall using a harmonic scalpel or electrocautery and clips (right to left). Upon completion of this the rectum is divided using a linear cutting stapler (Fig. 5).

Step Five: Resection. The sigmoid is then delivered through either a small incision in the midline similar to the right hemicolectomy or alternatively through a small low midline or Phannenstiel incision. The specimen is delivered and the proximal margin

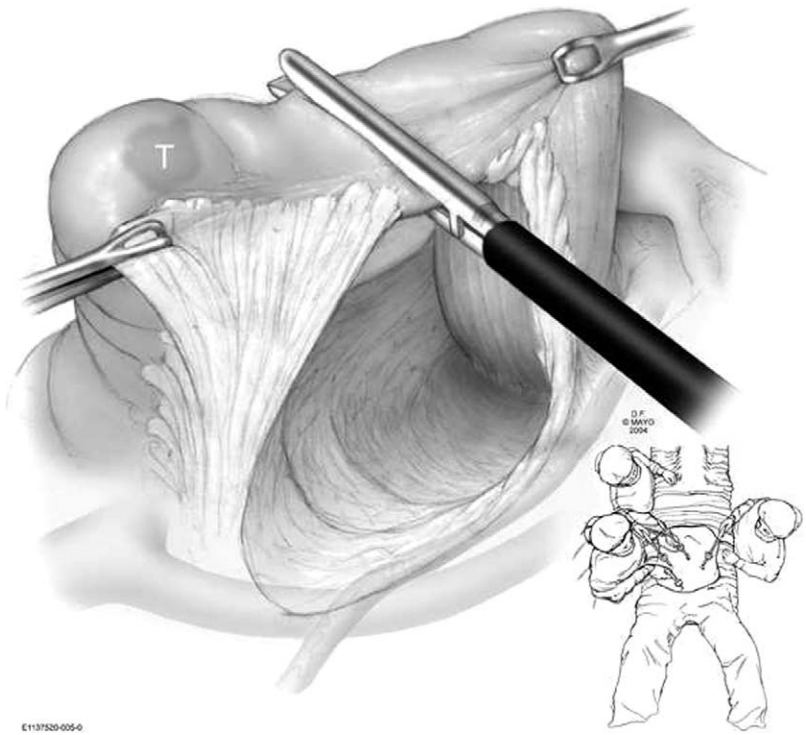

Fig. 5. Transection of the distal sigmoid is accomplished with a 45-mm linear gastrointestinal stapler. High ligation of the inferior mesenteric artery (not indicated) is likewise accomplished with a vascular linear stapler. Port-site location (insert).

Fig. 6. Intracorporeal colorectal anastomosis using a circular stapling device. Both ends are connected, maintaining proper mesentery orientation. A proctoscope may be used after making the anastomosis to evaluate anastomotic integrity.

identified. The bowel is cleared of mesentery and then is resected proximal to the tumor location.

Step Six: Anastomosis. After placing an anvil in the proximal bowel it is returned to the abdomen and the fascia is closed. The abdomen is reinsufflated and the anvil is attached to the shaft of the stapling device that has been introduced through the anus and advanced across the staple line (Fig. 6). The stapling device is closed, the bowel ends approximated, and the stapler fired. A proctoscope is then used to examine the anastomosis for hemostasis and integrity. The cannulas are all removed under direct visualization and the fascial defects and skin are closed.

CONCLUSION

Laparoscopic colectomy as a surgical procedure for benign colonic diseases has gained generalized acceptance as a safe, efficient, and beneficial therapeutic option. Laparoscopy for colon cancer will likely be an accepted alternative technique, pending sufficient results from large prospective randomized trials. The importance of experience cannot be overestimated. For those who are beginning to learn laparoscopic surgery the presence of a mentor or partner may greatly improve the learning curve. It is essential that one first gain experience with benign disease in uncomplicated optimal (thin) patients. After experience is gained and an uncompromised approach is adopted, a laparoscopic resection for colon cancer can be performed under trial.

Book Review

Surgery of the Trachea and Bronchi
Hermes C. Grillo, New York, NY: BC Decker, 2004, Pages: 872. Price: $199.

In the preface of *Surgery of the Trachea and Bronchi*, Hermes C. Grillo, the principal author, states that this seems "a rather large book to devote to an anatomic structure only 10 to 12 cm in length," and he hopes "the reader finds useful guidance in these pages." The author's goal is easily satisfied by this comprehensive explanation of what is currently known about surgical treatment of the trachea and bronchi.

The book is divided into two parts; the first describes the diseases, diagnoses, and results of treatment, and the second part deals with therapeutic techniques and management. The book is 872 pages long, printed on substantial white gloss paper, and includes 16 pages of color photographs of bronchoscopic and microscopic pictures from the author's extensive collection. In addition, the book includes a CD-ROM that contains the entire book on PDF files so they can be viewed on a laptop computer or used for educational purposes. Each chapter is extensively referenced; for example, the introductory chapter on the development of tracheal surgery has 325 cited references.

The first part of the book consists of 16 chapters, the first five of which describe the anatomy, physiology, pathology, imaging, and endoscopy of the windpipe. The chapters on pathology are written by Eugene J. Mark, pathologist at Massachusetts General Hospital with years of experience developed from receiving specimens from Dr. Grillo and others at Massachusetts General Hospital. The second half of part 1 is a comprehensive discussion of the diseases and results of airway diseases. All except one of these chapters are written by Dr. Grillo. The reader is treated to the insight of a surgeon who for the past 40 years has dedicated himself to the discovery and surgical correction of airway problems. Each chapter is an in-depth description of the particular problem infused with the advice from Dr. Grillo's years of experience in dealing with this problem. The diseases described range from the common, squamous cell carcinoma of the trachea, to the rare, Mounier-Kuhn syndrome. For each of these maladies, Dr. Grillo relates his experience gained throughout his career: the pitfalls to watch out for, the mistakes made (so as not to repeat them), and the successes.

The second part of the book, on technique, discusses each tracheal operation in a step-by-step fashion. The level of detail is surprising for this type of text book. For example, the description of the anastomotic technique of the trachea includes information about where to clip each hemostat that is holding the sutures to the drapes. The text is also filled with sage advice from Dr. Grillo that has heretofore only been available to his residents. At the opening of the chapter on tracheal reconstruction he states, "The best opportunity to correct a tracheal lesion is at the initial operation." In the discussion of granulomatous infections he warns, "The technical procedure may be very difficult and often requires judicious placement of a proximal tourniquet on the pulmonary artery prior to proceeding with further dissection." He even takes on the difficult question of who should perform tracheal surgery in the following statement: "Surgeons should ask themselves scrupulously whether the operation should indeed be performed. I have never seen a patient or a family who has faulted a surgeon for referring a patient elsewhere for initial tracheal surgery. I have, however, encountered many patients and families who have deeply resented receiving what they later recognized to be inexperienced or inappropriate surgery."

This book is a "must read" for all thoracic surgeons who deal with tracheal problems. It is the comprehensive text on the subject and a marvelous reference resource for any question on the airways. The book is a fitting reminder of a great surgeon who dedicated his career to surgery of the trachea and bronchi.

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