Management of the Biliary Tract in Acute Necrotizing Pancreatitis

*The SSAT, AGE, ASGE Consensus Panel**

Questions Addressed by the Consensus Panel

1. What are the clinical, biochemical, and radiologic criteria for the diagnosis of biliary pancreatitis in patients with acute necrotizing pancreatitis (ANP)?
2. What is the optimal method for biliary tract imaging in ANP?
3. When is early endoscopic retrograde cholangiopancreatography (ERCP) indicated in ANP? Should sphincterotomy be performed if no stone is seen?
4. What is the optimal timing for cholecystectomy in ANP? Is cholecystectomy necessary in patients who already have undergone endoscopic sphincterotomy?
5. What is the appropriate operative approach to the gallbladder and bile duct in patients with ANP?
6. Given the present state of the art, what clinical trials could be designed now that would most effectively address this clinical problem?

General Summary

The incidence of biliary pancreatitis parallels that of gallstone disease, and is more common in women between the ages of 50 and 70. Patients with biliary pancreatitis are as likely as those with pancreatitis of other etiologies to develop severe disease. Mortality from acute biliary pancreatitis (as determined from the placebo arm of treatment studies) averages approximately 6%.

Passage or impaction of a stone is generally accepted as an event common to all patients with gallstone pancreatitis. The precise mechanism whereby this phenomenon leads to pancreatitis and the factors determining whether an attack will be mild or severe remain largely unknown.

1. Differentiation of biliary from other forms of pancreatitis is based on a combination of serum tests and imaging. Abnormalities in liver function tests, in particular a threefold elevation of alanine aminotransferase (ALT), are very specific for the diagnosis. Ultrasound will detect gallstones in 70% to 80% of those with acute biliary pancreatitis. The combination of both tests is highly accurate for the diagnosis of acute biliary pancreatitis.
2. Data are insufficient to define the optimal method for biliary tract imaging in ANP. ERCP has been the "gold standard" and also has therapeutic potential. However, it is an invasive test with a high cost and potentially serious complications, especially in patients with pancreatitis. Ultrasound remains the test of choice for detection of cholelithiasis and bile duct dilatation, but has a very low sensitivity for common bile duct stones. Magnetic resonance cholangiopancreatography (MRCP) has now become more widely available and has a sensitivity of more than 90% for choledocholithiasis, and CT cholangiography is an emerging alternative that may prove to be equally useful. However, the utility of these tests has not been validated in the setting of acute pancreatitis, and their applicability in patients with severe pancreatitis is not clear.

Many prospective studies, using ERCP or intraoperative cholangiography as the gold standard, have shown that endoscopic ultrasound (EUS) is extremely accurate for the detection of choledocholithiasis. Most studies show sensitivity of more than 90% and specificity of 95% to 100%. However, evidence of similar accuracy in the setting of acute pancreatitis is limited.

Correspondence: Carlos Fernández-del Castillo, M.D., Department of Surgery, Massachusetts General Hospital, ACC/336, Boston, MA 02114.

*The Society for Surgery of the Alimentary Tract, American Gastroenterological Association, American Society for Gastrointestinal Endoscopy.

Although complication rates are very low, EUS should still be considered an invasive test.

3. Early ERCP with sphincterotomy and stone extraction is indicated for patients with pancreatitis and concomitant cholangitis or significant persistent biliary obstruction (usually serum bilirubin >5 mg/dl). Achieving adequate biliary drainage following the procedure is paramount, and therefore ERCP should be attempted only in settings where appropriate expertise is available. Evidence to support the use of ERCP in severe biliary pancreatitis without biliary sepsis or obstruction is conflicting. There are no data to support or refute the use of sphincterotomy if, at the time of ERCP done for suspected biliary pancreatitis, no stone is found. ERCP should not be performed acutely in patients with predicted mild pancreatitis of suspected or proven biliary etiology in the absence of biliary obstruction.
4. In general, patients with biliary pancreatitis should undergo cholecystectomy during their initial hospitalization to prevent recurrent pancreatitis or other biliary complications. Exceptions include elderly patients with high surgical risk in whom ERCP and endoscopic sphincterotomy may suffice. Other situations where delaying cholecystectomy may be advisable are in patients with necrotizing pancreatitis in whom inflammatory changes may need to subside to allow for a safer operation.

   There is no indication for routine preoperative ERCP in patients with gallstone pancreatitis who will undergo cholecystectomy. MRCP, EUS, and CT cholangiography all have a potential role in the preoperative assessment of these patients, but there is insufficient evidence to support or refute their use on a routine basis.
5. Barring contraindications, laparoscopic cholecystectomy is the procedure of choice for removal of the gallbladder in patients with biliary pancreatitis. Recent ERCP, MRCP, or EUS will usually have ruled out choledocholithiasis, but if not, intraoperative cholangiography or intraoperative ultrasonography should be performed in all of these patients. If a stone or stones are found at the time of surgery, the following options are available: transcystic laparoscopic removal, laparoscopic choledochotomy, endoscopic antegrade sphincterotomy, conversion to an open common bile duct exploration, or planned postoperative ERCP and endoscopic sphincterotomy. Data are insufficient to provide for a consensus regarding optimal management.

Areas for Future Clinical Investigation

6. Given the legitimate controversy regarding the indications for ERCP in acute pancreatitis in the absence of biliary obstruction, a randomized trial of ERCP with or without sphincterotomy early in the course of predicted severe biliary pancreatitis is needed.

   Future clinical trials should address the role of MRCP, EUS, and CT cholangiography in the evaluation of patients with biliary pancreatitis, both early in the course of the disease (to confirm the etiology of the pancreatitis and to detect the presence of persistent choledocholithiasis) and as part of the precholecystectomy workup.

Members of the Consensus Panel were:

Gregory Bulkley, M.D., Johns Hopkins Medical Institutions, Baltimore, Md.; **David L. Carr-Locke, M.D.,** Brigham and Women's Hospital, Boston, Mass.; **Eugene P. DiMagno, M.D.,** Mayo Clinic, Rochester, Minn.; **Carlos Fernández-del Castillo, M.D.,** Massachusetts General Hospital, Boston, Mass.; **Aaron S. Fink, M.D.,** Atlanta Veterans Administration Medical Center, Decatur, Ga.; **W. Scott Helton, M.D.,** University of Illinois, Chicago, Ill.; **Keith Lillemoe, M.D.,** Johns Hopkins Medical Institutions, Baltimore, Md.; **Keith Lindor, M.D.,** Mayo Clinic, Rochester, Minn.

Endoscopic Ultrasonography in Acute Biliary Pancreatitis

T. Rösch, M.D., P. Mayr, M.D., M.A. Kassem, M.D.

CLINICAL BACKGROUND

The necessity to diagnose common bile duct (CBD) stones fairly early in suspected acute biliary pancreatitis rests on the following two assumptions (1) the belief that (early) treatment of stones is beneficial for the course of the pancreatitis and (2) the belief that endoscopic retrograde cholangiopancreatography (ERCP) should be avoided if it is negative for stones, that is, if it is purely diagnostic and not followed by stone removal. Both hypotheses are poorly founded by prospective data. The role of urgent (i.e., within 72 hours) ERCP in suspected acute biliary pancreatitis is far from being established[1,2] despite four randomized studies,[3,6] one of which[6] still exists in abstract form only. The second assumption—that ERCP, possibly followed by sphincterotomy and stone extraction, may be detrimental for the subsequent course of the disease and should be avoided if it is not therapeutic—is not based on the four randomized studies, in which pancreatitis did not worsen in the ERCP group. However, in one of these four studies, ERCP patients did less well because of a higher frequency of pulmonary complications,[5] which may or may not be attributed to ERCP. That the complication rate of ERCP in the setting of acute pancreatitis is not any higher than in patients without pancreatitis is furthermore difficult to prove, since acute pancreatitis is the major complication of diagnostic and therapeutic ERCP. It is, however, beyond the scope of this report to discuss the necessity of early diagnosis and treatment of CBD stones and the relative contribution of ERCP in comparison with less invasive tests.

EXAMINATION TECHNIQUE OF ENDOSCOPIC ULTRASONOGRAPHY

Almost all studies on endoscopic ultrasonography (EUS) in CBD stones have been performed with radial scanning instruments, and only one retrospective study[7] suggested similar results with linear-type instruments. That radial and linear instruments may perform similarly is also confirmed by studies on linear echoendoscopes in patients with cholestasis,[8,9] in which similar accuracy rates in the detection of CBD stones were reached. The larger and prospective studies, however, were done with radial instruments (Table I). The technique of visualization of the bile ducts and the gallbladder is described in detail elsewhere.[10] Briefly, pancreatobiliary visualization starts when the echoendoscope has been introduced into the second portion of the duodenum; EUS is commonly performed under conscious sedation with a very low complication rate.[11] In the descending duodenum, the bile duct is seen from its entrance into the papilla (endoscope positioned at the papilla), through its course through the pancreatic head (descending duodenum to upper duodenal curve) and up to the hilum (duodenal bulb).[10] The proximal bile duct system including the hilum and intrahepatic ducts is less regularly and less well visualized by EUS. Gallbladder visualization is from either the descending duodenum, bulb, or antrum, depending on its position.[12]

The reported visualization rate of the biliary system is usually very high,[10] although most of the published data from normal patients are either from review or book chapters, or only published in abstract form. There is also a high visualization rate for the CBD in the studies on choledocholithiasis cited below, whenever this parameter is included: EUS visualization rates for the CBD of 94%,[13] 96%,[14,15] 97%,[16] 98,[17] and 100%[18-21] are reported. Reasons for nonvisualization are varied and include anatomic obstacles such as a Billroth II anatomy. Furthermore, only a few studies acknowledge whether or not visualization was complete. In one report with an overall visualization rate of 97%, the CBD was completely seen in 89% of cases and only partially seen in 8%.[16]

From the Department of Internal Medicine II, Technical University of Munich, Munich, Germany.
Correspondence: Thomas Rösch, M.D., Department of Internal Medicine II, Technical University of Munich, Klinikum rechts der Isar, Ismaningerstr. 22, D-81675 München, Germany. e-mail: Thomas.Roesch@lrz.tu-muenchen.de

Finally, a true "gold standard" will never be available, and published data on visualization rates must rely on the examiner's opinion that the longitudinal and echo-free structure he or she sees on the ultrasound screen is really the CBD. Application of Doppler ultrasound would be of great help to differentiate the CBD from larger vessels (e.g., the common hepatic artery), but no systematic studies on the application of Doppler ultrasound in the correct visualization of the CBD have been published. Similarly, the completeness of visualization, that is, prepapillary, distal (i.e., intrapancreatic), and mid-to-proximal CBD up to the hepatic bifurcation, has never been systematically documented in the literature. The normal pancreas on EUS is visualized from the duodenum and the stomach; details have been described on numerous occasions.[22,23] Difficulties in differentiating the normal texture from signs of early and minor pancreatitis may arise[22] but are also beyond the scope of this report.

ENDOSCOPIC ULTRASONOGRAPHY IN THE DIAGNOSIS OF BILE DUCT STONES

Studies on the value of EUS in the diagnosis of CBD stones rely on ERCP as the gold standard, but even this modality can overlook stones. The true gold standard of sphincterotomy with CBD curettage by basket or balloon to be performed in all study patients was available only in some of the studies reviewed, and such an approach may now be unethical, especially in low-risk patients. The vast majority of patients included in the studies on EUS in CBD stones did not suffer from concomitant acute biliary pancreatitis. In some studies, however, between 8% and 24% of patients with acute pancreatitis were included,[14,17,19,24] but it is mostly not specified whether EUS was done during or after the attack, and the results are not analyzed separately for patients with and without pancreatitis. It therefore must be assumed that results are similar for both groups. An overview of these studies is presented in Table I.* Most are prospective, and the majority of the studies deal with patients who have a rather high prevalence of stones. The fact that—for the reasons of having a reliable gold standard—patients included must undergo ERCP, necessarily leads to a selection of patients in whom ERCP is indicated. Some of the studies reviewed included only "high-risk" patients[26,30]; others tried to stratify patients into different risk categories[13,20] and EUS seemed to fare similarly well in all groups, although patient numbers in subgroups were quite small. It is also evident from Table I, that the methodologic approaches of the various studies were quite different, with blindness to other information (clinical, laboratory, ultrasound) obviously not maintained in some of the studies. There are also striking differences between stone prevalence and the diagnostic accuracy of transabdominal ultrasound—from a 21% prevalence/68% accuracy[20] to a 52% prevalence/25% accuracy[24]—which also sheds some light not only on the quality of transabdominal ultrasonography but also on the likelihood of stones to be expected by the EUS examiner.

Stone size was often not recorded in the studies, or stones were obviously relatively large, often approximately 1 cm[15,24,29]; only three studies have reported a smaller mean stone size.[13,21,30] Furthermore, the delay between EUS and ERCP or surgery as gold standard is short (<24 hours) only in some studies*; others have 1 to 3 days' lag time,[20,21] but some articles report on very long delays[7,17,29,30] where the validity of the gold standard can be questioned, since spontaneous stone passage could have occurred in the meantime. Nevertheless, the homogeneity of results—greater than 90% accuracy rates—is striking throughout the studies cited.

Some studies include a variable but small percentage of patients who were negative on ERCP, but had stones found after sphincterotomy or surgical exploration. In the study by Amouyal et al.,[24] 2 of 40 patients were EUS positive, but ERCP negative, and stones were only found after sphincterotomy. Similarly, Norton and Alderson[14] found stones in 19 of 24 patients at ERCP but in 21 patients with EUS. In other studies, however, EUS was slightly inferior to ERCP[13,20] or to intraoperative cholangiography[30] in a direct comparison.

There are also data on the follow-up of EUS-negative patients who did not undergo ERCP. In one study published in French,[31] of 125 patients undergoing EUS prior to laparoscopic cholecystectomy, stones were detected by EUS in 21 cases, which were confirmed in 19 (ERCP was not performed in one). On the other hand, of the 104 patients in whom EUS was normal, three underwent ERCP with one intrahepatic stone being detected. Ninety-one of 92 patients with follow-up (mean 8.5 months) were symptom free, and none of them required further intervention. Whether these results justify the use of EUS as a first-line diagnostic test after transabdominal ultrasonography[21,27,32] is unclear. Until larger prospective outcome studies, especially in comparison with magnetic resonance cholangiopancreatography

*References 7, 13-15, 17, 19-21, 24-29.

*References 13-15, 19, 25, 27.

Table I. Results of endoscopic ultrasonography in the diagnosis of choledocholithiasis

Study	No. of patients	Design	Blindness	Stone prevalence	Stone size	Gold standard	Delay	Sensitivity	Specificity
Edmundowicz et al.[25] (1992)	20	Pro	No	20%	?	ERCP	Same day	75%	100%
Amouyal et al.[24] (1994)	62	Pro, Con	US	52%	59% >1 cm	ERCP 65% OP 35%	?	97%	100%
Shim et al.[20] (1995)	132	Pro, Con	No	21%	?	ERCP	Within 48 hr	93%*	?
Palazzo et al.[17] (1995)	422	Retro	No	43%	?	Surgery (185) ERCP (219)	Mean 15.6 days Mean 20.2 days	95% Concordance	98% 91%
Prat et al.[26] (1996)	119	Pro	Lab, US	66%	?	ERCP	Same day	93%	97%
Aubertin et al.[19] (1996)	50	Pro	?	24%	?	IOC/OP	Same day	100%	97%
Norton and Alderson[14] (1997)	50	Pro	?	48%	?	ERCP	Within 24 hr	88%	96%
Sugiyama and Atomi[15] (1997)	142	Pro	US	36%	Mean 10.5 mm	ERCP	Usually same day	96%	100%
Burtin et al.[27] (1997)†	68	Pro	No	50%	?	ERCP	Within 24 hr	100%	?
Canto et al.[13] (1998)	64	Pro, Con	Lab, US	31%	Mean 5.3-6.9 mm	ERCP	Same day	95%	98%
Montariol et al.[30] (1998)	240	Pro, Con	?	19%	Mean 5.4 mm	IOC	7 days	85%	93%
Polkowski et al.[28] (1999)‡	52	Pro, Con	Lab, US	68%	Mean 11 mm	ERCP	3 days	91%	100%
de Ledinghen et al.[29] (1999)§	43	Pro, Con	?	31%	44% <10 mm	ERCP/OP	Mean 4.5 days	100%	95%
Materne et al.[21] (2000)†§	50	Pro, Con	No	26%	2 to 12 mm, sludge	ERCP OP	Mean 1 day Mean 3 days	92%	95%
Lachter et al.[7] (2000)‖	50	Retro	No	64%	?	ERCP	Mean 31 days	97%	77%

Design: Pro = prospective; Retro = retrospective; Con = consecutive patients.
Blindness: EUS examiner blinded to simple diagnostic tests such as ultrasound (US) and/or laboratory data (Lab); if EUS is compared to another sophisticated technique (e.g., MRCP in ref. 6), this is not taken into account for blindness.
Gold standard: ERCP = endoscopic retrograde cholangiopancreatography; IOC = intraoperative cholangiography; OP = operative exploration.
Delay: Delay between EUS and gold standard.
*Results of EUS plus ultrasound.
†Different protocol, prospective study in patients with unclear cholestasis.
‡Comparative study with CT cholangiography.
§Comparative study with MRCP.
‖Only study performed with a linear instrument; also includes the authors' learning period.

Table II. Comparison of endoscopic ultrasonography and helical CT cholangiography (CTC) or magnetic resonance cholangiopancreatography (MRCP)

Study	No. of patients	Stone prevalence	EUS sensitivity	Specificity	MRCP sensitivity	Specificity	CTC sensitivity	Specificity
de Ledinghen et al.[29] (1999)	43	31%	100%	95%	100%	73%	—	—
Materne et al.[21] (2000)	50	26%	92%	95%	77%	97%	—	—
Nandi et al.[33] (1999; abstract)	25	16%	75%	100%	25%	94%	—	—
Polkowski et al.[28] (1999)	52	68%	91%	100%	—	—	85%	88%

Table III. Results of two prospective studies on the accuracy of endoscopic ultrasound in the diagnosis of CBD stones in acute biliary pancreatitis

Study	No. of patients	Stone prevalence	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Chak et al.[16] (1999)	36	75%	91%	100%	100%	95%
Sugiyama and Atomi[18] (1998)	35	68%	100%	100%	—	—

(MRCP) become available, this discussion is beyond the scope of this review.

Comparisons with other methods have also been published. EUS has been found to be significantly superior to conventional ultrasonography and computed tomography (CT),[15] which is not surprising, although the differences between EUS and helical CT cholangiography were less dramatic (Table II). The most relevant comparison, however, is that of EUS and MRCP. Results of comparative studies are presented in Table II, with two original articles[21,29] and one abstract[33] indicating EUS to be superior to MRCP; other abstracts used parameters too general for a detailed analysis of stones and strictures and other pathology.[34] In a decision analysis using data from the literature and decision tree software,[35] it was concluded that compared to prelaparoscopic ERCP, EUS and intraoperative cholangiography were unlikely to reduce overall costs unless their accuracy and success rates were greater than 90% and their procedural costs were less than 60% to 70% of those of ERCP.

Other intraluminal ultrasound techniques that are substantially more invasive have been reported in noncomparative series for the diagnosis of choledocholithiasis, namely, intraductal miniprobes,[36,37] which require ERCP, and laparoscopic ultrasonography, which of course requires laparoscopy, and is rarely indicated in acute pancreatitis. Laparoscopic ultrasound could be useful in the elective situation for diagnosing CBD stones during cholecystectomy, and there is a large body of literature comparing this with intraoperative cholangiography,[38,41] but comparative studies with preoperative imaging methods such as EUS and MRCP have yet to be reported.

ENDOSCOPIC ULTRASONOGRAPHY IN THE DIAGNOSIS OF BILE DUCT STONES IN ACUTE PANCREATITIS

Only two studies deal with the EUS diagnosis of CBD stones in the special situation of acute pancreatitis[16,18]; results are shown in Table III. Both studies have similarly small patient numbers—36[16] and 35[18]—and were performed prospectively, but consecutive patients were probably not included, especially in the multicenter study with the inclusion initially of only 38 patients from five major centers.[16] In only one study, the EUS examiner was said to be blinded to the results of laboratory tests and conventional ultrasound.[16] The inclusion of only patients who then underwent ERCP, which has to serve as gold standard, necessarily again introduced a bias toward selecting patients with a high likelihood of having stones. Although the selection criteria cited in both studies are different—reportedly all pancreatitis patients in one study[16] but only those with pathologic ultrasound findings and laboratory values in the other[18]—both have a similar and very high prevalence of stones in their populations, 72% in both studies, further indicating patient selection.

Therefore, evidence to recommend EUS as an accurate tool in diagnosing CBD stones in suspected

biliary pancreatitis in the acute setting is based on small patient numbers and a patient population selected to have a very high likelihood of stones. How EUS fares in a low- or intermediate-risk group in the setting of acute pancreatitis is therefore still unclear and rests on indirect comparisons with literature data on EUS in choledocholithiasis in general, mostly in patients without pancreatitis (see above). Whether the very low complication rate of EUS may be increased in acute pancreatitis, especially the severe forms with duodenal edema and obstruction, is not known.

Other studies deal with the detection of a possible biliary etiology in acute pancreatitis, after the acute attack has subsided. In one report,[42] out of 89 patients with acute pancreatitis (in 85% the first attack) who were prospectively examined during a 14-month period, 72% had evidence of cholelithiasis by conventional radiologic methods, and the remaining 18 patients were classified as "idiopathic" and underwent EUS, but at a later time point, when the pancreatitis had subsided, and not during the acute attack. EUS identified small gallbladder stones in 14 patients and small CBD stones in three.[42] This is a rather high prevalence of gallbladder stones overlooked on transabdominal ultrasound imaging (sensitivity of only 82%), and sheds some doubt on the quality of their transabdominal ultrasound. Other studies examining the value of EUS in the setting of acute relapsing pancreatitis are available in abstract form only.[43,44]

ENDOSCOPIC ULTRASONOGRAPHY OF THE PANCREAS IN ACUTE PANCREATITIS

EUS findings relevant to the pancreas itself described in acute pancreatitis are pancreatic enlargement, parenchymal heterogeneity, a grainy or coarse texture, gastroduodenal wall edema, and peripancreatic fluid in a study in which none of the patients had severe pancreatitis. Some of the parameters, however, seemed to correlate with length of hospital stay.[16] Pancreatic necrosis and extrapancreatic inflammatory spread were reported in the other paper cited earlier and some correlation with the CT grading of pancreatitis appeared.[18] Other studies are available only in abstract form.[45] It is clearly premature to recommend using EUS for the grading of the severity of acute pancreatitis until prospective comparative studies with contrast-enhanced CT are reported.

CONCLUSIONS

EUS appears to be a very accurate test for diagnosing CBD stones in a relatively large number of studies using a variety of methodologic approaches, mostly in patients with a moderate-to-high suspicion of gallstones, however. Whether these results can be transferred to patient groups with low stone prevalence, and to other examiners outside the centers of excellence, is not fully known. In the setting of acute pancreatitis, the same seems to be true, but the evidence is based on only two studies, each with a rather small number of patients. In our opinion, the biggest competitor for EUS is MRCP, and further comparative studies will shed some more light on the relative value and cost-effectiveness of both tests in the setting of acute biliary pancreatitis.

REFERENCES

1. Fölsch UR. The role of ERCP and sphincterotomy in acute biliary pancreatitis. Endoscopy 1998;30:A253-A255.
2. Nowak A, Marek TA, Nowakoska-Dulawa E, et al. Biliary pancreatitis needs endoscopic retrograde cholangiography with endoscopic spincterotomy for cure. Endoscopy 1998;30: A256-A259.
3. Neoptolemos JP, Carr-Locke DL, London NJ, et al. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet 1988;2:979-983.
4. Fan ST, Lai EC, Mok FP, et al. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med 1993;328:228-232.
5. Fölsch UR, Nitsche R, Ludtke R, et al. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. N Engl J Med 1997;336:237-242.
6. Nowak A, Nowakowska-Dulawa E, Marek TA, et al. Final results of the prospective, randomized, controlled study on endoscopic sphincterotomy versus conventional management in acute biliary pancreatitis [abstr]. Gastroenterology 1995;108: A380.
7. Lachter J, Rubin A, Shiller M, et al. Linear EUS for bile duct stones. Gastrointest Endosc 2000;51:51-54.
8. Giovannini M, Seitz JF. Endoscopic ultrasonography with a linear-type echoendoscope in the evaluation of 94 patients with pancreatobiliary disease. Endoscopy 1994;26:579-585.
9. Kochman ML, Elta GH, Bude R et al. Effectiveness of a linear-array ultrasound endoscope in the evaluation of suspected pancreatic disease [abstr]. Endoscopy 1994;26:825.
10. Rösch T, Classen M. Gastroenterologic Endosonography. Stuttgart-New York:Thieme, 1992.
11. Rösch T, Dittler HJ, Fockens P, et al. Major complications of endoscopic ultrasonography: Results of a survey of 42105 cases [abstr]. Gastrointest Endosc 1993;39:A341.
12. Matsumoto J. Endoscopic ultrasonography diagnosis gallbladder lesions. Endoscopy 1998;30(Suppl I):A124-A127.
13. Canto MI, Chak A, Stellato T, et al. Endoscopic ultrasonography versus cholangiography for the diagnosis of choledocholithiasis. Gastrointest Endosc 1998;47:439-443.
14. Norton SA, Alderson D. Prospective comparison of endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in the detection of bile duct stones. Br J Surg 1997;84:1366-1369.
15. Sugiyama M, Atomi Y. Endoscopic ultrasonography for diagnosing choledocholithiasis: A prospective comparative study with ultrasonography and computed tomography. Gastrointest Endosc 1997;45:143-146.

16. Chak A, Hawes RH, Cooper GS, et al. Prospective assessment of the utility of EUS in the evaluation of gallstone pancreatitis. Gastrointest Endosc 1999;49:599-604.
17. Palazzo L, Girollet P, Salemeron M, et al. Value of endoscopic ultrasonography in the diagnosis of common bile duct stones: Comparison with surgical exploration and ERCP. Gastrointest Endosc 1995;42:225-231.
18. Sugiyama M, Atomi Y. Acute biliary pancreatitis: The roles of endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography. Surgery 1998;124:14-21.
19. Aubertin JM, Levoir D, Bouillot JL, et al. Endoscopic ultrasonography immediately prior to laparoscopic cholecystectomy: A prospective evaluation. Endoscopy 1996;28:667-673.
20. Shim CS, Joo JH, Park CW, et al. Effectiveness of endoscopic ultrasonography in the diagnosis of choledocholithiasis prior to laparoscopic cholecystectomy. Endoscopy 1995;27:428-432.
21. Materne R, Van Beers BE, Gigot JF, et al. Extrahepatic biliary obstruction: Magnetic resonance imaging compared with endoscopic ultrasonography. Endoscopy 2000;32:3-9.
22. Wiersema MJ, Wiersema LM. Endosonography of the pancreas: Normal variation versus changes of early chronic pancreatitis. Gastrointest Endosc Clin North Am 1995;5:487-496.
23. Giovannini M. Endoscopic ultrasonography with a curved-array transducer: Normal echoanatomy of the retroperitoneum. Gastrointest Endosc Clin North Am 1995;5:523-528.
24. Amouyal P, Amouyal G, Levy P, et al. Diagnosis of choledocholithiasis by endoscopic ultrasonography. Gastroenterology 1994;106:1062-1067.
25. Edmundowicz SA, Aliperti G, Middleton WD. Preliminary experience using endoscopic ultrasonography in the diagnosis of choledocholithiasis. Endoscopy 1992;24:774-778.
26. Prat F, Amouyal G, Pelletier G, et al. Prospective controlled study of endoscopic ultrasonography and endoscopic retrograde cholangiography in patients with suspected common bile duct lithiasis. Lancet 1996;347:75-79.
27. Burtin P, Palazzo L, Canard JM, et al. Diagnostic strategies for extrahepatic cholestasis of indefinite origin: Endoscopic ultrasonography or retrograde cholangiography? Results of a prospective study. Endoscopy 1997;29:349-355.
28. Polkowski M, Palucki J, Regula J, et al. Helical computed tomographic cholangiography versus endosonography for suspected bile duct stones: A prospective blinded study in nonjaundiced patients. Gut 1999;45:744-749.
29. de Ledinghen V, Lecesne R, Raymond JM, et al. Diagnosis of choledocholithiasis: EUS or magnetic resonance cholangiography? A prospective controlled study. Gastrointest Endosc 1999;49:26-31.
30. Montariol T, Msika S, Charlier A, et al. Diagnosis of asymptomatic common bile duct stones: Preoperative endoscopic ultrasonography versus intraoperative cholangiography—a multicenter, prospective controlled study. Surgery 1998; 124:6-13.
31. Meduri B, Aubert A, Chiche R, et al. Laparoscopic cholecystectomy and lithiasis of the common bile duct: Prospective study on the importance of preoperative endoscopic ultrasonography and endoscopic retrograde cholangiography. Gastroenterol Clin Biol 1998;22:759-765.
32. Napoleon B. Role of endoscopic ultrasound in the diagnosis of cholestasis. Endoscopy 1998;30:A116-A119.
33. Nandi PS, Barnett JL, Nostrant TT, et al. A prospective blinded comparison of EUS and MRCP with ERCP in patients with suspected extrahepatic biliary disease [abstr]. Gastrointest Endosc 1999;49,4:AB95.
34. Fantin AC, Fretz C, Binek JS, et al. Comparison between magnetic resonance-cholangio-pancreatography (MRCP), endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography in diagnosing pancreatobiliary diseases [abstr]. Gastroenterology 1999;116:A8.
35. Sahai AV, Mauldin PD, Marsi V, et al. Bile duct stones and laparoscopic cholecystectomy: A decision analysis to assess the role of intraoperative cholangiography, EUS, and ERCP. Gastrointest Endosc 1999;49:334-343.
36. Ueno N, Nishizono T, Tamada K, et al. Diagnosing extrahepatic bile duct stones using intraductal ultrasonography: A case series. Endoscopy 1997;29:356-360.
37. Ohashi A, Ueno N, Tamada K, et al. Assessment of residual bile duct stones with use of intraductal US during endoscopic balloon sphincteroplasty: Comparison with balloon cholangiography. Gastrointest Endosc 1999;49:328-333.
38. Rijna H, Eijsbouts QA, Barkhof F, et al. Assessment of the biliary tract by ultrasonography and cholangiography during laparoscopic cholecystectomy: A prospective study. Eur J Ultrasound 1999;9:127-133.
39. Falcone RA, Fegelman EJ, Nussbaum MS, et al. A prospective comparison of laparoscopic ultrasound vs intraoperative cholangiogram during laparoscopic cholecystectomy. Surg Endosc 1999;13:784-788.
40. Catheline J, Rizk N, Champault G. A comparison of laparoscopic ultrasound versus cholangiography in the evaluation of the biliary tree during laparoscopic cholecystectomy. Eur J Ultrasound 1999;10:1-9.
41. Siperstein A, Pearl J, Macho J, et al. Comparison of laparoscopic ultrasonography and fluorocholangiography in 300 patients undergoing laparoscopic cholecystectomy. Surg Endosc 1999;13:113-117.
42. Liu CL, Lo CM, Chan JKF, et al. EUS for detection of occult cholelithiasis in patients with idiopathic pancreatitis. Gastrointest Endosc 2000;51:28-32.
43. Choi WB, Lee SK, Kim MH, et al. A clinical evaluation of EUS in the workup of idiopathic pancreatitis (IP) with comparison to CT and ERCP [abstr]. Gastrointest Endosc 1999: 49:AB89.
44. Catalano MF, Alcocer E, Geenen JE, et al. Diagnostic evaluation of patients with idiopathic recurrent pancreatitis (IRP): Role of endoscopic ultrasonography (EUS) [abstr]. Gastrointest Endosc 1998;47:AB142.
45. Schoefer M, Rathgeber A, Lang J, et al. Prognostic value of endoscopic ultrasound in acute pancreatitis [abstr]. Gastroenterology 1998;114:A495.

Timing of and Indications for Biliary Tract Surgery in Acute Necrotizing Pancreatitis

Bruce Schirmer, M.D.

Biliary tract surgery for acute necrotizing pancreatitis is indicated when the etiology of the pancreatitis is thought to be secondary to choledocholithiasis. This essentially constitutes the diagnosis of gallstone pancreatitis. For patients with other etiologies of acute pancreatitis, biliary tract surgery is normally not indicated. Patients with gallstone pancreatitis are grouped into those with mild and those with more severe forms of the disease when determining criteria for when to perform surgery.

The goal of surgical therapy for patients with gallstone pancreatitis is to remove the biliary calculi that have precipitated the attack of pancreatitis as well as the source for future calculi. This generally involves the following two steps: performing cholecystectomy and clearing the common bile duct of calculi. Surgery may be used to accomplish both steps, or endoscopic therapy (endoscopic retrograde cholangiopancreatography [ERCP] plus endoscopic sphincterotomy [ES]) may be used instead to clear the common bile duct.

Most patients with mild forms of the disease, defined as the presence of three or fewer Ranson's criteria,[1] will have little if any pancreatic necrosis. Although these patients generally fall outside the spectrum of disease discussed here, recommendations for timing and indications for biliary tract surgery will be included for this group.

Patients with mild acute gallstone pancreatitis should undergo cholecystectomy and, if needed, a procedure to clear the common duct of stones. The timing of cholecystectomy relative to the symptoms of pancreatitis is less important in mild forms of the disease. Patients will generally tolerate surgery well, the operation will be technically feasible in terms of intraoperative anatomy, and there will be no significant incidence of increased complications, prolongation of hospitalization, or conversion to open cholecystectomy in comparison to elective cholecystectomy.[2] Surgical treatment is indicated during the initial hospitalization and should not be delayed until a second hospitalization; otherwise, a significant percentage of patients for whom such a course is recommended will return to the hospital for unscheduled admission with a second episode of gallstone pancreatitis. Therefore, to avoid subjecting patients to the risks of a second attack of gallstone pancreatitis, surgical treatment is recommended during the first hospitalization.

Laparoscopic cholecystectomy is the treatment of choice for gallstone pancreatitis. Studies have shown that preoperative ERCP is not indicated in mild forms of the disease as most patients will have long since passed the common duct stone that initiated the attack of pancreatitis.[3] Routine preoperative ERCP in mild-to-moderate pancreatitis is associated with increased costs and prolonged hospitalization[4] along with increased complications[5,6] compared to selective postoperative ERCP and common duct stone extraction based on intraoperative cholangiographic findings. Intraoperative biliary imaging is therefore preferred in these patients to determine presence of persistent choledocholithiasis. This is currently most often performed by means of intraoperative cholangiography but can also be performed accurately by experienced surgeons using intraoperative ultrasonography.[7,8] Both imaging methods are accomplished by means of a laparoscopic approach.

Patients are candidates for surgical treatment as long as they do not have excessively severe comorbid medical conditions that would preclude safe induction of general anesthesia. Other than severe comorbid medical conditions, there are few if any contraindications to surgery. There are also now few contraindications to laparoscopic surgery other than severe intra-abdominal scarring from previous surgery, inability to safely tolerate a pneumoperitoneum, or unavailability of the equipment needed to perform the operation.

In patients who have acute gallstone pancreatitis with complicating pancreatic necrosis and more than

From the Department of Surgery, University of Virginia Medical Center, Charlottesville, Va.
Correspondence: Bruce D. Schirmer, M.D., University of Virginia Medical Center, Box 181, Department of Surgery, Charlottesville, VA 22908.

three Ranson's criteria present, the goal of surgical treatment is the same as for patients with mild disease. Choledocholithiasis should be addressed early in the course of the disease. Obstruction for more than 48 hours is associated with a greatly increased incidence of pancreatic necrosis.[9] ERCP and ES should be used if stones in the common bile duct appear to persist and the patient is not improving with conservative treatment.[10] In settings where ERCP is not available, surgical intervention is accompanied by increased morbidity and technical difficulty if performed in a setting where the acute disease process has not resolved.

Laparoscopic cholecystectomy is the treatment of choice for patients with severe forms of pancreatitis.[11] The operation should be performed near the end of the hospitalization, once the acute symptoms have resolved, assuming no surgical intervention has been needed earlier for the pancreatitis. Uhl et al.[12] showed that patients with necrotizing pancreatitis required a mean duration of 14 days between onset of symptoms and attempted laparoscopic cholecystectomy, with 62% of patients undergoing cholecystectomy successfully using a laparoscopic approach. These investigators noted an increased risk of infection when biliary surgery was performed before a 3-week wait in patients with extensive pancreatic necrosis.

Intraoperative cholangiography or ultrasonography are also indicated to rule out persistent choledocholithiasis at the time of cholecystectomy for severe pancreatitis, if ERCP has not been done. Should persistent choledocholithiasis be present, removal via intraoperative laparoscopic or open or postoperative endoscopic means are all acceptable approaches. Individual expertise should determine the best approach in any individual case.

Patients with acute gallstone pancreatitis resulting in pancreatic necrosis may require surgical intervention to treat the necrosis. In such situations the main goal of surgical therapy is debridement of pancreatic necrosis and elimination of intra-abdominal infection. However, the addition of a simultaneous cholecystectomy and cholangiography is often appropriate, based on the individual setting of degree of inflammation and the patient's condition intraoperatively. The surgeon should consider adding these procedures if they can be safely accomplished, as this avoids the need for a second operation when treating the biliary tract cause of the pancreatitis. Postoperative ERCP and sphincterotomy may be a better alternative in the setting of more severe inflammation when exploration of the biliary tree is indicated based on intraoperative cholangiographic findings, since intraoperative exploration of the biliary tree in such a setting may be associated with increased technical difficulty and a higher incidence of morbidity.

In elderly patients with gallstone pancreatitis who are at a high risk for surgical intervention and cholecystectomy, the majority of evidence in the literature suggests that ERCP and ES alone without subsequent cholecystectomy may suffice as adequate treatment. Welbourne et al.[13] showed that 48 patients with a median age of 78 years who underwent a technically adequate ES for gallstone pancreatitis and no subsequent cholecystectomy had no further attacks of pancreatitis after a mean follow-up of 26.9 months. Siegel et al.[14] treated 49 patients with ES without cholecystectomy, and none experienced recurrent pancreatitis with a mean follow-up of 48 months. Nineteen high-risk patients treated with ERCP and ES were followed; one required rehospitalization for acute biliary pancreatitis and six had recurrent pain without amylasemia. Extrapolation of this treatment approach to the nonelderly should be avoided. ERCP and ES were recently shown to reduce the incidence of recurrent pancreatitis but not late biliary complications in a group of 96 patients with a median age of 74 years (range 30 to 93 years). Thirty-one percent of patients required subsequent cholecystectomy.

In summary, patients with mild gallstone pancreatitis should undergo laparoscopic cholecystectomy with intraoperative biliary imaging during the initial hospitalization. Patients with more severe pancreatitis should also undergo these operations but at a time when the pancreatic inflammation has subsided. Urgent ERCP and ES are indicated in patients with severe pancreatitis in whom persistent choledocholithiasis is suspected. Elderly high-risk surgical candidates can be adequately treated in most cases with ERCP and ES alone.

REFERENCES

1. Ranson JHC, Rifkind KM, Roses DG, et al. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet 1974;138:69-77.
2. Tang E, Stain SC, Tang G, et al. Timing of laparoscopic surgery in gallstone pancreatitis. Arch Surg 1995;130:496-500.
3. Himal HS. Preoperative endoscopic retrograde cholangiopancreatography (ERCP) is not necessary in mild gallstone pancreatitis. Surg Endosc 1999;13:782-783.
4. Chang L, Los S, Stabile BE, et al. Preoperative versus postoperative endoscopic retrograde cholangiopancreatography in mild to moderate gallstone pancreatitis: A prospective randomized trial. Ann Surg 2000;231:82-87.
5. Srinathan SK, Barkun JS, Mehta SN, Meakins JL, Barkun AN. Evolving management of mild-to-moderate gallstone pancreatitis. J GASTROINTEST SURG 1998;2:385-390.
6. Sees DW, Martin RR. Comparison of preoperative endoscopic retrograde cholangiopancreatography and laparoscopic cholecystectomy with operative management of gallstone pancreatitis. Am J Surg 1997;174:719-722.
7. Barteau JA, Castro D, Arregui ME, et al. A comparison of intraoperative ultrasound versus cholangiography in the evaluation of the common bile duct during laparoscopic cholecystectomy. Surg Endosc 1995;9:490-496.

8. Stiegmann GV, Soper NJ, Filipi CJ, et al. Laparoscopic ultrasonography as compared with static or dynamic cholangiography at laparoscopic cholecystectomy. A prospective multicenter trial. Surg Endosc 1995;9:1269-1273.
9. Acosta JM, Rubio Galli OM, Rossi R, et al. Effect of duration of ampullary gallstone obstruction on severity of lesions of acute pancreatitis. J Am Coll Surg 1997;184:499-505.
10. Soetikno RM, Carr-Locke DL. Endoscopic management of acute gallstone pancreatitis. Gastrointest Endosc Clin N Am 1998;8:1-12.
11. Pellegrini CA. Surgery for gallstone pancreatitis. Am J Surg 1993;165:515-518.
12. Uhl W, Muller CA, Krahenbuhl L, Schmid SW, et al. Acute gallstone pancreatitis: Timing of laparoscopic cholecystectomy in mild and severe disease. Surg Endosc 1999;13:1070-1076.
13. Welbourne CR, Beckly DE, Eyre-Brook IA. Endoscopic sphincterotomy without cholecystectomy for gallstone pancreatitis. Gut 1995;37:119-120.
14. Siegel JH, Veerappan A, Cohen SA, Kasmin FE. Endoscopic sphincterotomy for biliary pancreatitis: An alternative to cholecystectomy in high-risk patients. Gastrointest Endosc 1994;40:573-575.

Noninvasive Imaging of the Biliary Ducts

Joseph T. Ferrucci, M.D.

The goal of biliary tract imaging in acute necrotizing pancreatitis is twofold: (1) to detect the presence of biliary duct dilatation and (2) to identify common duct stones. Obstructive dilatation of the biliary duct system may be an incidental sequela of inflammatory swelling of the head of the pancreas compressing the intrapancreatic portion of the distal common bile duct. In such cases the ducts may return to normal caliber as the inflammatory reaction subsides. More important, bile duct dilatation may be an indication of an obstructing distal common duct stone. Thus the primary focus of noninvasive biliary tract imaging in acute necrotizing pancreatitis is to identify the inciting distal common bile duct stones. However, not all common duct stones produce bile duct dilatation, and the demonstration of stones in nondilated bile ducts is a more demanding imaging task by all techniques.

CONVENTIONAL IMAGING: ULTRASONOGRAPHY AND COMPUTED TOMOGRAPHY

Conventional imaging of acute pancreatitis invariably includes both computed tomography to document and stage the severity of the pancreatic inflammatory response and right upper quadrant ultrasonography to assess the status of the gallbladder and biliary ducts. Both techniques are highly accurate in demonstrating biliary duct dilatation—common bile duct caliber 8 mm or larger (95% to 100%)—but are less effective in demonstrating common duct calculi (30% to 50%).[1-4] Both methods are more sensitive when biliary duct dilatation is present because the fluid bile is able to contrast with the solid stone material. Ultrasonography is less effective when choledochal stones are located far distally in the head of the pancreas, when there is overlying bowel gas, or when obese patient habitus degrades image quality. Moreover, ultrasonography remains a highly operator-dependent method, and the results are always influenced by the skill of the examiner.

CT scanning, while not the primary method for screening survey of the biliary ducts, can demonstrate common bile duct stones with approximately 50% sensitivity or better. Noncontrast, unenhanced CT techniques often used for survey study of cases of pancreatitis are also ideal for demonstrating duct stones. Most primary CBD stones are composed of calcium bilirubinate and show higher CT attenuation than the surrounding low-density bile column. Cholesterol stones containing calcium can also be clearly visualized. Modern CT scanners with helical acquisition can obtain slices in the 1 to 2 mm thickness range affording excellent spatial resolution.[5] The newest generation of multislice CT scanners can now acquire full abdominal and pancreatic scans at high resolution in a matter of a single breath-hold (i.e., 10 to 15 seconds). Clinical results with this newest generation of CT technology are not yet available, but the accuracy for survey detection of common bile duct stones should increase further.

NEW METHODS

In instances where conventional ultrasound and CT imaging are nondiagnostic, newer noninvasive methods developed within the past several years, especially magnetic resonance cholangiopancreatography (MRCP) and CT cholangiography, have proved increasingly useful.

Magnetic Resonance Cholangiopancreatography

MRCP has evolved during the past several years as the new "gold standard" for noninvasive global imaging of the biliary and pancreatic ducts.[6-10] MRCP enjoys a broad range of indications, high accuracy, noninvasiveness, and near-universal availability on all modern MRI scanners. The basic imaging principle underlying MRCP is that body fluids such as bile and pancreatic secretions exhibit high signal intensity on heav-

From the Department of Radiology, Boston Medical Center, Boston University School of Medicine, Boston, Mass.
Correspondence: Joseph T. Ferrucci, M.D., Professor and Chairman, 88 East Newton St., Boston, MA 02118. e-mail: joseph.ferrucci@bmc.org

ily T_2-weighted magnetic resonance sequences (i.e., they appear white), whereas background tissues generate little signal (i.e., they appear dark). Fluids in static structures such as ducts or cysts can be selectively displayed as white on a black background with an overall appearance simulating the features of a direct radiographic cholangiopancreatogram. An added advantage of MRCP over endoscopic retrograde cholangiopancreatography (ERCP) is that duct morphology including adjacent cystic structures is demonstrated in its native or resting state more accurately depicting the native caliber of the duct. The vagaries of overdistention and underdistention so often occurring during clinical ERCP injections are thus avoided at MRCP.

Interpretation of magnetic resonance images follows basic principles of radiographic interpretation used during ERCP in terms of duct caliber, dilatation, filling defects (calculi), and extraductal collections of fluid (cysts, leaks, diverticula, etc.). Duct caliber is accurately depicted in nearly 100% of cases, whereas strictures appear as focal areas of narrowing or signal void with varying degrees of proximal dilatation.[6-10] Calculi are shown as localized filling defects within the high signal intensity of bile in both the biliary ducts and the gallbladder itself. The sensitivity of MRCP in diagnosing choledocholithiasis exceeds 90%.[7-14] Problems in detection occur mainly with small stones or gravel less than 3 mm in size. (It is noteworthy, however, that this is a similar failing of radiographic ERCP interpretation.) Experienced radiologists now agree that MRCP detection of common bile duct stones requires inspection of both the reformatted maximum intensity projection images as well as review of the source image data in all cases.[12-14] Pitfalls in the diagnosis of common bile duct stones include confusion with other intraluminal filling defects such as intraductal tumor, blood clot, gas bubble, or image artifact from previous cholecystectomy metallic clips.

MRCP techniques continue to improve with newer, faster scanners, especially in nonuniversity settings. With the most advanced scanners, the examination takes less time than moving the patient onto the scanning table. The present clearest indication for MRCP is following inconclusive ultrasound or CT imaging and failed or incomplete ERCP.[11]

CT Cholangiography

CT cholangiography is a new advanced application of CT scanning using modern helical (and the newest multislice) scanners to obtain ultrathin 1 mm and 2 mm slices allowing three-dimensional image reconstructions of ductal anatomy. Added bile duct contrast enhancement is obtained by the administration of contrast material, which exploits the sensitivity of CT attenuation to produce high-contrast detail within the biliary duct system. Early investigators used intravenous cholangiographic contrast material with good results. More recently the familiar oral cholecystographic contrast agent iopanoic acid (Telepaque, Winthrop) has been employed with equally good results and is more favored because of its greater safety profile. As with the traditional oral cholecystogram, the oral dosage is given the evening before the study, and the scan data containing the iodine-enhanced bile is reformatted with three-dimensional maximum intensity projection and shaded surface display renderings to produce familiar projectional images of the biliary tract.[15,16] This technique does have the limitation of requiring normal liver function, that is, the absence of significant biliary tract obstruction. Similarly there is no depiction of the pancreatic ducts. For these reasons CT cholangiography is still a less robust method than MRCP.

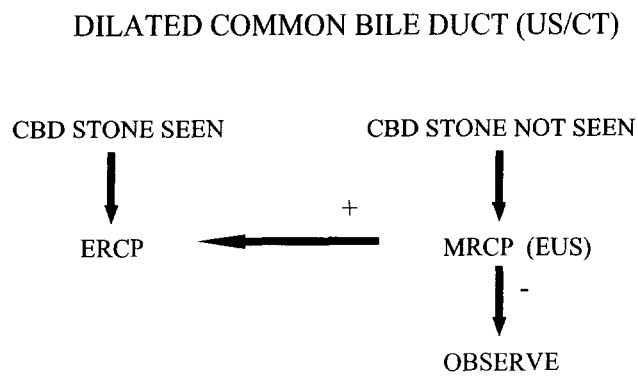

Fig. 1. Imaging algorithm.

CONCLUSION

The noninvasive imaging techniques of conventional ultrasound and CT scanning and the new methods of MRCP and CT cholangiography have advanced rapidly during the past decade in terms of availability, speed, and accuracy. In the vast majority of patients, the presence of common duct dilatation and the presence or absence of obstructing common bile duct stones can be determined by these noninvasive imaging methods (Fig. 1). When these techniques are available, the need for invasive diagnostic endoscopy should be minimized. Endoscopic techniques with their inherent cost and risk should increasingly be reserved only to guide therapeutic maneuvers.[17]

REFERENCES

1. Jeffrey RB, Federle MP, Laing FC, et al. Computed tomography of choledocholithiasis. AJR Am J Roentgenol 1983;140: 1179-1183.

2. Laing FC, Jeffrey RB, Wing VW. Improved visualization of choledocholithiasis by sonography. AJR Am J Roentgenol 1984;143:949-952.
3. Mitchell SE, Clark RA. A comparison of computed tomography and sonography in choledocholithiasis. AJR Am J Roentgenol 1984;142:729-733.
4. Cronan JJ. US diagnosis of choledocholithiasis: A reappraisal. Radiology 1986;161:133-134.
5. Neitlich JD, Topazian M, Smith RC, et al. Detection of cholelithiasis: Comparison of unenhanced helical CT and endoscopic retrograde cholangiopancreatography. Radiology 1997;203:753-757.
6. Barish MA, Yucel EK, Ferrucci JT. Magnetic resonance cholangiopancreatography. N Engl J Med 1999;341:258-264.
7. Soto JA, Barish MA, Yucel EK, et al. Pancreatic duct: MR cholangiopancreatography with a three-dimensional fast spin-echo technique. Radiology 1995;196:459-464.
8. Barish MA, Yucel EK, Soto JA, et al. MR cholangiopancreatography: Efficacy of three-dimensional turbo spin-echo technique. AJR Am J Roentgenol 1995;165:295-300.
9. Barish MA, Soto JA. MR cholangiopancreatography: Techniques and clinical applications. AJR Am J Roentgenol 1997;169:1295-1303.
10. Fulcher AS, Turner MA, Capps GW, et al. Half-Fourier RARE MR cholangiopancreatography: Experience in 300 subjects. Radiology 1998;207:21-32.
11. Soto JA, Barish MA, Chuttani R, et al. MR cholangiopancreatography after unsuccessful or incomplete ERCP. Radiology 1996;199:91-98.
12. Guibaud L, Bret PM, Rienhold C, et al. Bile duct obstruction and choledocholithiasis: Diagnosis with MR cholangiography. Radiology 1995;197:109-115.
13. Chan YL, Chan ACW, Lam WWM, et al. Choledocholithiasis: Comparison of MR cholangiopancreatography and endoscopic retrograde cholangiopancreatography. Radiology 1996; 200:85-89.
14. Regan F, Fradin J, Khazan R, et al. Choledocholithiasis: Evaluation with MR cholangiography. AJR Am J Roentgenol 1996;167:1441-1445.
15. Soto JA, Velez SM, Guzman J. Choledocholithiasis: Diagnosis with oral-contrast–enhanced CT cholangiography. AJR Am J Roentgenol 1999;172:943-948.
16. Caoili EM, Paulson EK, Heyneman LE, et al: Helical CT cholangiography with three-dimensional volume rendering using an oral biliary contrast agent: Feasibility of a novel technique. AJR Am J Roentgenol 2000;174:487-492.
17. Deviere J, Matos C, Cremer M. The impact of magnetic resonance cholangiopancreatography on ERCP. Gastrointest Endosc 1999;50:136-140.

The Clinical Problem of Biliary Acute Necrotizing Pancreatitis: Epidemiology, Pathophysiology, and Diagnosis of Biliary Necrotizing Pancreatitis

Chris E. Forsmark, M.D.

EPIDEMIOLOGY

In most countries, gallstones are the most common cause of acute pancreatitis. In the United States, Western Europe, and Asia, gallstones account for between one third and two thirds of cases, with an average of 40 to 50%.[1-4] There does appear to be substantial regional variation within countries as well as between countries. In some studies from areas of high prevalence of alcohol abuse, alcoholism may account for up to three fourths of all cases of acute pancreatitis.[3] The frequency of gallstone pancreatitis parallels the frequency of gallstones, being most common in women between 50 and 70 years of age.[2,4] The incidence of acute gallstone pancreatitis has not been carefully studied but varies inversely with the overall prevalence of alcohol abuse within the population being studied. In data from the United Kingdom, the overall incidence of acute pancreatitis has been rising from less than 100 cases per million population in the 1960s to as high as 750 cases per million in the 1980s.[1,5] The contribution of biliary pancreatitis to that rise in incidence is, however, unknown. In the United States, acute pancreatitis accounted for more than 124,000 hospital admission in 1987 and 911,000 office visits.[6] In a more recent analysis from 1999, the number of cases of acute pancreatitis requiring hospital admission in the United States is somewhere between 166,000 and 252,000.[7] One can only estimate the contribution of biliary pancreatitis to these formidable numbers but based on most estimates, biliary pancreatitis would probably account for 40% to 50%. If one includes pancreatitis due to microlithiasis, this number would probably be higher. Acute biliary pancreatitis is a recurrent disease in the absence of definitive therapy; relapse rates of 30% are commonly seen in those with the gallbladder left in situ.[8,9]

Studies of outcome and severity in patients with acute biliary pancreatitis are limited in that the vast majority report selected patients seen mainly at referral centers. Most studies would suggest, however, that patients with acute biliary pancreatitis are no more likely to develop clinically severe pancreatitis than patients with other etiologies of acute pancreatitis. In one study from the United Kingdom comprising a relatively unbiased population, clinically severe disease developed in 28% of patients admitted with acute gallstone pancreatitis, compared to 24% in those with acute alcoholic pancreatitis and 26% of those with other forms of acute pancreatitis.[10] Patients with acute biliary pancreatitis are at much greater risk of developing concomitant cholangitis compared to other forms of acute pancreatitis. Cholangitis appears to develop in approximately 6% to 10% of patients with acute biliary pancreatitis and causes an increase in both mortality and morbidity rates.[10-12]

The mortality rate from acute biliary pancreatitis from the study mentioned previously[10] was 8.1%, as compared to 4.1% in those with acute alcoholic pancreatitis and 14.5% of those with other forms of acute pancreatitis (differences not statistically significant). This mortality rate closely approximates the mortality from the placebo arms of studies evaluating therapy for acute biliary pancreatitis, which averages approximately 6%.[11,13-18] These data may still reflect a biased selection of patients; in one recent study of hospital admission for all forms of acute pancreatitis in the United States, the mortality rate was only 1.8% to 2.6%.[7]

There are far fewer data on the incidence of pancreatic necrosis in patients with acute biliary pancreatitis. In one study, pancreatic necrosis or abscess developed in 5.4% of those with acute gallstone pancreatitis compared to 7.6% of those with acute alcoholic pancreatitis and 12.7% of those with other forms of acute pancreatitis.[10] Other studies have also not documented any substantial differences in the rate of development of necrosis in patients with acute biliary

From the Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Florida, Gainesville, Fla. Correspondence: Chris E. Forsmark, M.D., Associate Professor of Medicine, Chief of Endoscopy, University of Florida, P.O. Box 100214, Gainesville, FL 32610.

pancreatitis compared to other etiologies. It is also clear from many studies that the presence of pancreatic necrosis is one predictor of increased morbidity and mortality in these patients but that the presence of necrosis is not invariably associated with a worse outcome.

PATHOPHYSIOLOGY

The pathophysiology of acute biliary pancreatitis remains unknown. Three major hypotheses continue to be debated. The suggestion by Opie almost 100 years ago that a common channel of the biliary and pancreatic ducts is important in causation remains central to most hypotheses of pathogenesis. These theories include the following: (1) an obstructing stone at the ampulla allows bile to reflux into the pancreatic duct; (2) an obstructing stone at the ampulla produces pancreatic duct hypertension; and (3) reflux of duodenal contents into the pancreatic duct occurs after passage of the stone through the disrupted sphincter mechanism. These theories are not mutually exclusive. All of these theories require passage or impaction of a gallstone. Numerous studies have demonstrated this event. Gallstones can be recovered from the feces in 90% of patients with gallstone pancreatitis compared to 10% to 15% of patients with symptomatic gallstones without pancreatitis.[19] Patients undergoing urgent surgery have a much higher incidence of common bile duct stones than those undergoing surgery later in their course (as high as 78% vs. 3% to 33%).[14,15,20,21] A stone actually impacted at the ampulla can be seen in up to 25% if surgery[15] or endoscopic retrograde cholangiopancreatography (ERCP)[18] is undertaken urgently, but far less commonly if evaluated later. These data suggest that the majority of patients pass the offending stone into the duodenum spontaneously. There are some data that those with residual or persistent common bile duct stones are at higher risk of morbidity and are more likely to have a severe attack of pancreatitis or die from the attack, suggesting repeated obstruction of the common channel may predispose to more severe pancreatitis. Residual or persistent common bile duct stones are frequently seen in those who die of biliary pancreatitis.[22,23] This has led some to propose a two-step model of pathogenesis, wherein repeated obstruction of the common channel leads to more extensive or severe pancreatitis.[24] These patients with residual or persisting common bile duct stones are certainly at higher risk of concomitant cholangitis with associated increased morbidity and mortality.

Those patients with gallstones who develop biliary pancreatitis have anatomic features that result in a predisposition to allow a gallstone to reach the common bile duct and affect the pancreatic duct. These predisposing features include more and smaller gallstones (allowing more opportunity for appropriately sized gallstones to reach the common channel), a wider cystic duct (allowing easier access for the stones), a wider main bile duct, an increased pancreaticobiliary angle, and a physical common channel.[25] All of these features make it more likely that a gallstone will reach the common channel and produce biliary pancreatitis.

The specific mechanisms by which the passage or impaction of a gallstone within the common channel actually causes acute pancreatitis are not known. According to animal models, there is clearly activation of pancreatic digestive enzymes within the acinar cell and pancreatic duct. Some have suggested that the primary event is a block in enzyme secretion, followed by colocalization of digestive proenzymes and lysosomes within the acinar cell, followed by activation of these enzymes.[26] It would seem most likely that trypsinogen is activated first, with subsequent activation of other digestive enzymes. The release of these activated digestive enzymes into and around the pancreatic parenchyma could certainly lead to autodigestion and necrosis. There is also evolving data that derangements in the pancreatic microcirculation are an important contributor to necrosis through an ischemic mechanism.[27] This local injury is followed, in severe cases, by activation of the systemic immune response syndrome and a cytokine cascade. These are responsible for the distant complications of severe acute pancreatitis. We have thus far failed, however, to identify the principal molecular events that produce acute biliary pancreatitis.

DIAGNOSIS OF ACUTE NECROTIZING BILIARY PANCREATITIS

The diagnostic approach can be separated into three serial goals: (1) diagnose acute pancreatitis and differentiate it from other abdominal conditions that could mimic acute pancreatitis; (2) differentiate biliary pancreatitis from other forms of acute pancreatitis; and (3) diagnose the presence or absence of necrosis. The diagnosis of acute pancreatitis is generally considered to be based on the presence of compatible signs and symptoms and elevations in serum amylase or lipase. Many other diseases can mimic not only some of the signs and symptoms of acute pancreatitis but also the elevations in amylase and lipase.[28] These include acute cholecystitis, biliary obstruction in the absence of acute pancreatitis, intestinal perforation, intestinal ischemia or infarction, and intestinal obstruction among others. These signs and symptoms and laboratory abnormalities are therefore not en-

tirely specific; neither are they perfectly sensitive. A number of postmortem studies note that 30% to 40% of patients who die of acute pancreatitis do not have the diagnosis established before death.[23,29,30] Clinicians most commonly missed making the diagnosis in these patients because the presentation was atypical (abdominal pain was not a major feature or other conditions masked the presence of pain [e.g., coma]).

Imaging studies are quite helpful in making a diagnosis of acute pancreatitis. Ultrasonography in particular plays a seminal role in the diagnosis of biliary pancreatitis but carries an overall sensitivity of 67% and a specificity of near 100% in the diagnosis of acute pancreatitis.[31] Computed tomography remains the most reliable method of diagnosing acute pancreatitis. Results of CT may occasionally be normal in those with mild disease but are invariably positive in more severe acute pancreatitis.[32] CT is useful both in establishing the diagnosis of acute pancreatitis and in differentiating it from other abdominal catastrophes that may mimic acute pancreatitis.

The differentiation of biliary pancreatitis from other forms of pancreatitis is based on a combination of serum tests and imaging tests. A number of studies have evaluated serum transaminases, serum alkaline phosphatase, gamma glutamyl transpeptidase, and serum bilirubin.[31,33-35] Each study chose slightly different cutoffs for these values. Obviously the higher the cutoff chosen the greater the specificity and the worse the sensitivity. Equally obvious, multiple abnormalities would seem to be more specific than isolated abnormalities of one laboratory test. It is difficult, however, to define a specific cutoff or a specific test as preferred. A recent meta-analysis of these studies reached the conclusion that elevation in alanine aminotransferase (ALT) the most clinically useful parameter.[36] They concluded that a threefold elevation in serum ALT (>150 IU/L) is 95% specific for a diagnosis of acute biliary pancreatitis. This is, unfortunately, only 48% sensitive. Aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin were all inferior diagnostic tests in this analysis. Other studies, however, have concluded that a cutoff of ALT or AST greater than 60 IU/L[34] or greater than 75 IU/L reaches acceptable sensitivity and specificity.[37]

Serum tests are not used in isolation to diagnose biliary pancreatitis; they should be combined with imaging studies. Ultrasound is the most useful imaging test and will detect cholelithiasis in 70% to 80% of those with acute biliary pancreatitis.[33,35] Repeated sonograms may occasionally show gallstones in those with an initial normal ultrasound scan or those in whom the initial ultrasound is limited by overlying bowel gas.[37,38] Ultrasonography can detect only a small fraction of common bile duct stones. A combination of abnormalities in serum tests and ultrasound images was found to be 95% sensitive and 100% specific in one study that combined both.[35] Computed tomography is not generally required for the detection of gallstones. It is inferior to ultrasound in detecting cholelithiasis and choledocholithiasis.[35] The use of noncontrast CT for the detection of choledocholithiasis shows some promise; in one study it demonstrated a sensitivity of 88% and a specificity of 97%.[39] Similarly the use of CT cholangiography may improve the diagnosis of choledocholithiasis with similar sensitivities and specificities.[40] Magnetic resonance cholangiopancreatography continues to evolve and we may expect improved accuracy with this technique as well.[41] Finally, endoscopic ultrasonography is highly sensitive for both cholelithiasis and choledocholithiasis.[42] The "gold standard" to which these tests are compared is usually ERCP. Thankfully, ERCP is rarely needed to reach a diagnosis of gallstone pancreatitis, although it may have important therapeutic contributions. The clinician is obviously interested in identifying the minority of patients with a residual or persistent stone in the common bile duct. Persistently elevated liver chemical values or a persistently dilated bile duct may assist in determining this, particularly if liver chemical values remain elevated or rise after 48 hours. The presence of cholangitis would also imply persistent choledocholithiasis. Similarly, a visible common bile duct stone on one of the preceding imaging modalities may make the determination. This may be particularly important in patients with severe gallstone pancreatitis or necrotizing gallstone pancreatitis, when attempts to clear the duct of stones may be undertaken, either to treat or prevent cholangitis or to attempt to minimize other complications associated with severe gallstone pancreatitis. We may certainly expect that our approach to these patients in the future will use these evolving imaging techniques to select patients with residual or persistent common bile duct stones who would be expected to reap the most benefit from ERCP with stone extraction.

The final step of the diagnostic algorithm mentioned earlier is the documentation of pancreatic necrosis. At the moment, dynamic CT is considered the gold standard. Areas of nonenhancement correlate, in a general way, to areas of pancreatic necrosis. It is worth repeating that the presence of necrosis does not always correspond to a clinically severe attack. In one study the positive predictive value of necrosis on CT for a clinically severe attack was only 59%.[43] In some studies the accuracy of CT is less than a multiple-factor scoring system (Imrie score) in predicting clinical severity.[44] Nonetheless, CT remains the only noninvasive method of quantifying pancreatic necrosis. In the largest study to date, the corre-

spondence between CT findings of necrosis and the presence of necrosis at surgery was 92%.[45] The risks of dynamic CT are probably low, but at least some investigators have noted worsening pancreatic necrosis in animal models given intravenous contrast injection. There is as yet no evidence that this occurs in humans.

REFERENCES

1. Thomson SR, Hendry WS, McFarlane GA, Davidson AI. Epidemiology and outcome of acute pancreatitis. Br J Surg 1987;74:398-401.
2. Imrie CW, Whyte AS. A prospective study of acute pancreatitis. Br J Surg 1975;62:490-494.
3. Ranson JHC, Rifkind KM, Turner JW. Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis. Surg Gynecol Obstet 1976;143:209-219.
4. Blamey SL, Imrie CW, O'Neill J, et al. Prognostic factors in acute pancreatitis. Gut 1984;25:1340-1346.
5. Wilson C, Imrie CW. Changing patterns of incidence and mortality from acute pancreatitis in Scotland, 1961-1985. Br J Surg 1990;77:731-734.
6. Go VLW, Everhart JE. Pancreatitis. In Everhart JE, ed. Digestive Diseases in the United States: Epidemiology and Impact. US Department of Health and Human Services, Public Health Service, National Institutes of Health. Washington, DC: US Government Printing Office, 1994, NIH Publication No. 94-1447, pp 691-712.
7. Grendell JH. Clinical and economic impact of acute pancreatitis in the United States [abstr]. Pancreas 1999;19:422.
8. Trapnell JE, Duncan EHL. Patterns of incidence in acute pancreatitis. Br Med J 1975;2:179-183.
9. Burch JM, Feliciano DV, Mattox KL, Jordan GL. Gallstone pancreatitis. Arch Surg 1990;125:853-860.
10. Winslet M, Hall C, London NJM, Neoptolemos JP. Relationship of diagnostic serum amylase levels to aetiology and severity of acute pancreatitis. Gut 1992;33:982-986.
11. Fan S-T, Lai ECS, Mok FPT, et al. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med 1993;328:228-232.
12. Neoptolemos JP, Carr-Locke DL, Leese T, James D. Acute cholangitis in association with acute pancreatitis: Incidence, clinical features and outcome in relation to ERCP and endoscopic sphincterotomy. Br J Surg 1987;74:1103-1106.
13. MRC Multicentre Trial. Death from acute pancreatitis. Lancet 1977;2:632-635.
14. Stone HH, Fabian TC, Dunlop WE. Gallstone pancreatitis: Biliary tract pathology in relation to time of operation. Ann Surg 1981;194:305-310.
15. Kelly TR, Wagner DS. Gallstone pancreatitis: A prospective randomized trial of the timing of surgery. Surgery 1988; 104:600-605.
16. Neoptolemos JP, Carr-Locke DL, London NJ, et al. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet 1988;2:979-983.
17. Folsch UR, Nitsche R, Ludrke R, et al. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. N Engl J Med 1997;336;237-242.
18. Nowak A, Nowakowska-Dulaw E, Marek TA, Rybicka J. Final results of the prospective, randomized, controlled study on endoscopic sphincterotomy versus conventional management in acute biliary pancreatitis [abstr]. Gastroenterology 1995; 108:A380.
19. Acosta JM, Ledesma CL. Gallstone migration as a cause of acute pancreatitis. N Engl J Med 1974;290:484-487.
20. Acosta JM, Pellegrini CA, Skinner DB. Etiology and pathogenesis of acute biliary pancreatitis. Surgery 1980;88:118-125.
21. Armstrong CP, Taylor TV, Jeacock J, et al. The biliary tract in patients with acute gallstone pancreatitis. Br J Surg 1985; 72:551-555.
22. Wilson C, Imrie CW, Carter DC. Fatal acute pancreatitis. Gut 1988;29:782-788.
23. Corfield AP, Cooper MJ, Williamson RCN. Acute pancreatitis, a lethal disease of increasing incidence. Gut 1985;26:724-729.
24. Neoptolemos JP. The theory of the "persisting" common bile duct stones in severe gallstone pancreatitis. Am R Coll Surg Engl 1989;71;326-331.
25. Kelly TR. Gallstone pancreatitis: Local predisposing factors. Ann Surg 1984;200:479-484.
26. Saluja A, Saluja M, Vill A, et al. Pancreatic duct obstruction in rabbit causes digestive zymogen and lysosomal colocalization. J Clin Invest 1989;84:1260-1266.
27. Klar E, Messmer K, Warshaw AL, Herfarth C. Pancreatic ischemia in experimental acute pancreatitis: Mechanism, significance, and therapy. Br J Surg 1990;77:1205-1210.
28. Steinberg WM, Goldstein SS, Davis ND, et al. Diagnostic assays in acute pancreatitis: A study of sensitivity and specificity. Ann Intern Med 1985;102:576-580.
29. Wilson C, Imrie CW. Deaths from acute pancreatitis: Why do we miss the diagnosis so frequently? Int J Pancreatol 1988;3:273-281.
30. Lankisch PG, Schirren CA, Kunze E. Undetected fatal acute pancreatitis: Why is the disease so frequently overlooked? Am J Gastroenterol 1991;86:322-326.
31. Neoptolemos JP, Hall AW, Finlay DF, et al. The urgent diagnosis of gallstones in acute pancreatitis: A prospective study of three methods. Br J Surg 1984;71:230-233.
32. Balthazar EJ. CT diagnosis and staging of acute pancreatitis. Radiol Clin North Am 1989;27:19-37.
33. Neoptolemos JP, London N, Bailey I, et al. The role of clinical and biochemical criteria and endoscopic retrograde cholangiopancreatography in the urgent diagnosis of common bile duct stones in acute pancreatitis. Surgery 1987;100:732-742.
34. Mayer AD, McMahon MJ. Biochemical identification of patients with gallstones associated with acute pancreatitis on the day of admission to hospital. Ann Surg 1985;201:68-75.
35. Wang SS, Lin XZ, Tsai YT, et al. Clinical significance of ultrasonography, computed tomography, and biochemical tests in the rapid diagnosis of gallstone-related pancreatitis: A prospective study. Pancreas 1988;3:153-158.
36. Tenner S, Dubner H, Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: A meta-analysis. Am J Gastroenterol 1994;89:1863-1866.
37. Ros E, Navarro S, Bru C, et al. Occult microlithiasis in "idiopathic" acute pancreatitis: Prevention of relapses by cholecystectomy or ursodeoxycholic acid therapy. Gastroenterology 1991;101:1701-1709.
38. Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. N Engl J Med 1992;326:589-593.
39. Neitlich JD, Topazian M, Smith RC, et al. Detection of choledocholithiasis: Comparison of unenhanced helical CT and endoscopic retrograde cholangiopancreatography. Radiology 1997;203:753-757.
40. Soto JA, Velez SM, Guzman J. Choledocholithiasis: Diagnosis with oral-contrast-enhanced CT cholangiography. AJR Am J Roentgenol 1999;172:943-948.

41. Bearcraft PW, Lomas DJ. Magnetic resonance cholangiography. Gut 1997;41:135-137.
42. Liu CL, Lo CM, Chan JK, et al. EUS for detection of occult cholelithiasis in patients with idiopathic pancreatitis. Gastrointest Endosc 2000;51:28-32.
43. London NJM, Leese T, Lavelle JM, et al. Rapid-bolus contrast-enhanced dynamic computed tomography in acute pancreatitis: A prospective study. Br J Surg 1991;78:1452-1456.
44. London NJM, Neoptolemos JP, Lavelle J, et al. Contrast-enhanced abdominal computed tomography scanning and prediction of severity of acute pancreatitis: A prospective study. Br J Surg 1989;76:268-272.
45. Block S, Maier W, Bittner R, et al. Identification of pancreas necrosis in severe acute pancreatitis: Imaging procedures versus clinical imaging. Gut 1986;27:1035-1042.

Laparoscopic Approach to the Biliary Tract in Acute Necrotizing Pancreatitis

Nathaniel J. Soper, M.D.

Gallstones are the most common cause of acute pancreatitis in North America. The pathophysiology of gallstone pancreatitis involves transient or persistent obstruction of the ampulla of Vater by a gallstone and nearly always is associated with an intact gallbladder containing gallstones. The spectrum of severity of pancreatitis ranges from mild edematous pancreatitis that quickly resolves spontaneously to severe life-threatening pancreatitis with pancreatic necrosis and infection. There are numerous controversial issues in the management of acute necrotizing pancreatitis (ANP), not the least of which is the role of laparoscopic therapy.

The timing of surgical intervention and cholecystectomy for gallstone pancreatitis has evolved considerably over the past few decades. Delayed cholecystectomy (at a second admission 6 to 8 weeks later) has been supplanted by operation during the initial admission after the acute manifestations of pancreatitis have resolved.[1,2] This approach has reduced the likelihood of recurrent pancreatitis and diminished the total duration of hospitalization. Urgent operation within 48 hours of admission for ANP has been shown to worsen outcome and should be avoided.[3] Although laparoscopic cholecystectomy has now replaced open cholecystectomy as the "gold standard" of therapy for patients with symptomatic gallstones, the well-established principles described above still apply to patients with gallstone pancreatitis. Several groups[4-8] have now shown that laparoscopic cholecystectomy is safe and effective for the treatment of patients with gallstone pancreatitis.

Increased inflammatory conditions around the gallbladder and porta hepatis may be found in some of these patients, but in our experience this has not led to increased complications or a higher rate of conversion to open operation. Early in the evolution of laparoscopic cholecystectomy, preoperative endoscopic retrograde cholangiopancreatography (ERCP) was used liberally to "clear the bile duct" prior to laparoscopy. However, with the development of laparoscopic techniques for exploring the bile duct and improved expertise in endoscopic clearance of the duct by ERCP, the role of ERCP has again become more selective. Preoperative ERCP is reserved for patients with severe or unremitting pancreatitis, cholangitis, jaundice, or a definite bile duct stone that has been visualized sonographically. Patients with mild biliary pancreatitis undergo laparoscopic cholecystectomy during the index admission once the pancreatitis has subsided clinically. The aim is to perform laparoscopic cholecystectomy the day before the patient's anticipated discharge.

After decompressing the biliary system by ERCP with sphincterotomy, patients with ANP are managed expectantly. Intravenous antibiotics, total parenteral nutrition, and analgesics are routinely used until the patient improves sufficiently to undergo cholecystectomy, which is generally 2 to 3 weeks after admission. If evidence of infected ANP develops, peripancreatic debridement is required. This operation has traditionally been performed by laparotomy with removal of all infected and necrotic tissue and placement of drains. Recent anecdotal reports suggest that laparoscopic debridement of peripancreatic necrosis may also be feasible.[9,10] Cholangiography or intraoperative ultrasonography[11] should be performed at the time of laparoscopic cholecystectomy in all patients. If a small stone or stones is seen in the common bile duct, an attempt is made to remove it laparoscopically using a transcystic duct approach if conditions are favorable.

In the setting of acute gallstone pancreatitis, the common bile duct stones are usually small and the cystic duct is usually dilated as a result of recent stone passage, thus facilitating transcystic duct stone removal. Stones smaller than 2 mm can usually be simply flushed into the duodenum after pharmacologic ampullary dilatation using intravenous glucagon.[11] Stones larger than this generally require basket extraction, with placement of the basket either under

From the Department of Surgery, Washington University School of Medicine, St. Louis, Mo.
Correspondence: Nathaniel J. Soper, M.D., Department of Surgery, Washington University School of Medicine, One Barnes Hospital Plaza, Box 8109, St. Louis, MO 63110.

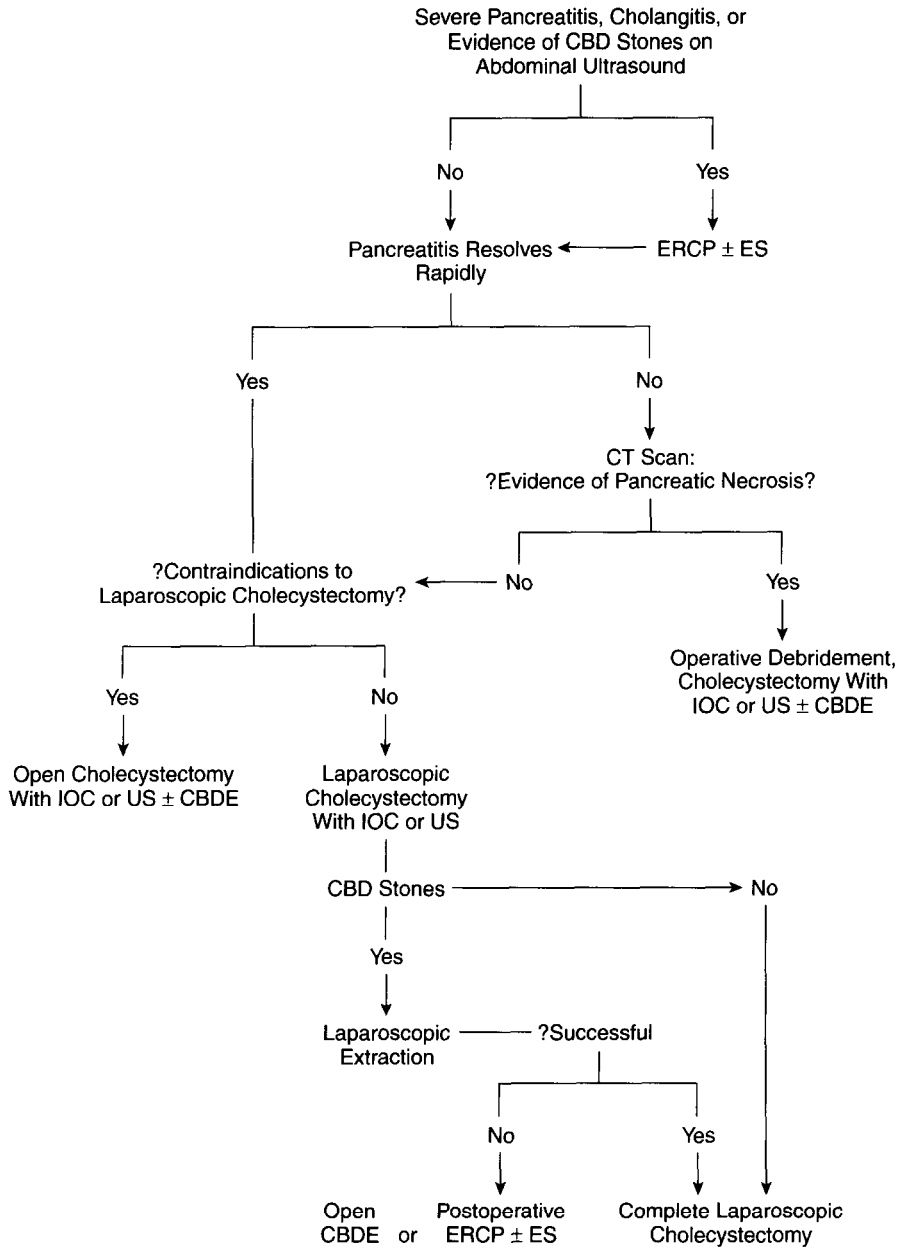

Fig. 1. Management of acute gallstone pancreatitis. CBD = common bile duct exploration; ERCP = endoscopic retrograde cholangiopancreatography; ES = endoscopic sphincterotomy; IOC = intraoperative cholangiography.

fluoroscopic guidance[12] or by means of a small (<10 Fr) choledochoscope.[13,14] Transcystic duct laparoscopic approaches are used successfully to treat choledocholithiasis in more than 85% of patients in reported series.[4,12-14] Common bile duct stones that are multiple or larger than 6 to 7 mm in diameter are often referred for postoperative ERCP. Alternatively, laparoscopic choledochotomy with direct stone extraction may be performed provided the bile duct is dilated and the surgeon is experienced in laparoscopic suturing.[15] If expertise in laparoscopic bile duct exploration and ERCP are lacking in a patient with a bile duct stone found during cholangiography, conversion to an open operation is indicated. Given the success of laparoscopic common bile duct exploration and ERCP, it should be possible to manage the majority of patients with gallstone pancreatitis by minimally invasive techniques.

Our current algorithm for the management of acute gallstone pancreatitis is shown in Fig. 1.

REFERENCES

1. Ranson JHC. The timing of biliary surgery in acute pancreatitis. Ann Surg 1979;189:654-663.
2. Stone HH, Fabian TC, Dunlap WE. Gallstone pancreatitis: Biliary tract pathology in relation to time of operation. Ann Surg 1981;194:305-312.
3. Kelly TR, Wagner DS. Gallstone pancreatitis: A prospective randomized trial of the timing of surgery. Surgery 1988;104: 600-605.
4. Soper NJ, Brunt LM, Callery MP, Edmundowicz SA, Aliperti G. Role of laparoscopic cholecystectomy in the management of acute gallstone pancreatitis. Am J Surg 1994;167:42-50.
5. Tate JJT, Lau WY, Li AKC. Laparoscopic cholecystectomy for biliary pancreatitis. Br J Surg 1994;81:720-722.
6. Tang E, Stain SC, Tang G. Timing of laparoscopic surgery in gallstone pancreatitis. Arch Surg 1995;130:496-500.
7. Delorio AV Jr, Vitale GC, Reynolds M, Larson GM. Acute biliary pancreatitis. The role of laparoscopic cholecystectomy and endoscopic retrograde cholangiopancreatography. Surg Endosc 1995;9:392-396.
8. Ballestra-Lopez C, Bastida-Vila X, Bettonica-Larranaga C, Zaraca F, Catarci M. Laparoscopic management of acute biliary pancreatitis. Surg Endosc 1997;11:718-721.
9. Alverdy J, Vargish T, Desai T, Frawley B, Rosen B. Laparoscopic intracavitary debridement of peripancreatic necrosis: Preliminary report and description of the technique. Surgery 2000;127:112-114.
10. Cambiez LP, Denimal FA, Porte HL, Saudemont A, Chambon JPM, Quandalle PA. Retroperitoneal approach and endoscopic management of peripancreatic necrosis collections. Arch Surg 1998;133:66-72.
11. Wu JS, Dunnegan DL, Soper NJ. The utility of intraoperative ultrasonography for screening the bile duct during laparoscopic cholecystectomy. J GASTROINTEST SURG 1998;2:50-60.
12. Hunter JG. Laparoscopic transcystic common bile duct exploration. Am J Surg 1992;163:53-58.
13. Carroll BJ, Phillips EH, Rosenthal R, Liberman M, Fallas M. Update on transcystic exploration of the bile duct. Surg Laparosc Endosc 1996;6:453-458.
14. Petelin JB. Laparoscopic approach to common duct pathology. Am J Surg 1993;165:487-491.
15. Dion Y-M, Ratelle R, Morin J, Gravel D. Common bile duct exploration: The place of laparoscopic choledochotomy. Surg Laparosc Endosc 1994;6:419-424.

Early Endoscopic Management of Acute Gallstone Pancreatitis—An Evidence-Based Review

Alan N. Barkun, M.D., C.M., M.Sc.

The short-term management of acute pancreatitis has evolved significantly over the past two decades. More specifically, the possible benefits brought about by biliary endoscopy have been examined, and a number of recommendations can now be made. The following evidence-based review will address the available data on the early endoscopic management of acute gallstone pancreatitis. Based on the results reviewed, a series of recommendations are listed with grading according to the level of evidence as suggested in the literature.[1] The subsequent management of complications of acute gallstone pancreatitis such as pancreatic necrosis and pseudocysts is beyond the scope of this review and will not be discussed.

RATIONALE FOR EARLY DECOMPRESSION

Following the pioneering work of Opie[2] linking gallstone impaction in the ampulla of Vater with acute pancreatitis, the works of Acosta and Ledesma[3] and Kelly[4] both subsequently demonstrated recovery of biliary stones in the stool of 85% of such patients. These and other works have led to postulates concerning the genesis of acute pancreatitis that include the common channel or bile reflux theory,[1,5,6] the duodenal reflux theory,[7] and the obstruction theory,[8] with arguments for and against each. In support of the latter theory, early decompression of experimental biliopancreatic ductal system occlusion has been shown to result in an improvement in outcome by halting progression of disease. This finding supports a biological rationale for early endoscopic decompression in patients with acute biliary pancreatitis.[9] No single theory, however, convincingly explains the realm of clinical observations in patients with acute biliary pancreatitis. It must be remembered, however, that early biliary decompression is primordial for the treatment of patients with cholangitis,[10] a condition that is often seen in association with acute biliary pancreatitis. This argument remains a pivotal consideration when evaluating trials of endoscopic decompression and will be further developed later in this review.

Inherent to the appropriate interpretation of trial results in early endoscopic intervention for patients with acute biliary pancreatitis is a familiarity with prognostic determinations of the severity of the pancreatitis and the likelihood that its cause is attributable to gallstone disease. Predictive models developed for each that were used in endoscopic efficacy trials will thus first be reviewed.

PREDICTIVE MODEL OF THE BILIARY CAUSE OF AN EPISODE OF PANCREATITIS

Biochemical Markers

A high serum amylase level[11] and an elevated amylase/lipase ratio[12] have been noted to be even higher in patients with gallstone pancreatitis as compared to those with an alcoholic etiology. A number of abnormalities of common liver tests have been suggested to indicate a biliary etiology for a bout of pancreatitis and include an elevated serum bilirubin,[13] aspartate aminotransferase (AST),[14] or alanine aminotransferase (ALT).[15] Combinations of biochemical tests have also been proposed. An accuracy of 98% has been reported with a predictive model that includes bilirubin, alkaline phosphatase, gamma glutamyl transferase, and the AST/ALT ratio in combination with ultrasonography.[16] A meta-analysis suggested that ALT was the single most useful predictor, with a positive predictive value of 95% when elevated at least threefold.[17] According to Neoptolemos et al.,[18] pancreatitis is suggestive of a gallstone etiology with a sensitivity of 73% and a specificity of 94%, if the patient is female, over age 50, and has a serum bilirubin level above 2.5 mg/dl, an alkaline phosphatase value greater than twice normal, and ALT more than 2.2 times the normal value.[18] Other predictive models

From the Division of Gastroenterology, McGill University, and the McGill University Health Centre, Montreal, Quebec, Canada.
Dr. Barkun is a research scholar funded by the Fonds de la Recherche en Santé du Québec.
Correspondence: Alan Barkun, M.D., The McGill University Health Centre, The Montreal General Hospital, Room D7.148, Montréal, Québec, Canada H3G 1A4. e-mail: alan.barkun@muhc.mcgill.ca

that have been proposed include a combination of serum and urine amylase, ALT, AST, and alkaline phosphatase.[18] Several specialized serum markers have been studied with varying tests being performed to determine the biliary etiology of an episode of pancreatitis. They are phospholipase A_2, trypsinogen-activating peptide, interleukin (IL)-2, IL-6, and IL-8, and tumor necrosis factor. Trypsinogen-activating peptide has been shown to correlate with disease severity.[19]

Imaging Tests

Ultrasound imaging remains the cornerstone in diagnosing gallbladder stones, although it fails to do so in 20% to 30% of patients with acute pancreatitis.[18] Ultrasound is a good method for detecting common bile duct (CBD) dilatation but displays poor accuracy in detecting CBD stones.[20] Although endoscopic retrograde cholangiopancreatography (ERCP) remains the "gold standard" cholangiographic method for diagnosing choledocholithiasis, noninvasive imaging technology such as endoscopic ultrasonography[21] and magnetic resonance cholangiopancreatography are very promising.[22] Furthermore, endoscopic ultrasound has also been shown to be useful in patients with acute idiopathic recurrent pancreatitis in demonstrating small stones or microscopic biliary crystal disease.[23,24]

PREDICTIVE MODELS OF THE SEVERITY OF ACUTE PANCREATITIS AND ITS CAUSE

Although most patients presenting with gallstone pancreatitis will experience a benign course with a good prognosis, a few will develop severe complications.[25] Thus it is this latter subgroup of patients in particular who must be considered for a therapeutic intervention. Stratification of the severity of an attack is thus an important consideration when analyzing the existing literature. Several clinical scales have been used to prognosticate the outcome of a bout of pancreatitis. They include the criteria proposed by Ranson et al.,[26] which assess five clinical variables at admission (age, leukocyte count, serum glucose, lactate dehydrogenase, and AST) and six at 48 hours (changes in hematocrit, blood urea nitrogen, fluid administration requirements, base deficit, levels of arterial oxygenation, and calcemia). Other clinical scales include the modified Glasgow scoring system, which takes into account age, leukocyte count, blood glucose, serum urea, arterial oxygen pressure, serum calcium, albumin, and lactate dehydrogenase, all applied 48 hours after admission,[27] and an immediate assessment of serum glucose and urea levels.[28] The APACHE II score assesses severity points based on physiologic factors as well as indices of chronic disease.[29] Other more specific markers have been developed but are not widely used. The classification of Balthazar et al.[30] stratifies patients in prognostic groups according to findings on computed tomography. Similar classifications are being developed for magnetic resonance imaging.[31]

Retrospective case series early on in the development of ERCP suggested possible benefits attributable to endoscopic biliary decompression.[32-35] Yet it is only since the performance of randomized trials in this therapeutic area that the more exact role of ERCP in this condition has been determined. The four randomized trials performed to date will be reviewed since it is only in the setting of a randomized trial that known and unknown confounders of outcome may be balanced between both the experimental and control study groups.[36] This consideration is especially true for patients with acute pancreatitis where a number of demographic, laboratory, diagnostic and therapeutic known (and perhaps as yet undetermined) factors may affect outcome.

REVIEW OF THE BEST AVAILABLE EVIDENCE ASSESSING THE ROLE OF EARLY ENDOSCOPY IN ACUTE GALLSTONE PANCREATITIS: FOUR RANDOMIZED TRIALS

UK Study

This was the first of the randomized trials and was published in 1988. A total of 223 consecutive patients presented with acute pancreatitis (amylase >1000 U/L with a compatible clinical picture) and were assessed for a possible biliary origin by Neoptolemos et al.[37] From these, 146 were selected using an aforementioned predictive scale indicating a possible biliary origin for the bout of pancreatitis.[18] The patients were stratified as to whether they suffered a mild (0 to 2 criteria) or severe attack (3 to 8 features) at 48 hours following admission according to the modified Glasgow scale.[27] From these patients the authors subsequently randomized a total of 131 adult, nonpregnant patients with no other obvious causes of pancreatitis to undergo ERCP performed 72 hours after admission with endoscopic sphincterotomy if a CBD stone was found (endoscopic group) or to conventional treatment (no initial ERCP considered). Ten patients were subsequently excluded because of alternate diagnoses, leaving 59 patients randomized to the endoscopic and 62 to the conventional treatment group. Both groups received antibiotics.[38] The two treatment groups were well matched except for age, which is discussed below. Using an intention-to-treat analysis, among the patients with a predicted mild bout of pancreatitis, the mean ages were 55 and 67.5 years, and for a predicted severe bout 74 and 76.5 years for patients randomized to the endoscopic and conventional groups, respectively. Overall 85% of pa-

tients were found to have gallstones. The overall mortality rate was 5%, and rates were similar in both the endoscopic group (2% [1 of 59]) and the conservative therapy group (8% [5 of 62]; $P = 0.23$). One of the patients in the latter group had an impacted stone at necropsy. The overall complication rate was greater in the conventional treatment group (17% [10 of 59] vs. 34% [21 of 62]; $P = 0.03$). No difference occurred in the complication rate (12%) in either group among patients with a predicted mild attack, even when only those patients with gallstones were considered (14%). A significant difference was noted, however, among patients with predicted severe pancreatitis for the endoscopic group (24% [6/25]) as compared to the conservative therapy group (61% [17/28]; $P < 0.01$), and the difference remained significant when only patients with gallstones were considered (18% [4/22] vs. 54% [13/24]; $P = 0.01$). No significant differences in complication rates existed between patients with predicted mild and severe attacks in the endoscopic group. In contrast, this difference was significant in patients treated conservatively ($P < 0.0001$). Only one complication occurred as a result of the ERCP, a lumbar osteitis. ERCP was carried out successfully in 90% of patients (52 of 59 in the endoscopic group and 14 of 14 in the conventional group), with sphincterotomy done in all cases attempted. Among patients in the endoscopic group with confirmed gallstones, CBD stones were found more often in the severe cases (63% [12 to 19] vs. 25% [7 of 28]; $P = 0.03$) with an overall incidence of CBD stones at 32% (19 of 59) in the endoscopic group with gallstones. Six patients in the endoscopic group and five in the conventional treatment group had acute cholangitis, for an overall rate of 9%. When these patients were excluded from the analysis, the complication rates among patients with severe attacks remained significantly lower in the endoscopic group (11% [6 of 53] vs. 33% [19 of 57]; $P = 0.02$). Length of stay was comparable among patients with mild pancreatitis (9 days for the endoscopic group vs. 11 days for the conventional group), but was significantly shorter for the endoscopic group among patients with severe pancreatitis (9.5 days vs. 17 days; $P = 0.03$). Moreover, there were no differences in duration of hospitalization between patients with mild and severe pancreatitis in the endoscopic group (9 days vs. 9.5 days), but this difference was significant in the conventional group (11 days vs. 17 days, $P = 0.01$). The authors did note that among the patients with mild pancreatitis, the conventional treatment group was older than the endoscopic group, but with no obvious resulting difference in outcomes attributable to this imbalance, as no between-group difference existed in this subpopulation.

The authors concluded that endoscopic management is beneficial in the subgroup of patients with acute pancreatitis due to gallstones who underwent early ERCP with a predicted severe attack of pancreatitis.

Criticisms of this study have included the advanced age in the severe disease group and the fact that this was a single-center study—both reasons that may limit the generalizability of the study. Moreover, the administration of antibiotics to both groups may have resulted in cointervention. Last, the study was criticized for the small number of patients randomized to ERCP with CBD stones in the severe pancreatitis group (n = 12).

Hong Kong Study

In this study published in 1993, 195 of 206 consecutive patients with acute pancreatitis (amylase >1000 U/L with a compatible clinical picture) were randomized to emergency ERCP within 24 hours of admission or initial conservative treatment.[39] Patients initially randomized to the latter group underwent ERCP if they later deteriorated as a result of biliary sepsis. Analysis of outcome considered the severity of the attack, but the randomization was not stratified according to this variable. This categorization was based on the presence of three Ranson criteria or less (mild) versus four or more (severe),[40] and on serum urea and plasma glucose levels at admission (>7.4 mmol/L or 11.0 mmol/L, respectively).[28] Patients were well matched in both groups for age, with means of 63 to 66 years, and for variables reflecting the severity of pancreatitis. Overall 65% of patients had a proven biliary cause of pancreatitis. Indeed 30 patients had nonbiliary causes of pancreatitis that were determined during the study (including alcoholism, hyperlipidemia, choledochal cysts, neoplasms, and ascariasis), and 38 additional patients had an idiopathic cause. Overall 114 patients (58%) had a predicted mild bout of pancreatitis. ERCP was successful in 90% of patients (87 of 97 in the ERCP group and 25 of 27 in the initially conservative group). Sphincterotomy was successful in all but one of the 47 patients in whom it was attempted (37 of 37 in the ERCP group), yet one patient in the initially conservative group had an episode of postpapillotomy bleeding and died of a pancreatic abscess. There was one false negative (versus later stone migration) result of ERCP. Overall complication and mortality rates did not differ significantly between the ERCP and conservative therapy groups (18% vs. 29% and 5% vs. 9% respectively). When only patients with biliary stones were considered, significantly different complication rates were noted (16% [10 of 64] for the ERCP group vs. 33% [21 of 63] for the conservative therapy group; $P = 0.03$), even though the mortality rates were not (2% vs. 8%, respectively; $P = 0.09$). One patient with severe pancreatitis died after CBD stone extraction. The post-ERCP incidences of abdominal

pain and postpapillotomy bleeding were, respectively, 4% (5 patients) and 6% (8 patients) and did not depend on the timing of the ERCP (comparing the early ERCP group to patients in the conventional treatment group undergoing later ERCP for biliary sepsis). CBD stones were demonstrated in 37 patients (38%) in the ERCP group. Impacted CBD stones were noted in 20 patients from the entire study, including 13 (13%) of the 97 in the ERCP group. There were no between-group differences in local or systemic complications except for the incidence of biliary sepsis, which was significantly lower in the ERCP group (0 of 97 patients vs. 12 of 98 patients; $P = 0.001$). This difference was principally attributable to a marked difference in the incidence of biliary sepsis among the group with severe pancreatitis (0 of 41 patients vs. 8 of 40 patients; $P = 0.008$).

The investigators conclude that emergency ERCP (with sphincterotomy if appropriate) is indicated in the treatment of patients with acute pancreatitis.

This single-center study has been criticized as to its generalizability because only 65% of the 195 patients had a proven biliary cause of pancreatitis; furthermore, nonbiliary causes of pancreatitis (such as hypertriglyceridemia and alcoholism) were also included with no clear anticipated benefits based on their postulated pathophysiology. In fact, even the pathophysiology of gallstone disease may differ between Asian and Western populations. The randomization was not stratified according to the anticipated severity of pancreatitis, yet the groups were well balanced for this variable.

German Study

This most recent study was designed to separate out any possible contamination that the presence of associated cholangitis may have had in the endoscopic treatment of patients with acute biliary pancreatitis in previously performed randomized trials.[41] Patients with acute pancreatitis (amylase or lipase levels more than three times the normal range with imaging proof of pancreatitis in a clinically suggestive context) of suspected biliary etiology (based on an ultrasound or CT scan showing gallstones or the presence of two of three biochemical markers that included an elevated alkaline phosphatase, AST, or bilirubin level[16,42] were considered for inclusion in the trial only if the serum bilirubin level was less than 90 μmol/L (5 mg/dl). The severity of the pancreatitis was graded prior to treatment using the modified Glasgow scale.[27] Practice guidelines for administering conservative therapy (and subsequent ERCP for patients in the conservative group if subsequent biliary sepsis developed) were agreed to across the 22 participating sites. Over a period of 4½ years, 339 consecutive patients were assessed and 238 were randomized, including 126 to early ERCP (within 72 hours of the onset of symptoms) and 112 to conservative therapy. A mean of 10.8 patients were enrolled at each center (range 6 to 29), but three sites included 20 or more patients each. The two groups were well matched with regard to age, sex, and severity of pancreatitis, although a full 13% of patients had an undefined severity (due to missing data). There were 26 patients (21%) with severe pancreatitis in the ERCP group and 20 in the conservative group (18%). Thirty-two patients were subsequently excluded because of protocol violations but were included in the analysis under the intention-to-treat principle. ERCP was successful in 95% of patients (141 of 148) with CBD stones detected in 58 patients (46%) in the ERCP group. Stones were successfully extracted in 69 (99%) of 70 patients. One patient developed postsphincterotomy bleeding, and one, who also suffered a hemorrhage, died of biliary sepsis after a failed attempt at removal of an impacted stone. Overall three-month mortality was 9% and did not differ between treatment groups. No differences in disease-related mortality were noted (10 patients [8%] in the ERCP and 4 [4%] in the conventional group; $P = 0.16$). The overall complication rates were similar in the two groups (58 patients [46%] in the ERCP group vs. 57 [51%] in the conservative therapy group). The early-ERCP group, however, had more severe complications, especially respiratory failure ($P = 0.03$), whereas jaundice was more frequent in the conservative therapy group ($P = 0.02$). The authors concluded that early ERCP and papillotomy are not beneficial in patients with acute biliary pancreatitis in the absence of presenting biliary obstruction or sepsis.

This study has been criticized from many points of view. Prophylactic antibiotics were not routinely given (or adjusted for) leading to possible confounding. The mortality rate noted in the early-ERCP group was much higher than had been shown in previous studies, and the incidence of respiratory failure had not been noted in previous studies and remains unexplained. Moreover, the participation of most institutions was poor, and significant operator variability may have affected the results, although it could be argued that this finding only increases the generalizability of results, especially in the face of good overall ERCP results as was the case. An important note is that patients with significant biliary obstruction (with serum bilirubin greater than 5 mg/dl or 90 μmol/l) were excluded. Indeed such patients represent a clinically relevant proportion of patients presenting with acute biliary pancreatitis, and thus the external validity of this latter study is accordingly decreased. Perhaps the most important criticism has not been addressed in the literature and relates to a diminished power of the study when attempting to assess outcomes in patients with severe pancreati-

tis because of the small numbers in this important subgroup.

Polish Study

In a study published only in abstract form to date, Nowak et al.[43] assessed 280 consecutive patients with acute biliary pancreatitis.[43] Duodenoscopy was performed within 24 hours of admission. An impacted stone was discovered at the ampulla of Vater in 75 (27%) patients (group 1), and sphincterotomy was performed immediately. The remaining 205 patients were randomized to undergo immediate ERCP and sphincterotomy (group 2; n = 103 patients) or conventional, nonendoscopic therapy (group 3; n = 102 patients). The complication rate was significantly lower in groups 1 and 2 as compared to group 3 (17% vs. 36%; 95% confidence interval [CI] on the difference = 0.01 to 0.32). The mortality rate for all patients (both predicted severe and mild) was also significantly lower in groups 1 and 2 (2% vs. 13%, 95% CI on the difference = 0.04 to 0.17). Moreover, the results were best in the group undergoing endoscopic therapy when the interval between the onset of the pancreatitis and the sphincterotomy was less than 24 hours (in this subgroup, 0% mortality and 7% complication rate). The outcomes were worst if this interval of time increased to more than 72 hours (8% mortality, 22% complication rate). These results were more significant in patients with a predicted severe attack as compared to a predicted mild bout.

The authors concluded that ERCP with sphincterotomy brings about a significant decrease in morbidity and mortality for all patients (regardless of severity prediction) and that endoscopic management should be carried out in all patients with biliary pancreatitis within 24 hours of onset of the disease. An update to this study was also published in abstract form.[44]

It is unclear why this study has not yet been published in full, which in itself limits the interpretation of its results, as many details relating to patient selection, the nature of the interventions, possible confounding variables, and subgroup analyses remain unspecified. Furthermore, this study was criticized for using no prospective grading of severity.

ATTEMPT TO ESTABLISH A SET OF EVIDENCE-BASED RECOMMENDATIONS

As is evident from the review of the four randomized trials, there exist significant individual differences in patient selection and the timing of ERCP as has been noted by others.[45] In addition, nonstandardized definitions of outcome, such as localized complications and unblinded assessment of complications, may have further influenced the observed results. A recently published meta-analysis attempted to pool the study results.[46] Considering all patients together, the authors describe a statistically significant absolute risk reduction in the complication rate of 13% in favor of early ERCP, with a number needed to treat of 7.6 (95% CI = 6 to 20). Similar results were found for mortality with an absolute risk reduction of 4%, and a number needed to treat of 26 (95% CI = 13 to 286). These authors should be lauded for their efforts to put forward conclusions based on the existing literature. Yet one must remain skeptical about these conclusions and the applicability of this particular methodology because of the heterogeneity in patient characteristics (and perhaps the timing of ERCP) as detailed in this review. Perhaps a more valid attempt at defining practice guidelines should be based on a review of the existing data and its grading carried out according to an accepted evidence-based classification (Table I).[1] The relevant information from the four randomized trials discussed herein is summarized in Table II.

Table I. Categorization of evidence and recommendations[1]

Quality of Evidence	
I	Evidence obtained from at least one properly randomized controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
II-3	Evidence obtained from comparisons between times or places with or without the intervention, or dramatic results in uncontrolled experiments
III	Opinions of respected authorities, based on clinical expertise, descriptive studies, or reports of expert committees
Classification of Recommendations	
A	There is good evidence to support the procedure or treatment
B	There is fair evidence to support the procedure or treatment
C	There is poor evidence to support the procedure or treatment, but recommendations may be made on other grounds
D	There is fair evidence that the procedure or treatment should not be used
E	There is good evidence that the procedure or treatment should not be used

Table II. Summary of results of three randomized clinical trials published in full and one published in abstract form only

Trial	Randomized (screened) ERCP group/control group	Selection as to suspected etiology	Severity stratification	Gallstone/CBD stone/cholangitis incidences
UK study[37] (1988)	121 patients (146 patients, up to 223 patients initially seen) 59 patients vs. 62 patients	Leicester (sex, age, ALT, bilirubin, AP)	Modified Glasgow scale Mild = 68 patients Severe = 53 patients Performed for stratification before randomization	85% of patients had gallstones/32% of those in ERCP group had CBD stones/9% overall rate of cholangitis
Hong Kong study[39] (1993)	195 patients/206 patients 97 patients vs. 98 patients	None applied, which is why only 65% of patients had a proven biliary cause of pancreatitis	Ranson criteria (≤3 vs. ≥4) also BUN + glucose Mild = 114 patients Severe = 81 patients	65% of all patients had gallstones/CBD stones in 38% of ERCP group/12% of patients in conventional group had cholangitis
German study[41] (1997)	238 patients/339 patients 126 patients vs. 112 patients	Gallstones seen on US or CT or if 2 of 3 criteria (high AP, ALT, or bilirubin >2.3 mg/dl, yet bilirubin <5 mg/dl)	Modified Glasgow scale Mild = 160 patients Severe = 46 patients Undefined = 32 patients	46% with CBD stones in ERCP group/7% of all patients had jaundice (patients with bilirubin >5 mg/dl excluded at entry)
Polish study (abstract only; 1995)	280 patients treated Group 1 = impacted stone at duodenoscopy with sphincterotomy Remaining 205 patients randomized Group 2 = 103 patients (ERCP) vs. group 3 = 102 patients (conventional treatment)	No details given	Method of stratification not detailed; treatment groups 2 and 3 comparable for predicted severity	27% (75 patients/280 patients) had impacted stones at ampulla and were treated before randomization of the other 205 patients; no further details

NOTE: All four trials are discussed in detail in the text.
ALT = alanine aminotransferase; AP = alkaline phosphatase; CBD = common bile duct; ERCP = endoscopic retrograde cholangiopancreatography; ES = endoscopic sphincterotomy.

RECOMMENDATIONS

The following are the recommendations that can be set forth with confidence based on the available evidence (see Table I):

1. Early ERCP (within 24 to 72 hours of the onset of symptoms and admission) is safe in patients with a predicted severe episode of suspected acute biliary pancreatitis (class B recommendation based on level 1 evidence)
2. Early ERCP (and sphincterotomy when bile duct stones are found) results in diminished biliary sepsis among patients with suspected biliary pancreatitis, especially in patients with a predicted severe attack. This in turn results in improved outcomes in this subgroup (class A recommendation based on level 1 evidence)
3. Early ERCP (and sphincterotomy when CBD stones are found) results in decreased complication rates in patients with acute biliary pancreatitis and a predicted severe attack (class A recommendation based on level 1 evidence)
4. At the present time, early ERCP should not be performed in patients with a predicted mild attack of acute pancreatitis of suspected biliary etiology (class D recommendation based on level 1 evidence)

AREAS OF FUTURE RESEARCH

The role of ERCP in a subgroup of patients with acute pancreatitis presenting without initial significant biliary obstruction remains unclear, mainly because of

Timing of ERCP, % success (% success for ES) complication	Mortality	Morbidity/complications (duration of hospitalization)	Comments
Within 72 hr of admission ERCP success in 90% (66 patients/73 patients) (100% of ES) 1 complication (lumbar osteitis)	Overall 5%; no between-group differences	Higher in conventional group (17% vs. 34%, P = 0.03); attributable to difference in patients with severe attack: 24% (9.5 days) vs. 61% (11 days)	Morbidity differences remained if patients with cholangitis were removed from analysis
Within 24 hr of admission ERCP success in 90% (112 patients/124 patients) (98% of ES) 11% complication rate (pain and hemorrhage)	Overall 7%; no between-group differences	Only differences in patients with stones ERCP = 16% Conventional group = 33%	ERCP reduced biliary sepsis significantly in all patients, mainly because of difference noted in patients with severe pancreatitis
Within 72 hr of onset of symptoms ERCP success in 95% (141 patients/148 patients) (99% of ES) 2 complications (2 hemorrhages with 1 death)	Overall 9%; no between-group differences	More severe complications in ERCP group (respiratory failure, P = 0.03); more jaundice in conservative group (P = 0.02)	Excluded patients with bilirubin >5 mg/dl Unexplained high mortality (11%) and incidence of respiratory failure in ERCP group
ERCP performed anywhere from <24 hr to >72 hr after presentation; no other details available	Decreased overall mortality rate for groups 1 + 2 vs. group 3 2% vs. 13% (95% CI on difference = 0.04 to 0.17)	Decreased overall complication rate for groups 1 + 2 vs. group 3 17% vs. 36% (95% CI on difference = 0.10 to 0.32)	Outcomes (both deaths and complications) improved as timing of ERCP became earlier (<24 hr vs. >72 hr after presentation), especially in patients with severe pancreatitis

unexplained negative outcomes, and a lack of power in the only randomized trial to have assessed this clinical question, especially with regard to patients with a prediction of severe pancreatitis. The role of endoscopic biliary sphincterotomy in patients without demonstrated CBD stones also remains poorly characterized. Further studies are required to confirm the optimal timing of ERCP, as very early ERCP may prove to be useful in a broader group of patients. This question will be limited by real-life issues of timely accessibility of the endoscopic expertise. As in the management of all acute biliopancreatic diseases, the cornerstone of optimal management of patients with acute biliary pancreatitis resides in adequate and appropriate resuscitation, and a collaborative approach uniting radiologists, general surgeons, and gastroenterologists.

REFERENCES

1. Canadian Task Force on Periodic Health Examinations. The periodic health examination: 1. Introduction. Can Med Assoc J 1986;134:721-723.
2. Opie E. The etiology of acute hemorrhagic pancreatitis. Johns Hopkins Hosp Bull 1901;121:182-188.
3. Acosta J, Ledesma C. Gallstone migration as a cause of acute pancreatitis. N Engl J Med 1974;290:484-487.
4. Kelly T. Gallstone pancreatitis: The timing of surgery. Surgery 1980;88:345-350.
5. Lancereaux E. Traité des maladies du foie et du pancréas. Paris: O Poin, 1899.
6. Jones BA, Salsberg BB, Bohnen JMA, Mehta MH. Common pancreatobiliary channels and their relationship to gallstone size in gallbladder pancreatitis. Ann Surg 1987;205:123-125.
7. McCutcheon AD. Gallstone pancreatitis [letter]. Lancet 1988;2:166.
8. Blackstone MO. Gallstone pancreatitis from intestinal reflux [letter]. Lancet 1988;1:1280-1281.

9. Runzi M, Saluja A, Lerch MM, et al. Early ductal decompression prevents the progression of biliary pancreatitis: An experimental study in the opossum. Gastroenterology 1993;105: 157-164.
10. Lai ECS, Mok FPT, Tan ESY, et al. Endoscopic biliary drainage for severe acute cholangitis. N Engl J Med 1992;326: 1582-1586.
11. Nordestgaard AG, Wilson SE, Williams RA. Correlation of serum amylase levels with pancreatic disease. Am J Surg 1987;154:490-492.
12. Gumaste VV, Dave PB, Weissman D, Messer J. Lipase/amylase ratio: A new index that distinguishes acute episodes of alcoholic from non-alcoholic acute pancreatitis. Gastroenterology 1991;101:1361-1366.
13. Neoptolemos JP, London N, Bailey I, et al. The role of clinical endoscopic, and biochemical criteria and ERCP in the urgent diagnosis of common bile duct stones in acute pancreatitis. Surgery 1986;100:732-742.
14. Mayer AD, McMahon MJ. Biochemical identification of patients with gallstones associated with acute pancreatitis on the day of admission to the hospital. Am Surg 1984;201:68-75.
15. Van Gossum A, Seferian V, Rodzynek J, et al. Early detection of biliary pancreatitis. Dig Dis Sci 1984;29:97-101.
16. Wang SS, Lin XZ, Tsai YT, et al. Clinical significance of ultrasonography, computed tomography, and biochemical tests in the rapid diagnosis of gallstone-related pancreatitis: A prospective study. Pancreas 198;3:153-158.
17. Tenner S, Dubner H, Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: A meta-analysis. Am J Gastroenterol 1996;91:2355-2359.
18. Neoptolemos JP, Hall AW, Finlay DF, et al. The urgent diagnosis of gallstone in acute pancreatitis: A prospective study of three methods. Br J Surg 1984;71:230-233.
19. Gudgeon AM, Heath DI, Hurley P, et al. Trypsinogen activation peptides assay in the early prediction of severity of acute pancreatitis. Lancet 1990;335:4-8.
20. Barkun AN, Barkun JS, Fried GM, et al. Useful predictors of bile duct stones in patients undergoing laparoscopic cholecystectomy. Ann Surg 1994;220:32-39.
21. Prat F, Amouyal G, Amouyal P, et al. Prospective controlled study of endoscopic ultrasonography and endoscopic retrograde cholangiography in patients with suspected common bile duct lithiasis. Lancet 1996;347:75-79.
22. Reinhold C, Atri M, Bret P, et al. Choledocholithiasis: Evaluation of MR cholangiography for diagnosis. Radiology 1998;209:435-442.
23. Dahan P, Andant C, Levy P, et al. Prospective evaluation of endoscopic ultrasonography and microscopic examination of duodenal bile in the diagnosis of cholecystolithiasis in 45 patients with normal conventional ultrasonography. Gut 1996;38:277-281.
24. Liu CL, Lo CM, Poon RT, Fan ST. EUS for detection of occult cholelithiasis in patients with idiopathic pancreatitis. Gastrointest Endosc 2000;51:28-32.
25. Thomson S, Hendy W, McFalane G, Davidson A. Epidemiology and outcome of acute pancreatitis. Br J Surg 1987;74: 398-401.
26. Ranson JHC, Rifkind RM, Roses DF. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet 1974;139:69-80.
27. Leese T, Shaw D. Comparison of three Glasgow multifactor prognostic scoring systems in acute pancreatitis. Br J Surg 1988;75:460-462.
28. Fan ST, Choi TK, Lai ECS, Wong J. Prediction of severity of acute pancreatitis: An alternative approach. Gut 1989;157: 544-547.
29. Knas WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985;13:818-829.
30. Balthazar E, Robinson D, Megibow A, et al. Acute pancreatitis: Value of CT in establishing a prognosis. Radiology 1990; 174:331:336.
31. Robinson PJ, Sheridan MB. Pancreatitis: Computed tomography and magnetic resonance imaging. Eur Radiol 2000;10: 401-408.
32. Classen M, Ossenberg FW, Wurbs D, et al. Pancreatitis: An indication of endoscopic papillotomy [abstr]. Endoscopy 1978; 10:223.
33. Safrany L, Neuhaus B, Kraus S, et al. Endoskopische Papillotomie bei akuter, bilaer dedingter Pankreatitis. Dtsch Med Wochenschr 1980;105:115-119.
34. Safrany L, Cotton PB. A preliminary report: Urgent duodenoscopic sphincterotomy for acute gallstone pancreatitis. Surgery 1981;89:424-428.
35. Hess W. Collective review: Gallstone pancreatitis. Ital J Surg Sci 196;16:13-18.
36. Bouchard S, Barkun AN, Barkun JS, Joseph L. Technology assessment in laparoscopic general surgery and gastrointestinal endoscopy—science or convenience? Gastroenterology 1996; 110:915-925.
37. Neoptolemos JP, London NJ, Carr-Locke DL, Bailey IA, Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet 1988;2:979-983.
38. Raraty MGT, Finch M, Neoptolemos JP. Acute cholangitis and pancreatitis secondary to common duct stones: Management update. World J Surg 1998;22:1155-1161.
39. Fan ST, Lai ECS, Mok FPT, et al. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med 1993;328:228-232.
40. Ranson JHC. The timing of biliary surgery in acute pancreatitis. Ann Surg 1979;189:654-663.
41. Foelsch UR, Nitsche R, Luedtke R, Hilgers RA, Creutzfeldt W, and the German Study Group on Acute Biliary Pancreatitis. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. N Engl J Med 1997; 336:237-242.
42. Goodman AJ, Neoptolemos JP, Carr-Locke DL, et al. Detection of gallstones after acute pancreatitis. Gut 1985;26:125-132.
43. Nowak A, Nowakowska-Dulawa E, Marek T, Rybicka J. Final results of the prospective, randomized, controlled study on endoscopic sphincterotomy versus conventional management in acute biliary pancreatitis [abstr]. Gastroenterology 1995;108(Suppl):A380.
44. Nowak A, Nowakowska-Dulawa E, Marek T, et al. Final results of the prospective randomized, controlled study on endoscopic sphincterotomy versus conventional management in acute biliary pancreatitis [abstr]. Gastroenterology 1995;108: A380.
45. Frakes JT. Biliary pancreatitis: A review. J Clin Gastroenterol 1999;28:97-109.
46. Sharma VK, Howden CW. Meta-analysis of randomized trials of endoscopic retrograde cholangiography and endoscopic sphincterotomy for the treatment of acute biliary pancreatitis. Am J Gastroenterol 1999;94:3211-3214.

Combination of Endoscopic Argon Plasma Coagulation and Antireflux Surgery for Treatment of Barrett's Esophagus

Harald Tigges, M.D., Karl H. Fuchs, M.D., Jörn Maroske, M.D., Martin Fein, M.D., Ph.D., Stephan M. Freys, M.D., Justus Müller, M.D., Arnulf Thiede, M.D.

Columnar-lined epithelium with specialized intestinal metaplasia of the esophagus (i.e., Barrett's esophagus) is a premalignant condition caused by chronic gastroesophageal reflux disease. Progression of intestinal metaplasia may be avoided by antireflux surgery, whereas regeneration of esophageal mucosa could be achieved by endoscopic argon plasma coagulation (EAPC). The aim of this prospective study was to show the early results of a combination of EAPC and antireflux surgery. Thirty patients with Barrett's esophagus were treated between August 1996 and December 1999. Regeneration of esophageal mucosa was achieved with several sessions of EAPC under general anesthesia. All patients were receiving a double dose of proton pump inhibitors. Endoscopic follow-up was performed 6 to 8 weeks after the last session. Antireflux surgery (Nissen [n = 26] or Toupet [n = 4] fundoplication) followed complete regeneration of the squamous epithelium in the esophagus. One year after laparoscopic fundoplication and EAPC follow-up with endoscopy and quadrant biopsies of the esophagus, 24-hour pH monitoring and esophageal manometry were performed. All 30 patients showed complete regeneration of the squamous epithelium after a median of two sessions (range 1 to 7) of EAPC. Twenty-two patients underwent 1-year follow-up studies. All showed endoscopically an intact fundic wrap. Recurrence of a 1 cm segment of Barrett's epithelium without dysplasia was present in two patients, both of whom had recurrent acid reflux due to failure of their antireflux procedure. Our results indicate that the combination of EAPC and antireflux surgery is an effective treatment option in patients with Barrett's esophagus with gastroesophageal reflux disease. Long-term follow-up of this therapy is necessary to evaluate its effect on cancer risk in Barrett's esophagus. (J GASTROINTEST SURG 2001;5:251-259.)

KEY WORDS: Barrett's esophagus, antireflux surgery, endoscopic ablation, GERD

Columnar-lined epithelium with intestinal metaplasia in the distal esophagus, also known as Barrett's esophagus, is a premalignant lesion, which increases the risk of adenocarcinoma for the involved person 30- to 125-fold.[1,2] Gastroesophageal reflux disease (GERD) has been shown to be the most important underlying disorder for the development of Barrett's esophagus and the start of the reflux–intestinal metaplasia–dysplasia-carcinoma sequence.[3-13] Effective medical and surgical methods are available to treat GERD, but the effect on Barrett's epithelium with regard to regression and replacement by squamous epithelium has been disappointing.[14-19]

It has always been the aim of therapeutists—both gastroenterologists and surgeons—not to wait until a patient developed dysplasia or cancer, but to initiate complete regression of Barrett's esophagus by means of either drugs or surgery in order to prevent malignant degeneration. The published results on regression, both for proton pump inhibitor (PPI) therapy and antireflux surgery, show usually partial and only occasionally complete reversal of Barrett's epithelium. PPI medication for Barrett's esophagus caused a median reduction in Barrett's mucosa of less than 1 cm within a period of 12 to 49 months.[20] After fundoplication, Hölscher et al.[21] found partial regression in 3

From the Department of Surgery, Institute of Pathology (J.M.), University of Wuerzburg, Wuerzburg, Germany.
Presented at the Forty-First Annual Meeting of The Society for Surgery of the Alimentary Tract, San Diego, Calif., May 21-24, 2000.
Reprint requests: Prof. Dr. K.H. Fuchs, Department of Surgery, University of Wuerzburg, Josef-Schneider Str. 2, D-97080 Wuerzburg, Germany.

of 48 patients with a median follow-up of 82 months. Remarkably, complete reversal of Barrett's esophagus was found in 5 of 56 operated patients.[19] On the other hand, Barrett's esophagus developed in many cases despite PPI therapy, and even adenocarcinoma has been observed in a few instances after antireflux surgery.[22,23]

With the development of intraluminal endoscopic mucosal ablation techniques, initial experience was accumulated following removal of dysplastic areas in the distal esophagus.[24-26] Several investigators initiated pilot studies on the ablation of Barrett's epithelium without any dysplasia (i.e., with no need for therapeutic action).[27-29] Some initial reports showed promising results regarding replacement of Barrett's epithelium by squamous epithelium; others were disappointing, thus creating a controversial situation. In addition, critics claimed that this type of possibly preventive therapy was unnecessary, expensive, and possibly dangerous.

Therefore more objective data are needed regarding the procedure itself, possible complications and their prevention, patient responses to this therapy, short-term and long-term effects on the esophageal mucosa, and the success rate in complete regression of Barrett's esophagus. The following pilot study was undertaken to evaluate the success rate and risk of a combination therapy for patients with Barrett's esophagus treated with endoscopic argon plasma coagulation (EAPC) and PPI therapy followed by laparoscopic antireflux surgery.

MATERIAL AND METHODS

In the present study, Barrett's esophagus was defined as specialized intestinal metaplasia on a biopsy taken from any length of endoscopically visible columnar-lined epithelium within the tubular esophagus. Short-segment Barrett's esophagus was identified as an abnormal-appearing esophageal lining at endoscopy that was less than 3 cm in length, whereas long-segment Barrett's esophagus was equal to or greater than 3 cm in length.

Based on these definitions, patients were evaluated for possible consideration as candidates for our study. Additional criteria were the exclusion of severe comorbidity and age over 18 years. It was also recommended that patients have a life expectancy of more than 5 years. Further exclusion criteria were history of upper gastrointestinal surgery, such as antireflux procedures, partial or total gastrectomy, and confirmation of high-grade dysplasia or carcinoma in Barrett's esophagus.

Participants in the study were recruited from patients in our gastrointestinal laboratory who had typical gastroesophageal reflux symptoms such as heartburn, regurgitation, and epigastric burning. Corresponding to patient history or prior endoscopic findings, special attention was focused on suspicious areas in the distal esophagus on first endoscopy. If there were any indications, lesions were defined as either circumferential, semicircumferential, or composed of islands and tongues. Length of columnar-lined epithelium was also documented.

From August 1996 to December 1999, we used a combination of EAPC, PPI therapy, and laparoscopic antireflux surgery in 30 patients. The 23 men and seven women had a median age of 53.5 years (range 31 to 77 years). All of them had had symptoms of GERD, such as heartburn, regurgitation, and epigastric pain, for a median of 10 years (range 0.5 to 50 years). As treatment for their complaints, all patients were placed on proton pump inhibitors (20 to 60 mg/day) for more than 6 months.

We performed a standardized endoscopic assessment of Barrett's esophagus with patients in the left lateral position. Length was measured from the incisor teeth to the upper border of the gastric mucosa folds to determine the gastroesophageal junction. The length of columnar-lined epithelium was assessed between the upper border of the gastric folds and the squamocolumnar junction. In all patients in whom Barrett's esophagus was suspected, four-quadrant biopsies were taken in 1 cm increments over the total length of visible Barrett's epithelium for histopathologic evaluation, which was always conducted by the same pathologist (J.M.) to guarantee low observer variability. Initially, of primary importance was the exclusion of any dysplasia or cancer by means of a thorough endoscopic examination and biopsies.

All patients had chronic GERD. All of them underwent functional foregut testing with standardized stationary esophageal manometry, 24-hour esophageal and gastric pH monitoring, and 24-hour esophageal and gastric bilirubin monitoring. Operative and conservative treatment options were discussed if GERD was confirmed based on pathologic acid exposure in the esophagus and Barrett's epithelium was proved by histologic examination. Indications for antireflux surgery were established based on the presence of the following: progressive reflux disease with a positive response to PPI therapy but with symptoms remaining, thereby necessitating an increase in the PPI dosage, lower esophageal sphincter incompetence, and/or mixed acid and duodenogastroesophageal reflux. These patients were all included in the study. All patients were informed about the exact nature of their disease and the problem of intestinal metaplasia, possible complications of treatment such as perforation and strictures; they were also made aware of the limited experience with this new method. Informed consent was obtained from all participants in the study.

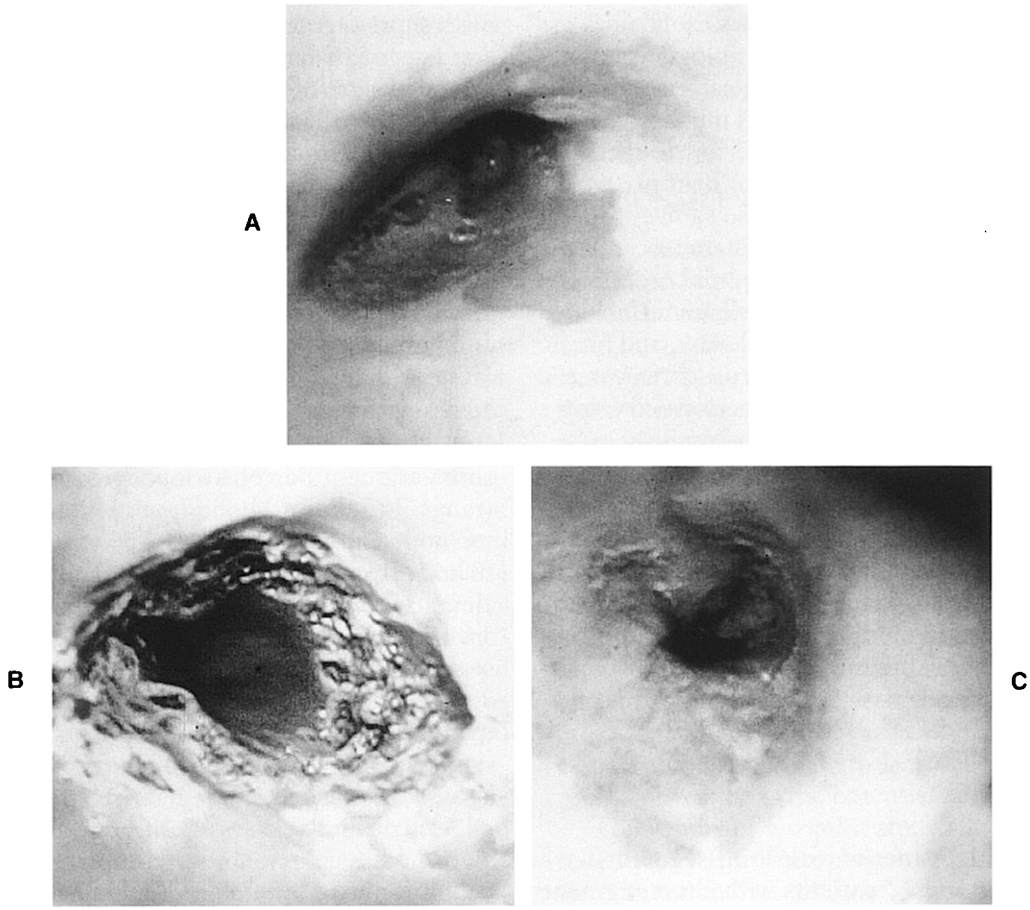

Fig. 1. Sequence of EAPC treatment on endoscopic view. **A,** Typical tongues of Barrett's epithelium. **B,** Completely coagulated and eradicated Barrett's epithelium. **C,** Total regression of Barrett's esophagus with squamous epithelium.

One or more sessions of endoscopic ablation therapy were performed using the APC 300 device (ERBE, Tuebingen, Germany) with the patients under general anesthesia. Argon plasma coagulation is an electrosurgical, monopolar, noncontact technique that applies high-frequency current to tissue via ionized and thus electrically conductive argon (electricity = 90 to 240 volts/50 to 60 Hz; power = up to 150 watts). The argon gas is ionized within an electrical field created between an electrode at the distal end of the probe used and the esophageal tissue (flow of 0.1 to 0.9 liters/min). The regenerated plasma beam directs its energy to the surface of the mucosa as this is the path of least resistance. Resistance keeps changing, that is, it keeps increasing at the surface of the esophageal tissue as soon as desiccation is achieved. The resulting coagulated and desiccated areas show limited depth of lesions to a maximum of 3 mm.

In this study, care was taken to systematically remove the columnar-lined epithelium until a burned surface was visible. Therefore this procedure was performed under general anesthesia in order to destroy all columnar epithelium in depth at the esophageal wall. This can be a time-consuming process and with the continuous flow of argon gas, it may not be well tolerated by patients. It was not sufficient to simply coagulate the mucosa (i.e., change the color of the mucosa). It was necessary to achieve by destruction of Barrett's esophagus from the distal to the proximal margin in a step-by-step fashion. General anesthesia provided optimal conditions for exact endoscopic targeting of the argon beam while performing EAPC. In patients with long-segment Barrett's esophagus, ablation therapy was first restricted to half the circumference to prevent strictures. In these patients, further sessions were used to complete the ablation therapy (Fig. 1). Regeneration of squamous epithelium under continuous PPI therapy (omeprazole, 40 mg/day) was achieved. The first follow-up endoscopy was performed 6 to 8 weeks after treatment. Standardized four-quadrant random biopsies at 1 cm intervals were repeated.

If complete regression of Barrett's esophagus was proved macroscopically and on histologic examination, laparoscopic Nissen fundoplication using the DeMeester technique, or in cases of impaired esophageal peristalsis a 240-degree posterior Toupet fundoplication, with combined posterior hiatoplasty, was performed. For this operation we used a five-port access to the abdomen, placing the camera trocar in the lower third of a line between the xiphoid process and the umbilicus. Important technical elements included crural and hiatal dissection, crural closure, and fundic mobilization by dividing the short gastric vessels. Placement of the fundic wrap was performed using a 45 to 60 Fr bougie inside the esophagus.

One-year postoperatively, endoscopic and histologic assessment of the regenerated squamous epithelium as well as possible recurrence of Barrett's esophagus was carried out. Functional foregut testing with stationary esophageal manometry and 24-hour esophageal and gastric pH monitoring was repeated.

For statistical evaluation, the Mann-Whitney U test and Student's t test were applied where appropriate. Significance was assumed at $P < 0.05$.

RESULTS

There were 18 patients with long-segment Barrett's esophagus and 12 patients with short-segment Barrett's esophagus. Dysplasia was not present in any of these patients. The median length of specialized columnar-lined epithelium was 3 cm (range 1 to 10 cm) before EAPC. Patients with short-segment Barrett's esophagus showed a median length of 2 cm (range 1 to 2 cm), whereas in patients with long-segment Barrett's esophagus median length was 5 cm (range 3 to 10 cm).

Functional foregut testing in all patients showed pathologic acid and/or bilirubin exposure in the esophagus. Twenty-seven of 30 patients proved to have pathologic gastroesophageal acid reflux on 24-hour pH monitoring. Median DeMeester score in these patients was 47.6 (range 3.6 to 193.2; normal <14.72). There were also 25 patients with increased reflux of bilirubin as shown on 24-hour bilirubin monitoring. The median bilirubin exposure of the esophagus in all patients was 19% (range 0.4 to 86.7%; normal <11%). On manometry all patients were found to have an incompetent lower esophageal sphincter (LES). A decrease in LES pressure was found in 26 patients. Nine had shortening of the total length of the LES, and 17 had shortening of the intra-abdominal length of the LES. All patients showed at least one pathologic LES-defining parameter. Patients with long-segment Barrett's esophagus had increased acid and bilirubin exposure compared to those with short-segment Barrett's esophagus. Patients with long-segment Barrett's esophagus had a median DeMeester score of 62.55 (range 7.7 to 193.2) compared to those with short-segment Barrett's esophagus whose median score was 24.25 (range 3.6 to 72.6) ($P < 0.01$). Median bilirubin exposure in patients with long-segment Barrett's esophagus was 25.8% of the time (range 1.4 to 86.7); in patients with short-segment Barrett's esophagus, exposure was 17.2% of the time (range 0.4 to 82.3; NS). Parameters for the LES incompetence and motility of the esophageal body were similar in both groups. Median pressure in patients with long-segment Barrett's esophagus was 3 mm Hg (range 0 to 10 mm Hg), and in those with short-segment Barrett's esophagus it was 4.5 mm Hg (range 2 to 8 mm Hg). The total length of the LES was found at median values of 3 cm (range 2 to 4 cm) in both groups, whereas intra-abdominal length in patients with long-segment Barrett's esophagus was 1 cm (range 0 to 2 cm) and in patients with short-segment Barrett's esophagus, 1.5 cm (range 0 to 2 cm). Impaired esophageal peristalsis on esophageal manometry was found in four patients, two with long-segment and two with short-segment Barrett's esophagus, respectively.

A median of two sessions (range 1 to 7) of EAPC were necessary to achieve complete eradication of columnar-lined epithelium (Table I). Treatment sessions under general anesthesia required a median of 35 minutes (range 15 to 50 minutes). Length of Barrett's esophagus correlated with the number of sessions. Patients with long-segment Barrett's esophagus underwent a median of three sessions for reversal of their disease, whereas short-segment Barrett's esophagus was eradicated after a median of two sessions. It must be emphasized that all patients had complete regression of columnar-lined epithelium, as documented on histologic examination, before surgery was performed.

Twenty-six patients underwent laparoscopic Nissen fundoplication. Because of impaired esophageal peristalsis, laparoscopic Toupet fundoplication was performed in four patients. Complications resulting from the 82 sessions of EAPC were rare. Two patients suffered from transient dysphagia and odynophagia, which were managed by doubling the PPI dose. Another patient developed a scar-like semicircumferential web formation in the lower third of the esophagus

Table I. Number of EAPC sessions (median 2)

Sessions	1	2	3	4	5	6	7
No. of patients	7	10	6	3	1	1	2

8 weeks after EAPC. This was resolved with another session of EAPC. We found no persistent dysphagia, esophageal perforation, or bleeding in any of these patients. During laparoscopic antireflux surgery, two cases of pneumothorax occurred and were treated with temporary drainage. Another patient developed skin emphysema secondary to pneumoperitoneum, but complete reversal was confirmed within a few days.

Until now, 1-year endoscopic follow-up with four-quadrant random jumbo biopsies were performed in 22 of the 30 patients. Two of these patients with a recurrence of reflux documented on 24-hour pH monitoring, which was due to fundoplication failure as documented on esophageal manometry, showed recurrence of short specialized columnar-lined epithelium at the gastroesophageal junction. One of these two patients had a Nissen fundoplication, and the other had a Toupet fundoplication; both were considered treatment failures. Lengths of Barrett's segments were less than 1 cm (Fig. 2). Histopathologic evaluation of localized jumbo biopsies proved Barrett's esophagus without dysplasia. Specimens from all other patients remained free of specialized columnar-lined epithelium (Fig. 3). Thus far, dysplasia has not been detected at any of the follow-up investigations. In six patients, antireflux surgery had been performed less than 1 year earlier. Two patients have refused follow-up assessment.

Postoperative functional foregut monitoring showed a decrease in acid exposure to normal values in 20 of 22 patients. The median DeMeester score changed from a preoperative value of 47.7 to 9.9 postoperatively (range 0.4 to 108) ($P < 0.01$). Two patients with recurrence of reflux did have failure of their fundoplications as mentioned earlier with manometric incompetence; in all other patients the LES was competent ($P < 0.01$ compared to preoperative assessment). The two patients with fundoplication failure were treated with PPI therapy and remain under surveillance.

DISCUSSION

The indications for using EAPC to eradicate columnar-lined epithelium without any dysplasia should be subject to critical evaluation. On the one hand, a reduction in cancer risk is desirable; on the other hand, the number of patients actually dying of Barrett's adenocarcinoma is low. Even the cost-benefit relationship of a patient surveillance program is open to discussion. And now an expensive and rather invasive therapeutic concept is offered to these patients, thus far with no proven benefit. As has often been the case with the introduction of new technologies in the past, methods are quickly embraced by many physicians before proper trials can be conducted to evaluate safety, feasibility, and efficacy. As a consequence, we have held frequent in-depth discussions and think it is important to assess these methods of endoscopic ablation as soon as possible to learn about the risks and problems as well as the potential benefits.

The results of our pilot study show that complete reversal of Barrett's esophagus could be achieved with a combination of EAPC and continuous PPI therapy. Regular squamous epithelium replaced Barrett's epithelium in all of the participants in our study. In contrast to most other studies on ablation of Barrett's esophagus, patients in our study were treated with fundoplication after the combination of EAPC and PPI treatment proved successful. EAPC was performed before surgery, since endoscopic inspections and manipulations in the distal esophagus are easier

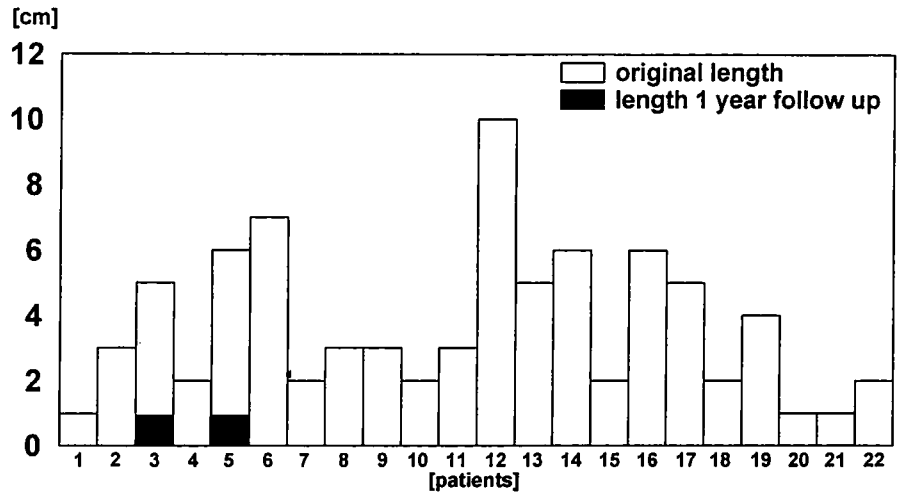

Fig. 2. Results of 1-year follow-up endoscopy with four-quadrant random jumbo biopsies in 22 patients.

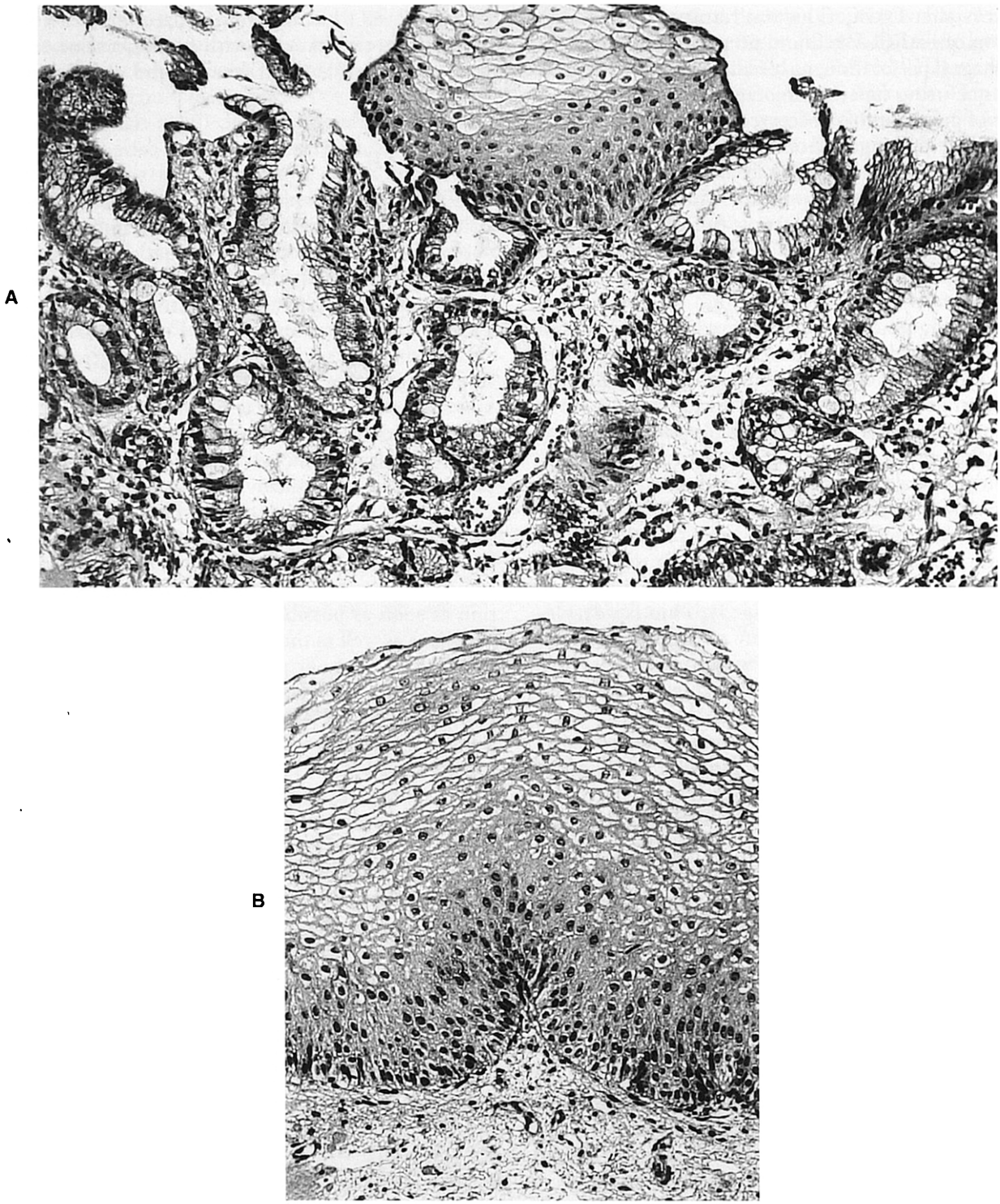

Fig. 3. Results of histologic examination. **A,** Barrett's esophagus with goblet cells before treatment. **B,** Complete reepithelization with squamous epithelium after EAPC.

to carry out in the preoperative state when the lumen is rather wide after air insufflation in contrast to the limited size of the lumen in the LES area postoperatively after fundoplication. Grade et al.[30] noted reepithelization with squamous epithelium after argon plasma coagulation of half the circumference of Barrett's esophagus. The untreated area of Barrett's esophagus in these patients served as an internal control but no regression of Barrett's epithelium was achieved despite medical acid suppression (PPI). An

endoscopic view showed that Van Laethem et al.[31] were successful in achieving complete reversal of Barrett's esophagus after argon plasma coagulation in 81% of their patients. These macroscopic results were quite different from the histopathologic findings as only 61% of these aforementioned patients showed no columnar-lined specialized intestinal metaplasia of the esophagus after ablation therapy. Another study of EAPC showed complete reversal of Barrett's esophagus in 13 of 15 patients. This was confirmed on both endoscopic and histopathologic evaluation after four-quadrant biopsies.[27]

Thus the previously cited studies of EAPC reported coincidentally high percentages of Barrett's regression. However, sometimes there was a remarkable discrepancy between macroscopic and histopathologic findings, which may be caused by overgrowing of regenerated squamous epithelium on remaining small islands of Barrett's esophagus if they are not completely removed. The incomplete removal of Barrett's esophagus creates two problems, one in leaving tissue with a potential increased cancer risk and second in the camouflage of remaining small islands of Barrett's esophagus by overgrowing squamous epithelium layers. This was one of our main concerns, which forced us to concentrate most of our efforts on a thoroughly time-consuming complete mucosal ablation with argon plasma coagulation performed under general anesthesia.

In the literature, a correlation between length of Barrett's esophagus and its potential for malignancy is emphasized.[14,32,33] However, it is clear that even short-segment Barrett's esophagus is a premalignant lesion, although the prevalence of dysplasia and carcinogenesis seems to be lower.[34] Therefore it is worthwhile to achieve near-complete eradication of Barrett's esophagus by careful step-by-step application of the argon beam.

PPI therapy is effective in reducing acid exposure in the esophagus.[35-39] Problems of PPI therapy are acid breakthrough and a limited reduction of duodenogastroesophageal reflux. In our study, antireflux surgery was employed in all patients. The rationale for this therapeutic concept was reversal of the premalignant lesion by EAPC and PPI therapy and correction of the functional defect by antireflux surgery, thus preventing further exposure of the regenerated squamous epithelium to noxious agents. Antireflux surgery is able to stop both acid and duodenogastroesophageal reflux, the latter being obviously involved in or associated with Barrett's esophagus.[6,9,12] This could be the reason for the high percentage of complete remissions in our study.

Only two of our patients revealed short tongues of recurrent Barrett's epithelium at the gastroesophageal junction without dysplasia. All others remained with complete regenerated squamous epithelium. It must be emphasized that both patients with recurrent Barrett's epithelium of the lower esophagus had failure of their antireflux procedure with increased esophageal acid exposure. A case report presented by Brandt et al.[40] noted similar findings. These investigators found recurrence of Barrett's esophagus after thermal ablation and PPI therapy once the proton pump inhibitors were discontinued.

Besides EAPC there are other endoscopic ablative therapies. Salo et al.[41] conducted a prospective study in 17 patients after antireflux surgery. With the use of the Nd:YAG laser, all treated patients had complete reversal of Barrett's esophagus, and only two showed specialized intestinal metaplasia of the cardia with a mean follow-up of 26 months. Successfully localized squamous reepithelization has also been reported with the use of laser and PPI therapy.[28,29] Critics of ablative laser therapy fear a higher rate of perforation, because even low-energy doses may be responsible for uncontrolled destruction of deeper esophageal tissue.[24]

Application of photodynamic therapy implies selective sensitization of precancerous or even malignant lesions of the esophagus for subsequent endoscopically controlled, photoinduced tissue ablation with remarkable success, but has less effect on nondysplastic intestinal metaplasia.[25,26,42-44]

Multipolar electrocoagulation (MPEC) offers a less expensive therapeutic option for eradicating Barrett's esophagus. Sampliner et al.[45] conducted a study in 10 patients, where in a first trial half of the Barrett's circumference was treated with MPEC under continued proton pump inhibitors, which showed effective reversal of Barrett's esophagus. A second trial was then begun on the untreated half of the remaining Barrett's esophagus, in which complete regression of Barrett's epithelium after MPEC was confirmed histologically in all patients for at least 1 year. The reported complications of MPEC, such as odynophagia, dysphagia, or chest pain, were only transient in character and were therefore similar to those known to occur following EAPC.

MPEC and EAPC both seem to have several advantages over laser and photodynamic therapy that make them more attractive and suitable for clinical studies. Both provide a relatively inexpensive power source and both are available in nearly all gastrointestinal endoscopy units.

CONCLUSION

EAPC in combination with antireflux surgery provides an effective treatment option in Barrett's esophagus with GERD. It has been shown that complete reversal of Barrett's esophagus in an anacid environment is possible. One year follow-up of the treated

patients proved persistence of regenerated squamous epithelium and total regression of Barrett's esophagus in most cases.

Future investigations on this subject must address the issue of whether regression of Barrett's esophagus results in the proposed interruption of the metaplasia-dysplasia-carcinoma sequence with reduced cancer risk. We should then be able to define which patients are at risk for developing adenocarcinoma of the esophagus. Therefore sensitive molecular and/or histologic markers must be identified in future studies. This would help to focus surveillance and ablation therapy on those few patients who are at risk for cancer, sparing the great majority.

REFERENCES

1. Hameeteman W, Tytgat GN, Houthoff HJ, van den Tweel JG. Barrett's esophagus: Development of dysplasia and adenocarcinoma. Gastroenterology 1989;96:1249-1256.
2. Pera M, Cameron AJ, Trastek VF, Carpenter HA, Zinsmeister AR. Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. Gastroenterology 1993;104: 510-513.
3. Bremner CG, Lynch VP, Ellis FH. Barrett's esophagus: Congenital or acquired? An experimental study of esophageal mucosal regeneration in the dog. Surgery 1970;68:209-216.
4. Champion G, Richter JE, Vaezi MF, Singh S, Alexander R. Duodenogastroesophageal reflux: Relationship to pH and importance in Barrett's esophagus. Gastroenterology 1994;107: 747-754.
5. Clark GW, Smyrk TC, Mirvish SS, Anselmino M, Yamashita Y, Hinder RA, DeMeester TR, Birt DF. Effect of gastroduodenal juice and dietary fat on the development of Barrett's esophagus and esophageal neoplasia: An experimental rat model. Ann Surg Oncol 1994;1:252-261.
6. Fein M, Peters JH, Chandrasoma P, Ireland AP, Öberg S, Ritter MP, Bremner CG, Hagen JA, DeMeester TR. Duodenoesophageal reflux induces esophageal adenocarcinoma without exogenous carcinogen. J GASTROINTEST SURG 1998;2: 260-268.
7. Gillen P, Keeling P, Byrne PJ, Healy M, O'Moore PR, Hennessy TPJ. Implication of duodenogastric reflux in the pathogenesis of Barrett's oesophagus. Br J Surg 1988;75:540-543.
8. Vaezi MF, Richter JE. Synergism of acid and duodenogastroesophageal reflux in complicated Barrett's esophagus. Surgery 1995;117:699-704.
9. Pera M, Trastek VF, Carpenter HA, Fernandez PL, Cardesa A, Mohr U, Pairolero PC. Influence of pancreatic and biliary reflux on the development of esophageal carcinoma. Ann Thorac Surg 1993;55:1386-1392.
10. Kauer WK, Peters JH, DeMeester TR, Ireland AP, Bremner CG, Hagen JA. Mixed reflux of gastric and duodenal juices is more harmful to the esophagus than gastric juice alone. The need for surgical therapy reemphasized. Ann Surg 1995; 222:525-531.
11. Sampliner RE. The Practice Parameters Committee of the American College of Gastroenterology. Practice Guidelines on the Diagnosis, Surveillance, and Therapy of Barrett's Esophagus. Am J Gastroenterol 1998;93:1028-1032.
12. Fuchs KH, Freys SM, Heimbucher J, Fein M, Thiede A. Pathophysiologic spectrum in patients with gastroesophageal reflux disease in a surgical GI-function laboratory. Dis Esophagus 1985;8:211-217.
13. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825-831.
14. Weston AP, Krmpotich PT, Cherian R, Dixon A, Topalosvki M. Prospective long-term endoscopic and histological follow-up of short segment Barrett's esophagus: Comparison with traditional long segment Barrett's esophagus. Am J Gastroenterol 1997;92:407-413.
15. Sharma P, Sampliner RE, Camargo E. Normalization of esophageal pH with high-dose proton pump inhibitor therapy does not result in regression of Barrett's esophagus. Am J Gastroenterol 1997;92:582-585.
16. Sampliner RE. Effect of up to 3 years of high-dose lansoprazole on Barrett's esophagus. Am J Gastroenterol 1994;89: 1844-1848.
17. Wellinger J, Ollyo JB, Savary M, Fontolliet C, Chapuis G. Le traitment chirurgical de l'endobrachy-oesophage. Helv Chir Acta 1989;55:695-698.
18. Williamson WA, Ellis FH, Gibb SP, Shahian DM, Aretz HT. Effect of antireflux operation on Barrett's mucosa. Ann Thorac Surg 1990;49:537-541.
19. Sagar PM, Ackroyd R, Hosie KB, Patterson JE, Stoddard CJ, Kingsnorth AN. Regression and progression of Barrett's oesophagus after antireflux surgery. Br J Surg 1995;82:806-810.
20. Sampliner RE. Are proton pump inhibitors alone able to induce regression in the length of Barrett's esophagus? In Giuli R, Galmich J-P, Jamieson GG, Scarpignato C, eds. OESO. The esophagogastric junction, Paris: John Libbey Eurotext, 1998, pp 1011-1012.
21. Hölscher H, Gutschow C, Beckurts KTE, Schneider P. What is the evolution of Barrett's mucosa after antireflux surgery? In Giuli R, Galmich J-P, Jamieson GG, Scarpignato C, eds. OESO. The esophagogastric junction, Paris: John Libbey Eurotext, 1998, pp 1047-1052.
22. Hamilton SR, Hutcheon DF, Ravich WJ, Cameron JL, Paulson M. Adenocarcinoma in Barrett's esophagus after elimination of gastroesophageal reflux. Gastroenterology 1984;86: 356-360.
23. Hakansson HO, Johnsson F, Johansson J, Kjellen G, Walther B. Development of adenocarcinoma in Barrett's oesophagus after successful antireflux surgery. Eur J Surg 1997;163:469-471.
24. Luman W, Lessels A, Palmer KR. Failure of Nd-YAG photocoagulation therapy as treatment of Barrett's esophagus—a pilot study. Eur J Gastroenterol Hepatol 1996;8:627-630.
25. Overholt BF, Panjehpour M. Photodynamic therapy in Barrett's esophagus: Reduction of specialized mucosa, ablation of dysplasia, and treatment of superficial esophageal cancer. Semin Surg Oncol 1995;11:372-376.
26. Overholt BF, Panjehpour M. Photodynamic therapy for Barrett's esophagus: Clinical update. Am J Gastroenterol 1996;91: 1719-1723.
27. Mörk H, Barth T, Kreipe HH, Kraus M, Al-Taie O, Jacob F, Scheurlen M. Reconstitution of squamous epithelium in Barrett's oesophagus with endoscopic argon plasma coagulation: A prospective study. Scand J Gastroenterol 1998;33:1130-1134.
28. Sampliner RE, Hixon LJ, Fennerty MB, Garewal HS. Regression of Barrett's esophagus by laser ablation in an anacid environment. Dig Dis Sci 1993;38:365-368.
29. Berenson MM, Johnson TD, Markowitz NR, Buchi KN, Samowitz WS. Restoration of squamous mucosa after ablation of Barrett's esophageal epithelium. Gastroenterology 1993;104:1686-1691.
30. Grade AJ, Shah IA, Medlin SM, Ramirez FC. The efficacy and safety of argon plasma coagulation therapy in Barrett's esophagus. Gastrointest Endosc 1999;50:18-22.

31. Van Laethem JL, Cremer M, Peny MO, Delhaye M, Deviere J. Eradication of Barrett's mucosa with argon plasma coagulation and acid suppression: Immediate and mid term results. Gut 1998;43:747-751.
32. Iftikhar SY, James PD, Steele RJ, Hardcastle JD, Atkinson M. Length of Barrett's oesophagus: An important factor in the development of dysplasia and adenocarcinoma. Gut 1992;33: 1155-1158.
33. Menke-Pluymers MB, Hop WC, Dees J, van Blankenstein M, Tilanus HW. Risk factors for the development of an adenocarcinoma in columnar-lined (Barrett's) esophagus. Cancer 1993;72:1155-1158.
34. Clark GWB, Ireland AP, Peters JH, Chandrasoma P, DeMeester TR, Bremner CG. Short-segment Barrett's esophagus: A prevalent complication of gastroesophageal reflux disease with malignant potential. J GASTROINTEST SURG 1997;1: 113-122.
35. Spechler SJ. Pathogenese und Epidemiologie des Barrett-Ösophagus. Chirurg 1994;65:84-87.
36. Peters FT, Ganesh S, Kuipers EJ, Sluiter WJ, Klinkenberg-Knol EC, Lamers CBHW, Kleibeuker JH. Endoscopic regression of Barrett's oesophagus during omeprazole treatment: A randomised double blind study. Gut 1999;45:489-494.
37. Gore S, Healey CJ, Sutton R, Eyre-Brook IA, Gear MW, Shepherd NA, Wilkinson SP. Regression of columnar lined (Barrett's) oesophagus with continuous omeprazole therapy. Aliment Pharmacol Ther 1993;7:623-628.
38. Sampliner RE, Mackel C, Jennings D, Greski-Rose P. Effect of 12 months of a proton pump inhibitor (Lansoprazole) on Barrett's esophagus: A randomized trial. Gastroenterology 1992;102:A157.
39. Fuchs KH, Feussner H, Bonavina L, Collard JM, Coosemans W. Current status and trends in laparoscopic antireflux surgery: Results of a consensus meeting. Endoscopy 1997; 29:298-308.
40. Brandt LJ, Blansky RL, Dauvar DR. Repeat laser therapy of recurrent Barrett's epithelium: Success with anacidity. Gastrointest Endosc 1995;41:267.
41. Salo JA, Salminen JT, Kiviluoto TA, Nemlander AT, Rämö OJ, Färkkilä MA, Kivilaakso EO, Mattila SP. Treatment of Barrett's esophagus by endoscopic laser ablation and antireflux surgery. Ann Surg 1998;227:40-44.
42. Overholt BF, Panjehpour M, Haydek JM. Photodynamic therapy for Barrett's esophagus: Follow-up in 100 patients. Gastrointest Endosc 1999;49:1-7.
43. Van den Boogert J, van Hillegersberg R, Siersema PD, de Bruin RWF, Tilanus HW. Endoscopic ablation therapy for Barrett's esophagus with high-grade dysplasia: A review. Am J Gastroenterol 1999;94:1153-1160.
44. Gossner L, Stolte M, Sroka R, Rick K, May A, Hahn EG, Ell C. Photodynamic ablation of high-grade dysplasia and early cancer in Barrett's esophagus by means of 5-aminolevulinic acid. Gastroenterology 1998;114:448-455.
45. Sampliner RE, Fennerty B, Garewal HS. Reversal of Barrett's esophagus with acid suppression and multipolar electrocoagulation: Preliminary results. Gastrointest Endosc 1996;44: 532-535.

Discussion

Dr. S. Atwood (Manchester, U.K.). I have two questions concerning the techniques you used. First, why did you use a general anesthetic and hospitalize your patients for 2 days? We conducted a similar study, as you probably know, and only used sedation, and we performed the procedure on an outpatient basis. Second, why did you perform the operation after EAPC? Would it not have been better theoretically to control the reflux first and then perform EAPC later on, rather than leave the patients on protein pump inhibitors?

Dr. H. Tigges. Recent studies show that there are islands of Barrett's esophagus underneath the squamous epithelium. Therefore our aim was to perform a complete ablation. We thought it best to do this under general anesthesia, to prevent side effects. With respect to the order of treatment, we initially did it the way you suggested. We found that this sequence was undesirable because the gastroesophageal junction is difficult to examine when the antireflux surgery has already been done. We found it is easier to do the other way around.

Dr. M.G. Sarr (Rochester, Minn.). Who should undergo this treatment—everyone with Barrett's esophagus or only those with dysplasia?

Dr. Tigges. Up to now we have not had enough experience to say which patients should have this therapy. We would suggest using this therapy only in patients without dysplasia for now with a study protocol.

Dr. J.G. Hunter (Atlanta, Ga.). Which is better, this or photodynamic therapy (PDT)? Which is more complete? Which is deeper? Do you have any comparative data?

Dr. Tigges. In recent publications it has been reported that recurrences of Barrett's epithelium can occur after PDT and after argon plasma coagulation or laser therapy. This may be due to the depths of the lesions, as you stated. With argon plasma coagulation and laser, it is possible to treat deeper lesions than with PDT.

Dr. Hunter. Is this why there are more complications?

Dr. Tigges. Yes, maybe.

Dr. K.H. Fuchs (Wurzburg, Germany). I want to come back to the first question about general anesthesia. The biggest concern in discussions on ablative therapy with EAPC is that islands are left in the depth, and that is why advocates of PDT say PDT should be used. However, PDT does not work as well on metaplasia as it does on dysplasia. With the patient under anesthesia, it is possible to spend time not just coagulating the mucosa but removing the mucosa in depth to make sure we do not leave islands of Barrett's esophagus.

Esophageal Dysmotility and Gastroesophageal Reflux Disease

Urs Diener, M.D., Marco G. Patti, M.D., Daniela Molena, M.D., Piero M. Fisichella, M.D., Lawrence W. Way, M.D.

Gastroesophageal reflux disease (GERD) produces a spectrum of symptoms ranging from mild to severe. While the role of the lower esophageal sphincter in the pathogenesis of GERD has been studied extensively, less attention has been paid to esophageal peristalsis, even though peristalsis governs esophageal acid clearance. The aim of this study was to evaluate the following in patients with GERD: (1) the nature of esophageal peristalsis and (2) the relationship between esophageal peristalsis and gastroesophageal reflux, mucosal injury, and symptoms. One thousand six consecutive patients with GERD confirmed by 24-hour pH monitoring were divided into three groups based on the character of esophageal peristalsis as shown by esophageal manometry: (1) normal peristalsis (normal amplitude, duration, and velocity of peristaltic waves); (2) ineffective esophageal motility (IEM; distal esophageal amplitude <30 mm Hg or >30% simultaneous waves); and (3) nonspecific esophageal motility disorder (NSEMD; motor dysfunction intermediate between the other two groups). Peristalsis was classified as normal in 563 patients (56%), IEM in 216 patients (21%), and NSEMD in 227 patients (23%). Patients with abnormal peristalsis had worse reflux and slower esophageal acid clearance. Heartburn, respiratory symptoms, and mucosal injury were all more severe in patients with IEM. These data show that esophageal peristalsis was severely impaired (IEM) in 21% of patients with GERD, and this group had more severe reflux, slower acid clearance, worse mucosal injury, and more frequent respiratory symptoms. We conclude that esophageal manometry and pH monitoring can be used to stage the severity of GERD, and this, in turn, should help identify those who would benefit most from surgical treatment. (J GASTROINTEST SURG 2001;5:260-265.)

KEY WORDS: Gastroesophageal reflux disease, esophageal peristalsis, lower esophageal sphincter, esophageal acid clearance, antireflux surgery

The symptoms of gastroesophageal reflux disease (GERD) range from mild to severe. The role of the lower esophageal sphincter (LES) in the pathogenesis of GERD has been studied extensively,[1-3] but less attention has been paid to esophageal peristalsis, even though peristalsis controls esophageal acid clearance.[4-6] Approximately 60% of patients with GERD have a mechanically defective LES,[1] and approximately 60% have abnormal peristalsis as shown by esophageal manometry.[4] The latter abnormalities have been referred to as nonspecific esophageal motility disorder (NSEMD), a heterogeneous syndrome that occupies the middle ground between patients with normal esophageal peristalsis and those with primary esophageal motility disorders such as achalasia.[7] Recent work has highlighted the subgroup of patients with GERD who have severely abnormal peristalsis (amplitude <30 mm Hg or nontransmitted contractions in >30% of wet swallows in the distal esophagus), a condition labeled ineffective esophageal motility (IEM). IEM patients have more severe reflux and a higher incidence of respiratory symptoms.[8,9]

The aim of this study was to determine the following in patients with GERD: (1) the nature of esophageal peristalsis and (2) the effect of esophageal dysmotility on gastroesophageal reflux, mucosal injury, and symptoms.

PATIENTS AND METHODS

One thousand six consecutive patients with GERD confirmed by 24-hour pH monitoring (defined by the percentage of time the pH was <4.0 and by the composite reflux score) were divided into the following

From the Department of Surgery, University of California, San Francisco, San Francisco, Calif.
Reprint requests: Marco G. Patti, M.D., Department of Surgery, University of California, 533 Parnassus Ave., Room U-122, San Francisco, CA 94143-0788. e-mail: pattim@surgery.ucsf.edu

Table I. Demographic data

	Peristalsis		
	Normal (n = 567)	NSEMD (n = 227)	IEM (n = 216)
Age (yr)	48 ± 14	51 ± 15	51 ± 15
Sex (female/male)	284/279	108/119	84/132
Weight (pounds)	175 ± 39	174 ± 36	177 ± 33
Duration of symptoms (mo)	81 ± 96	100 ± 102	105 ± 111

three groups based on the character of esophageal peristalsis as shown by esophageal manometry: (1) normal peristalsis (normal amplitude, duration, and velocity of peristaltic waves); (2) IEM (distal esophageal amplitude <30 mm Hg or >30% simultaneous waves in the distal esophagus); and (3) NSEMD (peristaltic abnormalities intermediate between the other two groups). Distal esophageal amplitude was between 30 and 59 mm Hg, and less than 30% of peristaltic waves in the distal esophagus were simultaneous). Table I summarizes the demographic data in these 1006 patients.

Every patient was questioned regarding the presence and duration of symptoms (heartburn, regurgitation, dysphagia, cough). The degree of mucosal injury was graded according to the Savary-Miller classification.[10] All patients were studied after an overnight fast using techniques previously described.[11] Medications that might interfere with esophageal motor function (i.e., nitrates, metoclopramide, cisapride, and calcium channel–blocking agents) were discontinued at least 48 hours before the study, and acid-suppressing medications were discontinued 3 days (H_2-blocking agents) to 14 days (proton pump inhibitors) before the study. Length and pressure of the LES were calculated using the station pull-through technique, with 0.5 cm increments between stations. Esophageal body function was recorded 3, 8, 13, and 18 cm above the upper border of the LES using 10 swallows of 5 ml of water. Amplitude of the peristaltic waves was calculated independently for the distal (3 and 8 cm above LES) and the proximal esophagus (13 and 18 cm above LES).[12] The data were analyzed using a commercial software program (Gastrosoft, Medtronic Functional Diagnostic, Shoreview, Minn.).

Ambulatory 24-Hour pH Monitoring

Acid-suppressing medications were discontinued 3 days (H_2-blocking agents) or 14 days (proton pump inhibitors) before the study. The pH catheters were calibrated in a standard buffer solution at pH 1 and 7 before and after monitoring. We used pH catheters with two antimony sensors located 15 cm apart. The catheters were passed transnasally in order to position the two sensors 5 cm and 20 cm above the upper border of the manometrically determined LES.[13] During the study the patients consumed an unrestricted diet and took no medications that could interfere with the results. Esophageal acid exposure (percentage of time pH <4) in the upright and supine positions and esophageal acid clearance (mean duration of a reflux episode) were calculated for the distal and proximal esophagus using a commercial software program (Gastrosoft).

Statistical Analysis

Analysis of variance, the Mann-Whitney rank-sum test, and the chi-square test were used for statistical evaluation of the data. All results are expressed as mean ± standard deviation. Differences were considered significant at $P < 0.05$.

RESULTS

The 1006 patients were classified as follows: 563 (56%) had normal peristalsis, 216 (21%) had IEM, and 227 (23%) had NSEMD.

Symptomatic Evaluation

Table II describes the symptoms in the three groups. Heartburn and dysphagia were less frequent among the normal patients compared to those with NSEMD and IEM. There were no differences in the prevalence and severity of dysphagia among the three groups of patients. There was no difference in the incidence of regurgitation among the three groups. The frequency of cough paralleled the severity of peristaltic dysfunction.

Endoscopy

The endoscopic findings were available for 814 (81%) of the 1006 patients. Endoscopy had been performed within 4 months of esophageal function testing. Grade 0 esophagitis was more frequent among

Table II. Symptoms

	Peristalsis		
	Normal (n = 567)	**NSEMD (n = 227)**	**IEM (n = 216)**
Heartburn (% of patients)	80	89*	89†
Regurgitation (% of patients)	71	78	75
Dysphagia (% of patients)	36	46*	44†
Dysphagia score (0-4)	2.5 ± 1	2.5 ± 1	2.5 ± 1
Cough (% of patients)	20	37*	49‡

$P < 0.05$ considered significant.
*Significant difference NSEMD vs. normal.
†Significant difference IEM vs. normal.
‡Significant difference IEM vs. NSEMD and normal.

Table III. Esophageal manometry

	Peristalsis		
	Normal (n = 567)	**NSEMD (n = 227)**	**IEM (n = 216)**
LES pressure (mm Hg)	11 ± 5	9 ± 5*	8 ± 5†
LES length (cm)	2.5 ± 0.9	2.3 ± 0.9*	2.1 ± 0.9†
LES abdominal length (cm)	1.7 ± 1	1.3 ± 0.9*	1.3 ± 0.9†
DEA (mm Hg)	91 ± 30	53 ± 25*	30 ± 17‡
PEA (mm Hg)	61 ± 25	44 ± 20	32 ± 18‡

LES = lower esophageal sphincter; DEA = distal esophageal amplitude; PEA = proximal esophageal amplitude.
$P < 0.05$ considered significant.
*Significant difference NSEMD vs. normal.
†Significant difference IEM vs. normal.
‡Significant difference IEM vs. NSEMD and normal.

Table IV. Ambulatory 24-hour pH monitoring (distal esophagus, 5 cm above LES)

	Peristalsis		
	Normal (n = 567)	**NSEMD (n = 227)**	**IEM (n = 216)**
No. of reflux episodes	148 ± 93	179 ± 117*	187 ± 142†
No. of reflux episodes >5 min	6 ± 5	8 ± 6*	9 ± 8†
Longest reflux episode (min)	31 ± 34	36 ± 34	48 ± 73†
% Time pH <4 (total)	13 ± 10	17 ± 12*	19 ± 16†
% Time pH <4 (upright)	14 ± 10	17 ± 13*	19 ± 14†
% Time pH <4 (supine)	11 ± 13	16 ± 16*	19 ± 21†
Combined reflux (% of patients)	60	70*	71†
Acid clearance (min)	1.4 ± 1.3	1.5 ± 1.6	2.1 ± 1.3‡
Reflux score (normal <14)	50 ± 33	63 ± 30*	71 ± 23‡

$P < 0.05$ considered significant.
*Significant difference NSEMD vs. normal.
†Significant difference IEM vs. normal.
‡Significant difference IEM vs. NSEMD and normal.

Table V. Ambulatory 24-hour pH monitoring (proximal esophagus, 20 cm above LES)

	Peristalsis		
	Normal (n = 567)	NSEMD (n = 227)	IEM (n = 216)
No. of reflux episodes	41 ± 38	39 ± 42	34 ± 43
No. of reflux episodes >5 min	0.9 ± 1.2	1.1 ± 4.4	0.9 ± 1.8
Longest reflux episode (min)	9 ± 17	9 ± 16	7 ± 13
% Time pH <4 (total)	2.5 ± 3.4	2.2 ± 3.1	2.1 ± 3.7
% Time pH <4 (upright)	2.6 ± 3.5	2.3 ± 3.6	2.0 ± 3.7
% Time pH <4 (supine)	2.2 ± 5.3	1.9 ± 4.2	2.0 ± 5.3
Acid clearance (min)	0.9 ± 2.0	0.9 ± 1.9	0.8 ± 1.9

There was no difference among the three groups of patients for any of the parameters considered.

the patients with normal (N) peristalsis (N = 56%; NSEMD = 42%; IEM = 47%; $P < 0.05$ N vs. NSEMD and IEM); grade I/II esophagitis was more common among the patients with NSEMD (N = 27%; NSEMD = 33%; IEM = 23%; $P < 0.05$ NSEMD vs. N and IEM); and grade III/IV esophagitis was more common among the patients with IEM and NSEMD than among those with normal peristalsis (N = 17%; NSEMD = 25%; IEM = 30%; $P < 0.05$ IEM and NSEMD vs. N).

Esophageal Manometry

The NSEMD and IEM patients had a shorter and weaker LES compared with the normal patients (Table III). By definition, the amplitude of peristaltic waves in the distal esophagus was progressively lower ranging from normal to NSEMD to IEM. The amplitude of peristaltic waves in the proximal esophagus was also lower in IEM patients compared to normal and NSEMD patients.

Ambulatory 24-Hour pH Monitoring

Distal Reflux (5 cm above the LES). Compared with the normal patients, those with abnormal peristalsis (NSEMD and IEM) had worse reflux, consisting of more episodes, more time with pH below 4 (both in the upright and supine positions), higher reflux scores, and slower esophageal acid clearance (Table IV).

Proximal Reflux (20 cm above the LES). There was no difference among the three groups of patients with regard to acid exposure and acid clearance (Table V).

DISCUSSION

Among these patients with GERD, esophageal peristalsis was normal in 56% and abnormal in 44%. About one fifth of all patients had IEM, with weak peristalsis in the distal and proximal esophagus and frequent nonpropagating peristaltic sequences. This group had more severe reflux, slower acid clearance, worse mucosal injury, and more frequent respiratory symptoms.

In general, the more abnormal the esophageal peristalsis, the worse the gastroesophageal reflux. Normal esophageal peristalsis was associated with less esophageal acid exposure, and fewer reflux episodes and episodes longer than 5 minutes, and acid clearance was usually normal. Combined reflux (upright and supine) was present in 60% of normal patients. Esophageal dysmotility (NSEMD and IEM) was associated with longer esophageal acid exposure, more and longer reflux episodes, and slower esophageal acid clearance. Approximately 70% of patients with dysmotility had combined reflux.

These findings coincide with others,[5] which show that the amplitude of peristalsis is the main determinant of esophageal acid clearance. Bolus clearance in the proximal esophagus requires contractions with a minimal amplitude of 16 mm Hg, and clearance in the distal esophagus requires contractions with a minimal amplitude of 30 mm Hg.[5] Leite et al.[8] reported that patients with IEM have increased esophageal acid exposure and slower esophageal acid clearance in the supine position. In contrast, we found more severe reflux in both the supine and upright positions in patients with IEM.

Worse esophageal peristalsis was also accompanied by more severe mucosal injury. Most normal patients had endoscopic esophagitis in the grade 0 to II range; only 17% of normal patients had grade III or IV esophagitis. In contrast, among patients with esophageal dysmotility, grade III/IV esophagitis was present more often. For instance, the incidence of histologically proved Barrett's esophagus was almost twice as common in patients with IEM than in those with normal peristalsis. Other investigators have found a sim-

ilar relationship between the degree of peristaltic dysfunction and the degree of mucosal injury, the latter being worse in patients with Barrett's esophagus or esophageal strictures.[4,14]

Whether the disorders of peristalsis are a consequence of esophagitis or just another component (along with sphincter dysfunction) of a complex foregut motor disease is still being debated. Although some investigators argue in favor of the former opinion, evidence for it is scant. Furthermore, neither medical[15] nor surgical[16] treatment of esophagitis improves peristaltic dysfunction appreciably. Thus the balance of evidence supports the view that the abnormal peristalsis is part of the disease rather than a side effect of the reflux. However, these manometric findings are a brief snapshot in time of an individual's esophageal performance, and it is not known if they remain constant over time.

Patients with IEM presented more often with cough. In fact, almost half of all IEM patients listed unexplained cough as a major complaint. Our data confirm the findings of Fouad et al.,[9] who found that IEM was the most common motility abnormality in patients with GERD-associated respiratory symptoms. Whereas in most patients cough is probably due to bronchoconstriction secondary to a vagal reflex,[17] in some patients respiratory symptoms may result from aspiration of acid refluxate.[12] In this latter group, a panesophageal motor disorder has often been found, where acid refluxes in the distal esophagus through a hypotensive LES, and because of impaired peristalsis it reaches the pharynx and spills into the tracheobronchial tree.[12] Nevertheless, we found no difference in the proximal esophageal acid exposure and acid clearance among the three groups of patients, suggesting that peristalsis, per se, was not the major determinant of the proximal extent of the refluxate. Based on our data, the higher incidence of respiratory symptoms in patients with GERD and IEM could be explained by their more hypotensive LES, increased esophageal acid exposure, and delayed acid clearance. The volume of the gastric refluxate must be important, but it cannot be measured with the available tests.

Dysphagia was also more common among patients with esophageal dysmotility. In the absence of a stricture (nonobstructive dysphagia), dysphagia is thought to reflect abnormalities of peristalsis. A properly constructed fundoplication relieves nonobstructive dysphagia, as well as heartburn and regurgitation, in most patients.[18]

Esophagitis, stricture formation, or Barrett's esophagus occurs in approximately half of patients with gastroesophageal reflux documented by prolonged pH monitoring.[19] Barrett's esophagus is found in approximately 13%.[20] More liberal use of esophageal manometry and pH monitoring should help identify the patients at risk of developing these complications. These patients with more advanced disease are the ones with abnormal motility and abnormal esophageal acid clearance, who also may have respiratory symptoms in addition to heartburn. Earlier surgical intervention in this group should be of benefit to prevent the development of strictures or Barrett's metaplasia and to avoid severe lung damage.[21-27]

In conclusion, severe esophageal dysmotility was present in 21% of our patients with GERD. Severe dysmotility was associated with more severe GERD, which included more reflux and slower esophageal clearance. Not surprisingly, therefore, these patients had more severe mucosal injury and more frequent respiratory symptoms.

REFERENCES

1. Zaninotto G, DeMeester TR, Schwizer W, Johansson K-E, Cheng S-C. The lower esophageal sphincter in health and disease. Am J Surg 1988;155:104-1011.
2. Stein HJ, DeMeester TR, Naspetti R, Jamieson J, Perry RE. Three-dimensional imaging of the lower esophageal sphincter in gastroesophageal reflux disease. Ann Surg 1991;214:374-384.
3. Dodds WJ, Dent J, Hogan WJ, Helm JF, Hauser R, Patel GK, Egide MS. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med 1982;307:1547-1552.
4. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterology 1986;91:897-904.
5. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. Gastroenterology 1988;94:73-80.
6. Rakic S, Stein HJ, DeMeester TR, Hinder RN. Role of esophageal body function in gastroesophageal reflux disease: Implications for surgical management. J Am Coll Surg 1997; 185:380-387.
7. Castell DO, Richter JE, Boag Dalton C. Esophageal Motility Testing. New York: Elsevier Science, 1987.
8. Leite LP, Johnston BT, Barrett J, Castell JA, Castell DO. Ineffective esophageal motility (IEM). The primary finding in patients with nonspecific esophageal motility disorder. Dig Dis Sci 1997;42:1859-1865.
9. Fouad YM, Katz PO, Hatlebakk JG, Castell DO. Ineffective esophageal motility: The most common motility abnormality in patients with GERD-associated respiratory symptoms. Am J Gastroenterol 1999;94:1464-1467.
10. Armstrong D, Monnier P, Nicolet M, Blum AL, Savary M. The "MUSE" system. In Giuli R, Tygat GNJ, DeMeester TR, Galmiche JP, eds. The Esophageal Mucosa. New York: Elsevier, 1994.
11. Arcerito M, Patti MG. Esophageal function testing: Indications, methods and interpretation. Prog Chirurg 1995;6:33-36.
12. Patti MG, Debas HT, Pellegrini CA. Clinical and functional characterization of high gastroesophageal reflux. Am J Surg 1993;165:163-168.

13. Jamieson JR, Stein HJ, DeMeester TR, Bonavina L, Schwizer W, Hinder RA, Albertucci M. Ambulatory 24-h esophageal pH monitoring: Normal values, optimal thresholds, specificity, sensitivity, and reproducibility. Am J Gastroenterol 1992;87:1102-1111.
14. Stein HJ, Eypasch EP, DeMeester TR, Cmyrk TC, Attwood SEA. Circadian esophageal motor function in patients with gastroesophageal reflux disease. Surgery 1990;108:769-778.
15. Allen ML, McIntosh DL, Robinson MG. Healing or amelioration of esophagitis does not result in increased lower esophageal sphincter or esophageal contractile pressure. Am J Gastroenterol 1990;85:1331-1334.
16. Patti MG, Feo CV, De Pinto M, Arcerito M, Tong J, Gantert W, Way LW. Effect of laparoscopic antireflux operations on esophageal motor function. Can J Gastroenterol 1998;12:25B.
17. Ing AJ, Ngu MC, Breslin ABX. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med 1994;149:160-167.
18. Patti MG, Feo CV, De Pinto M, Arcerito M, Tong J, Gantert W, Tyrrell D, Way LW. Results of laparoscopic antireflux surgery for dysphagia and gastroesophageal reflux disease. Am J Surg 1998;176:564-568.
19. Stein HJ, Barlow TP, DeMeester TR, Hinger RA. Complications of gastroesophageal reflux disease. Role of the lower esophageal sphincter, esophageal acids and acid/alkaline exposure, and duodenogastric reflux. Ann Surg 1992;216:35-43.
20. Patti MG, Arcerito M, Feo CV, Worth S, De Pinto M, Gibbs V, Gantert W, Tyrrell D, Ferrell LF, Way LW. Barrett's esophagus: A surgical disease. J GASTROINTEST SURG 1999;3:397-404.
21. Monnier P, Ollyo J-B, Fontolliet C, Savary M. Epidemiology and natural history of reflux esophagitis. Semin Laparosc Surg 1995;2:2-9.
22. Kauer WKH, Peters JH, DeMeester TR, Ireland AP, Bremner CG, Hagen JA. Mixed reflux of gastric and duodenal juices is more harmful to the esophagus than gastric juice alone. The need for surgical therapy re-emphasized. Ann Surg 1995;222:525-533.
23. Tobin RW, Pope CE II, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;158:1804-1808.
24. Wetscher GJ, Glaser K, Hinder RA, Perdikis G, Klingler P, Bammer T, Wieschemeyer T, Schwab G, Klingler A, Pointner R. Respiratory symptoms in patients with gastroesophageal reflux disease following medical therapy and following antireflux surgery. Am J Surg 1997;174:639-643.
25. Allen CJ, Anvari M. Gastro-oesophageal reflux related cough and its response to laparoscopic fundoplication. Thorax 1998;53:963-968.
26. Spivak H, Smith CD, Phichith A, Galloway K, Waring JP, Hunter JG. Asthma and gastroesophageal reflux: Fundoplication decreases need for systemic corticosteroids. J GASTROINTEST SURG 1999;3:477-482.
27. Patti MG, Arcerito M, Tamburini A, Diener U, Feo CV, Safadi B, Fisichella P, Way LW. Effect of laparoscopic fundoplication on gastroesophageal reflux disease-induced respiratory symptoms. J GASTROINTEST SURG 2000;4:143-149.

Discussion

Dr. D.O. Castell (Philadelphia, Pa.). We described ineffective esophageal motility about 5 years ago, and your criteria are a little different from the way we described it. We suggested that more than three contractions out of 10 that were less than 30 mm Hg would qualify as ineffective. However, the results are very similar. Abnormal clearance has been well documented in these patients, both by barium studies and radionuclide studies, so I think you are quite correct that when you have the ineffective pattern, it means a poorly functioning esophagus. In our laboratory we find this abnormality in roughly one third of patients with documented GERD, again similar to your findings, and also much more common in persons who have supraesophageal symptoms such as cough.

Results of a New Strategy for Reconstruction of Biliary Injuries Having an Isolated Right-Sided Component

Steven M. Strasberg, M.D., Daniel D. Picus, M.D., Jeffrey A. Drebin, M.D., Ph.D.

Poor results after repair of biliary injuries are most common when injuries are above the bifurcation of the left and right hepatic ducts or involve aberrant ducts. We have developed a novel approach to the right-sided component of such injuries. Preoperatively all isolated sections of the biliary tree are intubated percutaneously. At surgery the left duct is found by the Hepp-Couinaud approach. Dissection is continued to the right, staying within the coronal plane of the left hepatic duct, and continuing across the gallbladder plate into segment 5 between the hepatic parenchyma and the Wallerian sheath of the right portal pedicle. Hepatic parenchyma, anterior to the sheath, is resected. After a length of portal pedicle is exposed, right-sided bile ducts are opened on their anterior surface, using the percutaneous transhepatic stents as a guide, and hepaticojejunostomy is performed. Twenty-three patients were treated from May 1993 to February 1999. Injury types and (number of patients) were as follows: B (n = 2), C (n = 5), E4 (n = 10), and E5 (n = 6). There were no perioperative deaths. Follow-up ranged from 8 months to 7 years (median 3 years). There have been no cases of restricture, reoperation, or jaundice, and no interventional procedures. Serum bilirubin is normal in all patients. Alkaline phosphatase is normal or less than two times the normal value in 21 of 22 living patients. This novel approach brings the benefits of the Hepp-Couinaud approach to the right hepatic ducts. Very satisfactory results were obtained in the most severe types of biliary injury. (J GASTROINTEST SURG 2001;5:266-274.)

KEY WORDS: Biliary injury, aberrant bile ducts, laparoscopic cholecystectomy

Biliary injury is the most serious complication of cholecystectomy. It is a morbid, costly, and occasionally fatal complication,[1-4] the incidence of which increased sharply when laparoscopic surgery for cholelithiasis was introduced.[5-10] Many of the injuries referred to tertiary centers are high in the biliary tree and involve ducts above the bifurcation of the common hepatic duct. Also, aberrant right ducts seem particularly prone to injury during laparoscopic cholecystectomy.[11,12] Fig. 1 shows a classification of these injuries,[12] which we will use in this report.

The standard approach used by many biliary surgeons for repair of biliary injuries is to locate the left hepatic duct in its extrahepatic course along the base of segment 4 and then perform a side-to-side anastomosis between it and a Roux-en-Y loop of jejunum. This technique was introduced by Hepp[13] and is called the Hepp-Couinaud approach in reference to Couinaud's description of the extrahepatic position of this duct. The method has found wide acceptance around the world. It minimizes dissection behind the ducts, making the dissection technically easier and less hazardous, and decreasing the chance of devascularizing the duct at the site of anastomosis. The technique permits a wide anastomosis even when ducts are not large, since the entire length of the extrahepatic left duct can be used. It is particularly suitable for injuries at or just below the bifurcation (E1 to E3).

The results of repairs of biliary injuries that have been reported in recent years are quite variable, but a consistent feature, even in series reporting excellent overall outcomes, is that results are poorest when the injury is above the bifurcation or involves a combination of injuries to the common bile duct and an aberrant duct—type E4 and E5 injuries.[14-16] These injuries are the most complex[17] because they produce two or

From the Section of Hepatobiliary-Pancreatic Surgery and the Division of Interventional Radiology, Washington University School of Medicine, St. Louis, Mo.
Presented at the Forty-First Annual Meeting of The Society for Surgery of the Alimentary Tract, San Diego, Calif., May 21-24, 2000.
Reprint requests: Steven M. Strasberg, M.D., Box 8109, Suite 17308 West Pavilion Tower, 1 Barnes Hospital Plaza, St. Louis, MO 63110. e-mail: strasbergs@msnotes.wustl.edu

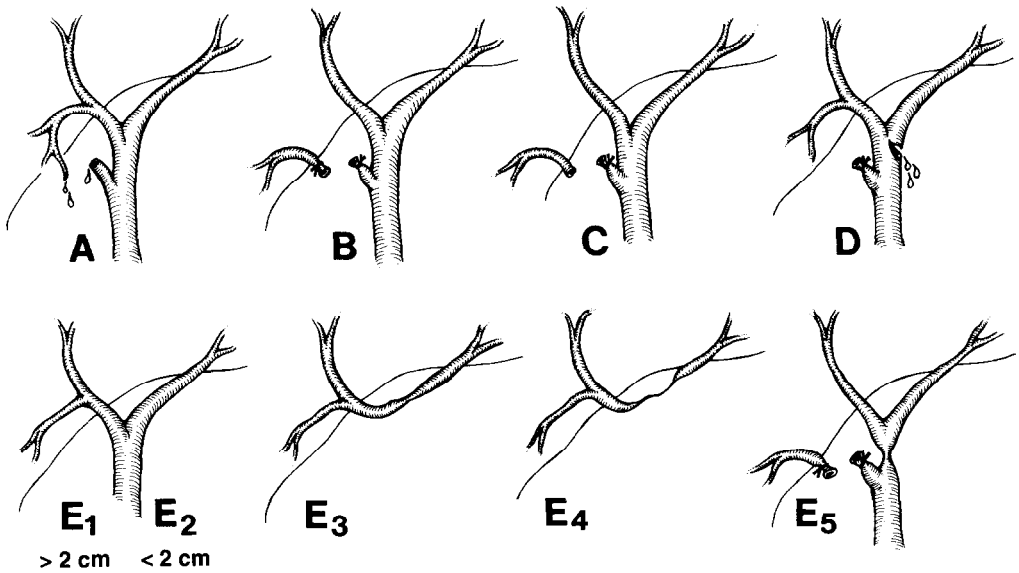

Fig. 1. Classification of injuries to the biliary tract. Injuries type A to E are illustrated. Type E injuries are subdivided according to the Bismuth classification. Type B and C injuries almost always involve aberrant right hepatic ducts. The notations >2 cm and <2 cm in type E1 and type E2 injuries indicate the length of common hepatic duct remaining. The injuries with an isolated right duct component and which are the subject of this report are types B, C, E4, and E5.

more areas of the intrahepatic biliary tree that are no longer in communication. The isolated areas will not be drained by a single anastomosis to the left hepatic duct, as in the Hepp-Couinaud approach. Consequently the Hepp-Couinaud technique is useful only for management of the left-sided component, and the isolated right-sided ducts must also be individually identified and joined to intestine. There is no standard approach for performing this part of the procedure. The purpose of this report is to present a method we have used to gain access to the right hepatic ducts in a standard fashion based on an anatomic rationale in such injuries. Results are presented for type B and C injuries as well as for type E4 and E5 injuries, since the former also involve isolated right-sided portions of the biliary tree, which cannot be managed by the Hepp-Couinaud method—and our approach to these injuries at operation has been the same.

METHODS

Patients with these types of injuries may present within or beyond a 3-month period from the initial injury or the last attempt at repair. We manage these groups somewhat differently since 3 months is the approximate time that we normally allow for inflammation to subside and for ischemia of the bile ducts, if it is present, to reach a final level. The four components of our approach to management of these injuries are as follows: (1) to control sepsis and establish drainage from all parts of the biliary tree, (2) to diagnose conclusively the complete extent of injury to the biliary tree preoperatively, (3) to prepare the patient for surgery by insertion of guide stents into each isolated area of the biliary tree, and (4) to then perform the operation. The terminology used in this report to identify the three levels of ducts on each side of the liver includes the following: main ducts, sectional ducts, and segmental ducts.[18]

Control of Biliary Drainage and Sepsis

Patients Presenting Within a Period of 3 Months From the Initial Injury or the Last Attempt at Repair. Most patients in this series were referred after their injuries had been diagnosed intraoperatively or in the early postoperative period after laparoscopic cholecystectomy. Unlike patients with lesser type E1 to E3 injuries, who may have simple clip occlusions of the common bile duct, these patients almost invariably had bilomas in the right upper quadrant or bile ascites or peritonitis, often with external bile fistulas. Therefore they were unsuitable for immediate repair. Some patients were very ill with systemic sepsis on transfer, whereas others were quite stable. Often treatment with systemic antibiotics in the intensive care unit was required on admission. Two of these patients had definitive repairs that failed before 3

months had elapsed and are included in this early-presenting group.

The goal of initial management is to control sepsis and establish biliary drainage from all parts of the biliary tree. The usual approach is to first perform a CAT scan to ascertain the position and extent of bile collections. Endoscopic retrograde cholangiopancreatography (ERCP) is then performed in all patients presenting with jaundice, and fistulagrams are obtained when a bile fistula is present. Percutaneous cholangiography is used during this stage when necessary to establish drainage from isolated portions of the biliary tree. Multiple percutaneous drains are avoided at this time, if possible, because they increase patient discomfort and reduce mobility. One percutaneous transhepatic drain can often serve to drain two isolated portions of the biliary tree; for instance, a right-sided transhepatic drain can also drain bile coming from transected left bile ducts by positioning the end of the drain in the biloma in the porta hepatis at the cut end of the left duct. This avoids the need for a separate left-sided transhepatic drain at this point in the care of the patient. Supplementary percutaneous drains are used to drain bilomas in other parts of the abdomen or occasionally to supplement transhepatic drains when the upper abdominal bile collections are large. Laparotomy is required only when hemorrhage is present at the time the patient is transferred or when adequate bile drainage cannot be obtained by other methods, for example, in the presence of frank bile peritonitis. An exact formula for the order of these investigations cannot be given since the approach varies with the type of presentation and the condition of the patient.[12] This portion of the treatment is not unique to injuries having an isolated right-sided component.

As noted, early repair of these injuries was not performed. Surgery was delayed for 3 months from the laparoscopic cholecystectomy to allow resolution of the bilomas and attendant inflammation. Also, there is often a vascular component to these injuries, and we have occasionally observed the biliary injury to progress on the basis of ischemia during the first few weeks after the cholecystectomy. Therefore a second reason for delay is to allow the injury to stabilize before repair. We have not routinely assessed the vasculature, since repair of injured arteries in this group of patients is not a practical option. Instead, repair of the injury is delayed until the final level of injury due to ischemia is reached.

Patients are seen at intervals during the period between presentation and repair. Subhepatic drains are frequently removed during these visits after the bilomas resolve and the transhepatic stents are drawn through the tract of the subhepatic drain, converting them to U tubes, which have greater stability.

Patients Presenting With a Diagnosis of Biliary Injury More Than 3 Months After the Cholecystectomy or the Last Repair. These patients usually present after a repair has failed or less commonly because of a type B injury that has become symptomatic. Bilomas, inflammation, and progressive ischemic injury are not issues in these patients. In the case of failed repairs, bilateral transhepatic drains are usually in place at presentation. Surgery may be performed after diagnosis of the injury is complete.

Diagnosis of the Extent of the Injury

This is a critical component of the workup of these patients. All ducts must be accounted for prior to surgery. The entire biliary tree must be visible on cholangiography. Assurance that this has been achieved is obtained by reconciling cholangiograms with CAT scans of the liver. Livers vary greatly in shape, and the CAT scan is a useful guide to ensure that the ducts seen on the cholangiograms fill the liver seen on the CAT scans. Complete cholangiography may be performed in a retrograde manner through subhepatic drains after the bilomas have resolved, partly or completely, or in a prograde manner using transhepatic cholangiography. Often a combination of these techniques is used.

Preparation for Surgery

The principle here is to have a percutaneous transhepatic stent in every isolated section of the biliary tree at the time the operation to aid in identification of the particular ducts that need to be joined to the intestine at surgery. Patients are often admitted the day before surgery for placement of these guide stents. Although a subhepatic drain may be adequate to control bile drainage, it is of no use as a guide to bile ducts. Finding all bile ducts at the time of surgery without stents may be difficult, especially in complex E4 injuries. One stent on the left side is usually adequate, the exception being when there is an anomalous left system. Often two stents are required on the right, that is, when the level of injury has been carried up above the level of the main right duct to the right anterior and posterior sectional ducts.

Operative Technique

The key to dissection using this method is based on the fact that the main right and left bile ducts lie in the same coronal plane, invested in their fibrous Wallerian sheaths. The left duct lies on the underside of segment 4 in an extrahepatic position, whereas the right duct passes into the liver substance at the base of segment 5. Also of importance in the dissection is the gallbladder (or cystic) plate, a layer of fibrous tissue on which the

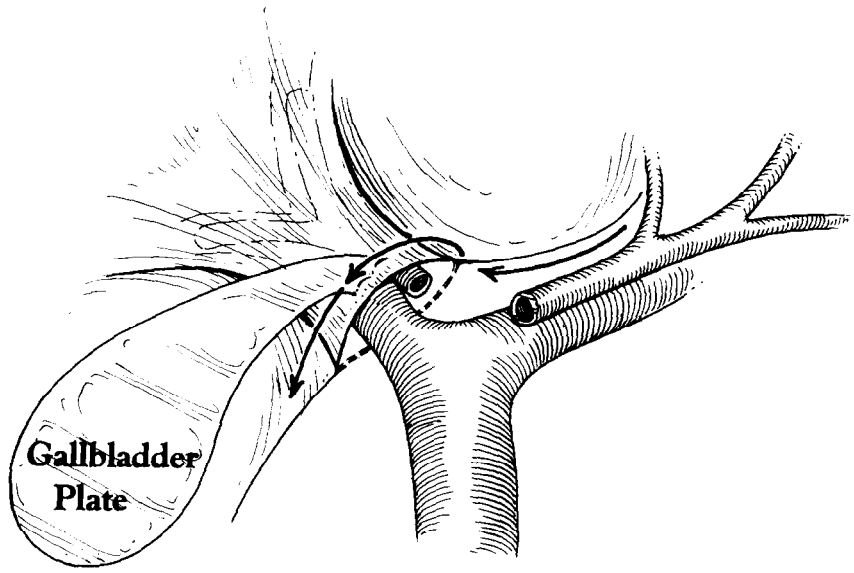

Fig. 2. Schematic diagram of the operative technique for display of the isolated right ductal injuries. The amputated left and right ducts are shown, as well as the portal vein and the sheath of the right portal pedicle. The hepatic artery is not shown. Note that the gallbladder plate is a part of the Wallerian system of fibrous connective tissue that invests portal structures as they enter the liver. It attaches posteriorly to the sheath of the right portal pedicle. The left and right ducts are in the same coronal plane. The dissection is shown at a stage when the left hepatic duct has been isolated by the Hepp-Couinaud approach. The arrows indicate the direction of dissection from that point (see text for details).

gallbladder normally rests. The base of the plate, that is, its most posterior portion, attaches to the anterior surface of the sheath of the main right portal pedicle (Fig. 2). Therefore, to find the bile duct within the sheath of the right portal pedicle, which also contains the portal vein and hepatic artery, the cystic plate must be detached from the anterior surface of the sheath of the right portal pedicle (see Fig. 2).

The rationale for the dissection is to find the left hepatic duct and use its position to define the coronal plane in which the main right duct lies. The dissection is carried to the right in this coronal plane until the cystic plate is encountered, which is divided, bringing the dissection onto the right portal pedicle invested in its sheath, in which the right bile ducts lie.

The initial portion of the dissection is identical to the Hepp-Couinaud approach to the left hepatic duct.[13] Dissection commences at the free edge of the liver along segment 4. Adhesions are cleared off the entire inferior surface of the liver but concentrating on clearing off segment 4. Aids to the dissection are to divide the bridge of liver tissue between segment 4 and the left lateral section (segments 2 and 3) and to open the lips of the gallbladder fossa if they have become fused. As the dissection is carried down the inferior face of segment 4, the segment is retracted upward with a malleable retractor. To find the left hepatic duct, it is necessary to persist in this dissection, rolling the base of segment 4 upward until the liver substance is entered. This may result in venous bleeding, but this is quite controllable by temporary packing with a hemostatic agent or by use of the Argon beam cautery. The left hepatic duct itself is not usually easily seen at this point because it is invested in its sheath, but its position can be confirmed by palpation of the stent in the left hepatic duct. What has been described up to this point is the standard Hepp-Couinaud approach.

The subsequent portion of the operation consists of bringing the dissection over to the right, staying within the same coronal plane as the left duct. The tip of a right-angled clamp is placed in the liver substance, just anterior to the position of the most rightward portion of the left hepatic duct, its point facing to the right. It is drawn toward the operator until the liver capsule is encountered and the capsule is divided. As the dissection is carried more toward the right, the cystic plate is met where it attaches to the sheath of the right portal pedicle. It is a stout ribbon of fibrous tissue approximately 2 mm in thickness and 5 to 8 mm in breadth. After it is divided, the liver lifts off the right portal pedicle. The division of the liver capsule is carried approximately 1 cm beyond the cystic plate. Now the liver (segment 5) may be dissected off the portal pedicle by lifting and coring the base of segment 5.

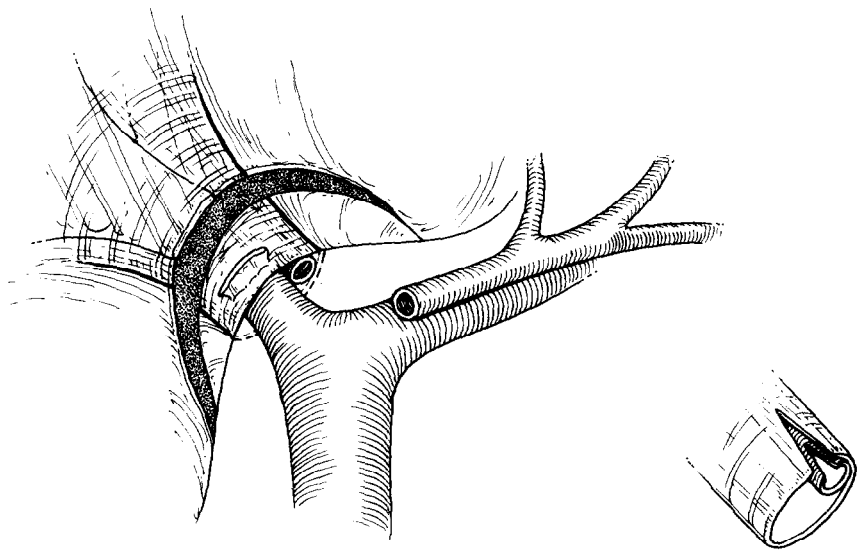

Fig. 3. Schematic diagram of a later stage in the dissection. The gallbladder plate has been cut and the liver pushed back off the right portal pedicle. The liver at the base of segment 5 has been cored away. The duct is isolated with the aid of the indwelling stent and opened on its anterior surface (right and below on the diagram).

Resection of liver tissue may not be necessary at all if viable duct is projecting beyond the liver edge, but this is uncommon. In most cases, the base of segment 5 is cored out to some extent using the ultrasonic dissector or small pieces of liver are resected with cautery. This exposes the anterior surface of the sheath of the right portal pedicle (Fig. 3). The position of the right duct(s) in the pedicle is evident from the position of the stent(s). In cases in which the injury is above the bifurcation of the right hepatic duct, that is, the main right duct has been resected or is congenitally absent and only the two right sectional ducts remain, the dissection continues until the sheath(s) anterior to the two sectional ducts (right anterior and right posterior) is exposed.

In some cases, especially those in which there have been repeated bouts of cholangitis and the liver has become swollen and fibrotic—a condition most frequently seen after failed hepaticojejunostomy—segment 4b may overhang the upper bile ducts. In these cases, resection or coring of segment 4b is also a useful adjunct. Resection provides excellent access to the upper part of the porta hepatis without relying on forceful retraction of the liver and provides room for the bowel to rest when the hepaticojejunostomy is performed. The latter maneuver is not restricted to operations in which a portion of the right biliary tree has been isolated. It is also useful for type E3 and some type E2 injuries. It is not necessary, however, for most injuries in which a portion of the right biliary tree has been isolated.

To prepare the bile ducts for anastomosis, they are opened on their anterior surface. On the left side this is usually straightforward and has been well described in the Hepp-Couinaud approach.[13] An opening of at least 1 cm is desirable. At the left most extent incision, near the umbilical fissure, one must be careful not to injure the artery to segment 4, which passes anterior to the left hepatic duct. Also, at this time it is our practice to amputate the curved termination of the stent and to sew a monofilament suture to the freshly cut end of the stent. In this way the stent may be drawn back and forth into and out of the liver while the duct is opened, without losing the end of the stent. Having the stent out of the way often improves visualization when opening the duct and while placing sutures in the duct. Once these steps are performed, the stent can be drawn back down and placed across the anastomosis. Usually the preoperatively placed stents are replaced with softer 8F feeding tubes by sewing the feeding tubes to the stents and pulling the feeding tubes through the liver.

On the right side, the bile ducts are also opened on the anterior surface. Ideally the duct(s) is opened for 1 cm and the end of the duct is closed with 5-0 or 6-0 absorbable sutures. The entire anastomosis is then performed to the anterior surface of the duct. However, because of the level of the injury and the variations in anatomy this is not always possible. In some cases, multiple small ducts may be encountered before opening the anterior surface for this distance. In these instances the end of the duct, as well as the slit that has been made in the anterior surface, is used. Only enough dissection is performed to place sutures into firm tissue at the end of the duct. The key is to place the sutures into ductal tissue having well-vascularized

mucosa. In some cases, the right posterior duct may enter the field of dissection from behind and present as an anteriorly facing orifice. Such ducts cannot be opened on their anterior surface and an end-to-side (end of duct to side of jejunum) anastomosis must be performed. Again we recommend the least dissection of the duct that will provide the ability to take good bites of tissue including well-vascularized mucosa. In our opinion, minimizing dissection reduces the chance of devascularizing the duct.

The actual anastomosis is performed to a 60 cm long Roux-en-Y loop. 5-0 Absorbable sutures are used. When the right and left ductal orifices are in close proximity, a "cloacal" anastomotic technique is used in which the edges of a single opening in the bowel are sutured to the ducts and to the fibrous tissue between the ducts. When the right and left ducts are separated by more than 1 cm, a double-barreled anastomosis with two intestinal openings is made. In type E5 injuries it may be the right posterior duct that is separated from the right anterior and left ducts, and then it is separately anastomosed on the loop. Cut ducts in close proximity may be sutured together to create a single orifice for part or all of the anastomosis. It has not been necessary in our experience to make more than two openings in the bowel. The actual technique of anastomosis is to place the anterior row of sutures in the bile ducts, followed by the placement and tying of the posterior row of sutures on the inside of the anastomosis. The anterior row of sutures in the bowel is then placed and tied on the outside of the anastomosis. Anastomoses are drained with one posteriorly placed No. 19 Blake drain.

RESULTS

The case series includes all patients with type B, C, E4, or E5 (with one exception—see below) injuries whom we treated from May 1993, when this approach was initiated on the hepatobiliary-pancreatic service at Washington University, to February 1999—allowing at least 6 months' follow-up. A total of 23 patients were treated during this time, constituting almost half of all biliary injuries that were managed surgically during this time in our hepatobiliary-pancreatic unit. Seventeen females and six males (mean age 44.8 years [range 17 to 78 years]) had repairs. The injury types and (number of patients) described using our classification (see Fig. 1) were as follows: B ($n = 2$), C ($n = 5$), E4 ($n = 10$), and E5 ($n = 6$). Most patients presented within days of a laparoscopic cholecystectomy, but seven patients presented more than 3 months after cholecystectomy or a previous repair. Six patients had failed repairs and one had a type B injury in which the main right hepatic duct had been clipped approximately 2 years before referral. One of these patients presented 30 years after hepaticojejunostomy and another 6 years after hepaticojejunostomy.

Twenty injuries occurred in patients undergoing laparoscopic cholecystectomy, two during open cholecystectomy, and one during a minicholecystectomy. Among the 16 patients who were referred in the early postoperative period, four were diagnosed intraoperatively at the time of laparoscopic cholecystectomy and 12 were diagnosed within the first few days to 2 weeks after surgery. Six of the latter patients presented with biliary fistulas: four with jaundice and abdominal pain and two with cholangitis. Of the seven patients who were referred for treatment more than 3 months after their last surgery, four presented with repeated bouts of cholangitis, two with jaundice, and one with right upper quadrant pain and heaviness, the latter patient being the one with the type B injury. Several had intrahepatic stones and most had multiple attempts at percutaneous dilatation, stent placement, and stone extraction. In all, eight patients had attempts at definitive repairs at other institutions: two in the early-presenting group and six in the group presenting after 3 months.

One patient required immediate laparotomy for bleeding and hypotension days after a laparoscopic cholecystectomy; 2 liters of fresh blood was found in the abdomen and several small bleeding vessels were oversewn. There was also a large amount of bile in the peritoneal cavity. Three biliary orifices were seen. The right upper quadrant was drained and no attempt was made to repair the injury at this time. No other laparotomies were performed prior to the definitive repair, and the patients were managed as described earlier, between the time of presentation and surgery. There was no instance of failure to cannulate an isolated portion of the biliary tree by percutaneous transhepatic means in the preoperative period, that is, stents were available for all ducts that were being sought at surgery.

The repairs were all hepaticojejunostomies as described above. Seventeen of 23 anastomoses were to a single opening in the intestine, although to more than one duct in the E4 injuries, and six were double-barreled anastomoses. Five patients who had been diagnosed as having intrahepatic stones underwent intraoperative intrahepatic bile duct exploration and choledochoscopy with stone clearance. Sometimes the liver could simply be pushed off the involved right-sided ducts, once the gallbladder plate was cut, as described earlier. However, most patients required coring of the base of segment 5 or segments 4 and 5. Seven patients underwent resection of segment 4b because this segment was overhanging and preventing adequate access to the upper porta hepatis. Several patients had evidence of increased portal pressure, and one patient had cavernous transformation of the portal vein with

high-pressure, thin-walled veins surrounding the biliary tree. Four units of blood were transfused in this patient who was operated on without venovenous bypass, which was available, however; otherwise, blood transfusion was usually not needed.

There were no intraoperative or postoperative deaths (30-day or in-hospital deaths). There were four postoperative complications. One patient developed atrial fibrillation, two developed atelectasis and fever, and one had *C. difficile* colitis associated with poor postoperative oral intake and a prolonged hospital stay. The mean length of stay was 8.0 days (range 6 to 22 days).

Postoperatively, stents were used for obtaining cholangiograms and were generally removed before the patient was discharged from the hospital or at the first postoperative visit within 2 to 3 weeks of surgery. In one case, a stent was left in place for 3 months when an anastomosis was made to a very small right posterior sectional hepatic duct.

Patients were followed at intervals during the first year, then annually with physical examinations and liver function tests. For those patients who lived a considerable distance from Saint Louis, follow-up was performed by local physicians and by telephone interview. Results of liver function tests were available for all patients. Follow-up ranged from 8 months to 7 years (median 3 years). Follow-up was complete for all patients as of the autumn of 1999.

To date, there have been no cases of restricture, reoperation, or jaundice, and no interventional procedures. One patient, a 68-year-old man who currently resides in a noncontiguous state, was admitted to an outside hospital with a febrile illness 7 years after our repair. It is unclear from available records whether the problem was pneumonia or cholangitis. Liver function tests were abnormal during the episode but the patient was not clinically jaundiced. The patient has been well for the subsequent 6 months and has normal liver function tests. Another patient, a 65-year-old woman, had been well, with normal liver function tests 6 months after repair, but died of myocardial infarction 3 months later. All other patients are asymptomatic.

Liver function tests were normal or the alkaline phosphatase value was less than two times higher than the upper limit of normal at last follow-up in 21 of the 22 patients who are still alive. The other patient, an individual who had multiple bouts of cholangitis over 3 years following a previous failed repair and transhepatic stenting for 2 years, had fibrosis of the liver at the time of surgery. Ten months after our repeat repair, she has a bilirubin level of 1.4 mg/dl, an aspartate transaminase level of 95 IU, and an alkaline phosphatase level of 1334 IU, which is only slightly lower than the preoperative values (upper limit of normal 128 IU). The latter patient has had a magnetic resonance cholangiogram which shows a patent anastomosis. It is believed that the abnormal liver function tests represent chronic liver disease induced by multiple bouts of cholangitis. As noted earlier, she has been asymptomatic since the repair.

One patient who actually had a type E5 injury is not included in this series. At the time of surgery in 1993, she was thought to have an E3 injury and was treated by the Hepp-Couinaud approach instead of the technique described in this report, since we were unaware that there was also an injury to an aberrant right posterior hepatic duct. An excluded aberrant right hepatic duct was diagnosed 2 years later when the patient was noted to have an alkaline phosphatase level three times greater than the upper limit of normal. She also complained of intermittent right-sided upper abdominal pain. The patient has not required treatment and is currently asymptomatic. This patient is considered a treatment failure due to misdiagnosis.

DISCUSSION

The Hepp-Couinaud technique for the repair of biliary injuries was a novel and important advance in the treatment of these difficult problems. Its main novelty rested with its use of the fact that the left hepatic duct, while hidden in a sheath of fibrous tissue, was actually in an extrahepatic position and could be accessed at the base of segment 4. Doing so permits the surgeon to drain the entire biliary tree through a normal well-vascularized left hepatic duct, provided that the bifurcation of the hepatic duct has not been resected. Therefore it is ideal for repair of type E1 to E3 injuries. Another novelty was that the aim of the surgical approach was to go above the injury without dissecting through the area of injury and scarring, which had been the standard approach for many years.

The Hepp-Couinaud approach is not adequate for repair of all biliary injuries. When an injury involves ducts above the bifurcation of the common hepatic duct, resulting in separation and isolation of the right and left sides of the biliary tree, the Hepp-Couinaud approach can only be used for draining the left ductal system. Many injuries, especially those in patients referred to specialized hepatobiliary-pancreatic units, lie above this level (E4) or involve aberrant right ducts (E5, B, and C). There is good evidence in the literature that these injuries, especially E4 injuries, which may involve sectional branches on the right side of the liver, and even segmental branches, have the poorest outcome.[14-17] The failure may result from difficulty in finding adequate lengths of well-vascularized ducts on the right side of the liver. In this report we describe a standard method of accessing these ducts at operation, based on an anatomic rationale, which seems to

provide many of the same advantages that the Hepp-Couinaud approach has on the left side of the liver.

The key anatomic points in the dissection are that the left hepatic duct and the right hepatic duct lie in the same coronal plane, that the right hepatic duct(s) enters the liver within the sheath of the right portal pedicle, and that the gallbladder plate attaches to the front of the sheath of the right portal pedicle and obstructs dissection out onto the pedicle. The rationale for our method of dissection is to then locate the left duct, move to the right in the same coronal plane, detach the gallbladder plate, and uncover the right portal pedicle. In other words, the position of the main left hepatic duct is used to locate the right hepatic ducts; the key to the dissection is to stay in the coronal plane of the left hepatic duct. This approach usually uncovers the anterior surface of the right hepatic duct(s), which can then be incised for a side-to-side anastomosis with the bowel. Liver resection is used liberally to aid in displaying the ducts. Coring out of the base of segment 5 is usually employed to clear off the front of the sheath of the right portal pedicle. Resection of segment 4 is very useful when the liver is overhanging the upper ducts, as has recently been advocated by Mercado et al.[19] However, as noted earlier, this maneuver was needed in only about one third of those lesions having an isolated right-sided component and has also been used by us in cases in which the bifurcation of the bile ducts was intact and the liver was overhanging (e.g., type E3 injury). Stated otherwise, it is a useful adjunct rather than an integral component of the approach we are describing. The results of the present study show that this method provides very satisfactory results at a median follow-up of 3 years in these very difficult biliary injuries.

The operative approach is only one component of success. The importance of accurate preoperative diagnosis cannot be overly emphasized. If an isolated ductal segment is not appreciated preoperatively, it is unlikely that it will be discovered intraoperatively, as seen in our patient who was thought to have a type E3 injury but who actually had an E5 injury. We also believe that guide stents in each isolated segment are very important for consistent success. In fact, the anatomic approach described merely brings the dissection to the area of the right ducts. It is the position of the guide stents that permits the "fine tuning" in the operation in which each of the isolated ducts is actually located and opened for anastomosis. It has been noted by several investigators that repair of high biliary injuries should be performed in centers specializing in hepatobiliary-pancreatic surgery.[15,20] Specialized biliary interventional radiology is probably of equal importance to specialized surgical skills in the success of these operations.[21] It should be noted that the purpose of the stents is to guide the dissection, and to provide access for postoperative cholangiography, rather than to maintain the patency of the anastomoses.

It is our practice to wait 3 months from the time of the injury or the last attempt at repair before performing our repair. This allows time for the inflammation to subside and for ischemic injury, if present, to proceed to a final level of injury in the biliary tree. We have no evidence that it is necessary to wait this long. Our decision to wait this long is based on the observation that at least in some patients operative conditions continue to improve after severe inflammation for as long as 3 months. These operations, especially those involving type E4 injuries, may be challenging technically and we have sought to have every available advantage when performing them. We do not wait this long to repair simpler injuries, particularly if the injury is an occlusive injury without extensive right upper quadrant inflammation.

Anatomic variability in the biliary tree is extremely common and some unusual variants were seen in our patients. One patient had two "left hepatic ducts," that is, the duct from segment 4 was separate from the duct from the left lateral section and both were injured. Various patterns of union of the right ducts were seen including trifurcations. Therefore once the ducts are isolated at surgery, the actual repair (i.e., the "fine tuning") must be individualized—but the principles are identical in all repairs—all injured ducts must be discovered, the anastomoses must be performed to well-vascularized ducts, mucosa to mucosa, and without tension. If these goals are accomplished, biliary injuries, even of the most severe types, can usually be repaired with only a small incidence of recurrent stricture.

REFERENCES

1. Savader SJ, Lillemoe KD, Prescott CA, et al. Laparoscopic cholecystectomy-related bile duct injuries: A health and financial disaster. Ann Surg 1997;225:268-273.
2. Woods MS. Estimated costs of biliary tract complications in laparoscopic cholecystectomy based upon Medicare cost/charge ratios. A case-control study. Surg Endosc 1996;10:1004-1007.
3. Bauer TW, Morris JB, Lowenstein A, et al. The consequences of a major bile duct injury during laparoscopic cholecystectomy. J GASTROINTEST SURG 1998;2:61-66.
4. Carroll BJ, Birth M, Phillips EH. Common bile duct injuries during laparoscopic cholecystectomy that result in litigation. Surg Endosc 1998;12:310-313.
5. Bernard HR. Laparoscopic cholecystectomy: The New York experience. J Laparoendosc Surg 1993;3:371-374.
6. Russell JC, Walsh SJ, Mattie AS, Lynch JT. Bile duct injuries, 1989-1993. A statewide experience. Connecticut Laparoscopic Cholecystectomy Registry. Arch Surg 1996;131:382-388.
7. Wherry DC, Rob CG, Marohn MR, Rich NM. An external audit of laparoscopic cholecystectomy performed in medical treatment facilities of the Department of Defense. Ann Surg 1994;220:626-634.

8. Adamsen S, Hansen OH, Funch-Jensen P, et al. Bile duct injury during laparoscopic cholecystectomy: A prospective nationwide series. J Am Coll Surg 1997;184:571-578.
9. Buanes T, Mjaland O, Waage A, et al. A population-based survey of biliary surgery in Norway. Relationship between patient volume and quality of surgical treatment. Surg Endosc 1998; 12:852-855.
10. Richardson MC, Bell G, Fullarton GM. Incidence and nature of bile duct injuries following laparoscopic cholecystectomy: An audit of 5913 cases. West of Scotland Laparoscopic Cholecystectomy Audit Group. Br J Surg 1996;83:1356-1360.
11. Meyers WC, Peterseim DS, Pappas TN, et al. Low insertion of hepatic segmental duct VII-VIII is an important cause of major biliary injury or misdiagnosis. Am J Surg 1996;171:187-191.
12. Strasberg SM, Hertl M, Soper NJ. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. J Am Coll Surg 1995;180:101-125.
13. Hepp J. Hepaticojejunostomy using the left biliary trunk for iatrogenic biliary lesions: The French connection. World J Surg 1985;9:507-511.
14. Mirza DF, Narsimhan KL, Ferraz Neto BH, et al. Bile duct injury following laparoscopic cholecystectomy: Referral pattern and management. Br J Surg 1997;84:786-790.
15. Stewart L, Way LW. Bile duct injuries during laparoscopic cholecystectomy: Factors that influence the results of treatment. Arch Surg 1995;130:1123-1129.
16. Murr MM, Gigot JF, Nagorney DM, et al. Long-term results of biliary reconstruction after laparoscopic bile duct injuries. Arch Surg 1999;134:604-609.
17. Jarnagin WR, Blumgart LH. Operative repair of bile duct injuries involving the hepatic duct confluence. Arch Surg 1999;134:769-775.
18. The Brisbane 2000 Terminology of Liver Anatomy and Resections. Terminology Committee of the International Hepato-Pancreato-Biliary Association. HPB 2000;2:333-339.
19. Mercado MA, Orozco H, de la Garza L, et al. Biliary duct injury: Partial segment IV resection for intrahepatic reconstruction of biliary lesions. Arch Surg 1999;134:1008-1010.
20. Gigot J, Etienne J, Aerts R, et al. The dramatic reality of biliary tract injury during laparoscopic cholecystectomy. An anonymous multicenter Belgian survey of 65 patients. Surg Endosc 1997;11:1171-1178.
21. Lillemoe KD, Martin SA, Cameron JL, et al. Major bile duct injuries during laparoscopic cholecystectomy. Follow-up after combined surgical and radiologic management. Ann Surg 1997;225:459-468.

Discussion

Dr. M.P. Callery (Worcester, Mass.). You mentioned briefly the interval between injury and presentation described. Could you elaborate on some of the decisions you make as to the timing of the operation? Do you sometimes wait for a period of time with the external drains in place, and how do you make that decision?

Dr. S. Strasberg. Patients with very high injuries usually have bilomas and are almost always very sick. This differs from patients who have type E1, E2, even E3 injuries, particularly those who have a simple clip across the bile duct. You may see patients with these lesser injuries 2 to 3 days after the injury and it is quite fine to operate on them at that time. In contrast, the patients presented in our report usually have a great deal of bile in the right upper quadrant, or their injuries are complicated, so we delay surgery in these patients to allow time for the bilomas and the inflammation to resolve. In addition, many of these injuries are accompanied by an injury to a vascular structure, and the injury may progress within the first few weeks following laparoscopic cholecystectomy. We want the ischemic process to progress to a final level so that there is no ongoing duct ischemia at the time of repair.

Dr. L.W. Traverso (Seattle, Wash.). Most of your patients presented within days after the injury, and I am wondering if you can give us some guidance, based on your experience, as to when an anastomosis to a right segmental duct should not be done, but rather the duct should be ligated allowing that portion of the liver to atrophy if no infection is present.

Dr. Strasberg. An anastomosis should not be done when there has been extensive vascular injury and the right side of the liver must be resected. However, resection is rarely needed. We have always performed an anastomosis because all of these injuries have involved ducts supplying the entire right side of the liver or ducts supplying the entire anterior or posterior sections of the liver. I think it is probably safe to ligate ducts that are supplying a segment or less than a segment of liver, and probably it is the safer thing to do if a duct is extremely narrow, rather than performing an anastomosis that will be stenotic. However, a clipped aberrant duct may become symptomatic 15 years after it is clipped.

Dr. F.G. Moody (Houston, Tex.). Tell us a little more about this technique of dropping down the left Couinaud approach and then going to get the right duct. Is it anatomic? Is it bloody?

Dr. Strasberg. Once the liver plate is lowered, the hepatic parenchyma is encountered. If you are not in hepatic parenchyma, you have not dropped the liver plate. Some venous bleeding can occur when the liver is cut into, but this is easily controlled with packing for 5 minutes or use of the argon beam coagulator. As the dissection is continued, by placing a right angle in the hepatic parenchyma and drawing it toward yourself, you will encounter the liver capsule, and you continue to do that as you go over to the right and then you will find the cystic or gallbladder plate and divide it. As soon as this is done, the liver can be raised up off the right bile ducts.

Dr. Moody. I did not pick up on the details of your anastomosis. Do you parachute it down?

Dr. Strasberg. Our anastomosis is very standard. We use fine absorbable sutures. The anterior row is placed in the bile duct first, then the posterior row in the bile duct and in the intestine. After the posterior row of sutures is tied, the anterior row on the jejunum is completed. All sutures are interrupted in type.

Toxicity and Effects of Adjuvant Therapy in Colon Cancer: Results of the German Prospective, Controlled Randomized Multicenter Trial FOGT-1

Ludger Staib, M.D., Karl Heinz Link, M.D., Hans Günther Beger, M.D., F.A.C.S., and Members of the Forschungsgruppe Onkologie Gastrointestinaler Tumoren (FOGT)

In this adjuvant three-arm multicenter trial, we studied whether modulating the standard 5-fluorouracil (5-FU) treatment with either folinic acid (FA) or interferon-alpha-2a (IFN-α) was superior to the recommended standard of adjuvant treatment in R0 resected colon cancer, 5-FU plus levamisole (LEV) for 12 months, in terms of toxicity and outcome. From July 1992 to October 1999, a total of 813 patients with resected colon cancer in stage II (T4N0M0; n = 63) or stage III (TxN1-3M0; n = 750) were randomized into three treatment groups and stratified according to N stage and participating centers (64 hospitals). The patients received a postoperative loading dose of 5-FU (450 mg/m^2 on days 1 to 5 [arms A and C]) or 5-FU (450 mg/m^2) plus FA (Rescuvolin, Medac, Hamburg, Germany, 200 mg/m^2 on days 1 to 5 [arm B]). After completion of the first chemotherapy cycle, LEV was administered orally at a dosage of 150 mg per day on days 1 to 3, once every 2 weeks. After a 4-week chemotherapy-free interval, the treatment was continued weekly for 52 weeks. Treatment in one arm A ("standard") (n = 279) consisted of 5-FU intravenously (450 mg/m^2 on day 1, once a week) plus LEV. 5-FU plus LEV was modulated in arm B (n = 283) with FA (200 mg/m^2 on day 1, once a week) and in arm C (n = 251) with IFN-α at 6 million units three times a week repeated weekly. Treatment dosages were adjusted if toxic events above WHO grade 2 occurred. Patients were closely followed to determine recurrence and survival; the latter was calculated according to Kaplan-Meier analysis. Toxic events above WHO grade 2, mainly leukopenia, diarrhea, and nausea, occurred in 113 (14%) of 649 patients who had completed treatment in arms A (8.4%), B (13.5%), and C (31.7%). Discontinuance rates were as follows: 28% for all patients, 29% in arm A, 21% in arm B, and 34% in arm C. Overall relapse rates were 27% for all patients, 30% in arm A, 24% in arm B, and 28% in arm C. Relapses were local (8%), distant (78%), or combined (12%). Four-year overall survival rates in arms A, B, and C were 66.1%, 77.5%, and 66.2%, respectively. The 4-year survival rate in arm B was significantly higher compared to arm A ($P < 0.02$, log-rank test) with arm A being equal to arm C. Adjuvant therapy with 5-FU plus FA plus LEV for 12 months is superior to the recommended standard (5-FU + LEV for 12 months). IFN-α modulation of 5-FU (plus LEV) adds to the toxicity with no therapeutic benefit. (J GASTROINTEST SURG 2001;5:275-281.)

KEY WORDS: Adjuvant chemoimmunotherapy, colon cancer, FOGT-1 trial, toxicity, effectiveness

Adjuvant chemoimmunotherapy with 5-fluorouracil (5-FU) and levamisole (LEV) for 12 months has been the standard treatment for stage III colon cancer since it was recommended by the National Institutes of Health consensus conference in 1990. This was based on studies suggesting a 10% to 15% survival benefit in comparison to surgical control groups.[2,3] From palliative phase II/III trials it became apparent that double modulation with either folinic acid (FA) or interferon-alpha (IFN-α) was superior to 5-FU treatment in terms of response and progression-free survival.[4] It was not known at that time whether the same findings were applicable to the adjuvant situation. The rationale for combining FA with 5-FU is an increased 5-FU cytotoxicity mediated by stabilization of the ternary complex between 5-deoxyuridine monophosphate and thymidylate synthase.[5,6] IFN-α has an unspecific immunostimulatory effect on the host, an an-

From the Department of General and Visceral Surgery, University of Ulm, Ulm, Germany.
Reprint requests: Prof. Dr. med. Hans Günther Beger, Department of General and Visceral Surgery, University of Ulm, Steinhövelstraße 9, 89075 Ulm/Donau, Germany. e-mail: hans.beger@medizin.uni-ulm.de

tiangiogenic effect on the tumor, and interferes with 5-FU metabolism.[7-9]

The hypothesis of this multicenter trial, FOGT-1, which was initiated by the German "Forschungsgruppe Okologie Gastrointestinaler Tumoren" (FOGT), was that the recommended systemic adjuvant treatment of colon cancer, consisting of 5-FU and LEV, could be improved by double modulation of 5-FU with either FA or IFN-α.

PATIENTS AND METHODS

Patients

Colon cancer patients with completely resected (R0) tumors classified as UICC stage II (T4N0M0) and stage III (TxN1-3M0) were included in this three-arm open multicenter trial, which was conducted between July 1992 and October 1999. Distant metastases were excluded preoperatively by abdominal ultrasonography, chest radiography, or computed tomography. Secondary cancers were excluded by preoperative colonoscopy, and in case of emergency operations (ileus, bleeding, perforation); if colonoscopy was not performed preoperatively, it was done postoperatively within 3 months. Patients with multicentric colon cancers were included if all tumors were completely removed and if they were staged according to the most advanced tumor. Colon cancers were defined as adenocarcinomas located between the cecum and a distance ≥15 cm above the anal verge (or above the peritoneal reflection). Surgery was performed according to published guidelines of the German Surgical Society[10] and included removal of the tumor and drainage of lymphatic tissue up to the vessels supplying the particular colon segment. If tumors infiltrated adjacent organs, multivisceral resections were performed. Patients undergoing laparoscopic resection were not included. The histopathologic reports adhered to the guidelines of the German Cancer Society[11] with more than 10 lymph nodes being examined.

Treatment Protocols

Patients were randomized postoperatively after informed consent was obtained, and with full knowledge of the histopathologic report, by the central study office in Ulm, Germany. Patients were divided into the three treatment arms and stratified according to N stage (N0 vs. N1 vs. N2) and participating centers (64 hospitals). The systemic standard treatment (arm A; 5-FU + LEV) consisted of 5-FU plus levamisole (Ergamisol, Janssen, Neuss, Germany). In the experimental arms, 5-FU was double modulated with Rescuvolin (Medac, Hamburg, Germany) in arm B (5-FU + LEV + FA) or with Roferon (Roche, Grenzach-Wyhlen, Germany) in arm C (5-FU + LEV + IFN-α).

Within 14 days after resection, a 5-day loading course of chemotherapy was begun. Patients in arms A and C received 5-FU, 450 mg/m^2 intravenously on days 1 to 5; patients in arm B received, in addition, 200 mg/m^2 of FA, which was given intravenously over a 10-minute period, followed immediately by a 1- to 2-hour infusion of 5-FU. The 5-FU infusion protocol was based on in vitro studies,[12] and the 5-FU plus FA protocol was identical to the original protocol of Machover et al.[13]

Four weeks after completion of the loading course, once-a-week chemotherapy was continued for up to 52 weeks. At this time, patients in arm C were started on interferon treatment, which consisted of 6×10^6 IU of IFN-α injected subcutaneously three times a week by the patient. All patients received oral LEV, 3×50 mg daily on three subsequent days every 2 weeks, starting with the initial chemotherapy loading course (i.e., days 1 to 3, days 14 to 16, etc.). Toxicity grades of WHO 1 and 2 were tolerated. Higher toxicity grades (WHO grades 3 or 4) led to drug-specific dosage reductions (first IFN-α, then LEV, then 5-FU). All toxic events of WHO grade 3 or higher were recorded, WHO grade 4 was reported to the German Federal Office of Drug Safety (Bundesministerium für Arzneimittel und Medizinprodukte). The rationale for the FOGT protocol was outlined in detail in a recent review,[14] and the protocol has been approved by the Ethics Review Boards of the University of Ulm and other participating centers.

Toxicity status and outcome were evaluated and discussed at study meetings every 6 months with representatives of the participating hospitals. The data as of October 1999, when recruitment was completed, are reported herein.

Follow-Up

Patients were enrolled in an intensive carefully outlined follow-up program, which included a graduated series of annual visits (3 visits during years 1 and 2, 2 visits during years 3, 4, and 5, and annual visits until year 10) with tests for occult fecal blood and carcinoembryonic antigen (CEA). Chest radiography, abdominal ultrasonography, and colonoscopy were performed annually up to 5 years. The follow-up results presented here were obtained up to October 1999.

Statistical Analysis

Overall survival time was calculated according to the Kaplan-Meier method.[15] An adaptive interim analysis[16] was started after randomization of 756 pa-

tients to determine toxicity in arm C. This analysis revealed a toxicity that was higher in arm C compared to arms A and B. Therefore recruitment for arm C was stopped as of February 1999. Comparison of the remaining arms, A and B, for the primary outcome variable (overall survival) demonstrated the superiority of arm B at the 5% significance level with a P value of 0.0218.

RESULTS

Sixty-four participating hospitals have randomized 922 patients since July 1992 at a constant or even increasing recruitment rate. Among these 922 patients, there were a total of 109 dropout cases (11.8%): 22 in arm A, 35 in arm B, and 52 in arm C. Reasons for dropping out included patient's request (n = 44), mistakes in randomization (n = 32), treatment delays due to postoperative complications (n = 11), protocol violations (n = 11), and withdrawal of hospital participation (n = 11). A total of 813 patients were evaluated according to "intention to treat" (Table I). The patients were balanced within the arms in terms of age, sex, and tumor stage; 750 (92%) of 813 patients were lymph node positive.

Toxic events greater than WHO 2 (Table II) occurred 186 times in 649 patients (28.6%); in arms A (11.9%) and B (19.4%) these occurred less often than in arm C (57.9%) (see "Statistical analysis"). These toxic events concerned 113 (14%) of 649 patients: 19 patients (8.4%) in arm A, 30 patients (13.5%) in arm B, and 14 patients (31.7%) in arm C. The leading toxic events in arm C were leukopenia (10.3%), nausea (6.9%), and diarrhea (6.4%). There was one toxic death (arm A; pneumonia after grade IV leukopenia).

Reasons for withdrawal from the study are listed in Table III. The overall rate of withdrawal was 28%, with withdrawal rates of 29%, 21%, and 34%, in arms

Table I. Recruitment of colon cancer patients in the FOGT-1 study (July 1992 to October 1999)

	Arm A	Arm B	Arm C	Total
UICC stage II (T4N0M0)	19	22	22	63
UICC stage III (TxN1-3M0)	260	261	229	750
TOTAL	279	283	251	813

Table II. Toxic events (>WHO grade 2) in colon cancer patients treated with adjuvant chemoimmunotherapy in the FOGT-1 study*

Toxic events†	A (n = 226)	B (n = 221)	C (n = 202)	Total (n = 649)
Leukocytes	1	3	21	25
Thrombocytes	—	2	2	4
Hemoglobin	—	—	2	2
Fever	2	—	7	9
Nausea	2	5	14	21
Allergic reaction	—	1	—	1
Constipation	—	—	1	1
Diarrhea	4	8	13	24
Cutaneous	1	—	5	6
Neurologic	2	3	1	6
Pain	3	3	7	13
Renal	—	—	1	1
Cardiac	—	1	1	2
Infection	—	—	—	—
Various	1	3	10	14
Undetermined	11	14	32	57
TOTAL	27	43	117	186
No. of patients affected	19	30	64	113

*All patients (n = 813) were evaluable according to "intention to treat" analysis, and 649 patients have completed their treatment (date of analysis, October 1, 1999).
†Multiple toxicities per patient are also listed.

Table III. Withdrawal from the FOGT-1 study over a 52-week period (n = 813 patients, intention to treat analysis)

Reason for withdrawal	A (n = 279)	B (n = 283)	C (n = 251)	Total (n = 813)
Patient's request	29	32	33	94
Toxicity	6	5	20	31
Progression	38	21	29	88
Secondary cancer	4	1	3*	8
Death	1	1	0	2
Various†	1	—	1	2
Undetermined	1	—	—	1
TOTAL	80	60	86	226

*One patient had secondary tumor plus metastases.
†Reasons included apoplectic insult (A) and pancreatitis (C).

Table IV. Local and distant recurrence among patients in the FOGT-1 study (n = 223 patients with recurrence of 813 total, intention to treat analysis)

Site of recurrence	A (n = 279)	B (n = 283)	C (n = 251)	Total (n = 813)
Local	6	6	6	18
Distant,* of these:	63	56	56	175
Liver	41	34	38	113
Lungs	15	6	8	29
Bone	—	—	2	2
Peritoneum	11	12	14	37
Various	16	17	10	43
Both	14	7	9	30
TOTAL	83	69	71	223

*Multiple sites per patient are also listed.

Table V. Overall survival after 4 years for patients in the FOGT-1 study (n = 813 patients, intention to treat analysis)

	A (n = 279)	B (n = 283)	C (n = 251)	Total (n = 813)
4-year overall survival (%)	66.1	77.5*	66.2	70.1

*$P = 0.0218$ vs. A; C is equal to A.

A, B, and C, respectively. Patient's request (11.6%), disease progression (10.8%), and intolerable toxicity (3.8%) were the main reasons for withdrawal. Seventy-two percent of all patients received the scheduled 12 months of treatment (71%, 78%, and 66% in arms A, B, and C, respectively). An additional 14% of all patients received at least 6 months or more of treatment (12%, 11%, and 19% in arms A, B, and C, respectively).

Tumor recurrence was observed in 223 (27.4%) of 813 patients (Table IV): recurrence rates were 29.7%, 24.4%, and 28.3%, respectively, in arms A, B, and C. Recurrence was either local (8%), distant (78%), or combined (12%). Liver metastases (51%), peritoneal carcinosis (16%), and lung metastases (13%) were the main recurrence sites.

Overall survival after 4 years in arms A, B, and C was 66.1%, 77.5%, and 66.2%, respectively (Table V). The 4-year survival rate in arm B was significantly higher than that in arm A (see "Statistical analysis"), with arm A being equal to arm C.

DISCUSSION

Surgeons influence prognosis in colorectal cancer not only by their identification of correct indications for surgery and their surgical technique but also by their recommendation for postoperative adjuvant

therapy without treatment delay. In this multicenter phase III trial, the "Forschungsgruppe Onkologie Gastrointestinaler Tumoren (FOGT)" compared the recommended standard of 5-FU plus LEV (arm A) with two experimental arms, in which 5-FU double modulation was used (i.e., 5-FU + LEV + FA in arm B and 5-FU + LEV + IFN-α in arm C) in patients with curatively resected colon cancer. The rationale for this trial has been extensively discussed elsewhere.[14] Briefly, the standard treatment (arm A) was chosen and administered according to the Intergroup protocol that had proved the efficacy of 5-FU plus LEV in adjuvant therapy after resection of stage III colon cancer.[3,17] Stage II patients (T4N0M0) were included in our study because their risk of recurrence is comparable to that of stage III patients and there is an absolute gain in survival of 7% to 8% with adjuvant treatment.[18-21]

Although both treatment arms B and C have been studied in other large-scale adjuvant treatment trials,[14] the comparison of the three treatment modalities remains original and scientifically founded. Up to now, one patient has died of treatment toxicity, due to pneumonia after grade IV leukopenia, as mentioned earlier. No multifocal leukoencephalopathy has been documented. Analysis of toxicity in arms A, B, and C of our study revealed that toxic events above WHO grade 2 occurred in 14% of 649 patients evaluated. The adjuvant treatment was discontinued in 15.4% of the evaluated patients either because of toxicity (3.8%) or at the patient's request (11.6%). These data compare well with the experience of the Intergroup trial, since 30% of the colon cancer patients in that trial, who were receiving 5-FU plus LEV as adjuvant treatment, permanently discontinued treatment.[3] In patients receiving 5-FU plus FA as adjuvant therapy, the compliance rate was 80%.[22,23]

As expected from palliative trials, toxicity in arm C was higher than that in arms B and A—with the leading symptoms being "leukopenia," "nausea," and "diarrhea," although the doses of IFN-α and 5-FU were lower than in palliative protocols, such as that of Wadler et al.,[24] and strict prescriptions for dosage reductions in cases of toxicity above WHO grade 2 were built into the protocol.

Despite a positive report from Frasci et al.[25] in a nonrandomized study of 106 patients with stage III colorectal cancer, which showed a significant difference in 5-year survival between patients treated with 5-FU plus IFN-α vs. those treated with 5-FU alone (64% vs. 46%), our results have not confirmed these findings. In this trial, toxicity of 5-FU plus IFN-α consisted mainly of fever, arthralgia, anorexia, and nausea, with neurologic symptoms occurring more often after IFN-α treatment. In the FOGT-1 study, neurologic symptoms such as persistent neurotoxicity[26] were not observed any more often in the IFN-α arm. Meanwhile the National Surgical Adjuvant Breast and Bowel Project has finished a randomized trial (NSABP-C05) of 2176 patients with stage II or stage III colon cancer, similar to our study design, comparing 5-FU plus LEV vs. 5-FU plus LEV plus IFN-α.[27] In this trial IFN-α treatment showed no benefit with equal 4-year survival (80% vs. 81%) and recurrence rates (30% vs. 31%). In addition, in a subset of 23 patients, we were unable to show any immunologic advantage of IFN-α during 1 year of immune monitoring using flow cytometry analysis, cytotoxicity and stimulation assays, and skin tests for recall antigens. Although in arm B, at the end of the 5-day loading course, lysis of allogeneic colon cancer target cells was maximal and natural killer cells increased during the adjuvant treatment, these changes were not observed in arm C.[28] The inferiority of IFN-α in terms of survival, toxicity, and immune response seems to be even more remarkable if the total treatment costs are analyzed. These costs were $2500 for arm A, $3500 for arm B, and $11,000 for arm C. Thus from an economic point of view, arm C treatment does not seem to be justified. Arm B treatment for 1 year, in contrast, is somewhat more expensive than the recommended standard treatment or passive immunotherapy treatment ($3000 for five infusions) with a monoclonal antibody (Panorex, Edrecolomab, Centocor, Leiden, Holland) that, after initial enthusiasm,[29,30] has recently been withdrawn from the market, because the interim analysis in one of two large randomized trials (protocols 157-002 and 157-001) in colon cancer did not show any benefit of the antibody treatment compared to standard adjuvant chemotherapy.[31]

Important questions in adjuvant treatment of colon cancer are currently addressed by large-scale randomized trials and concern the length of treatment (6 to 8 months vs. 12 months), the FA dose (high vs. low), and the role of LEV in FA-modulated 5-FU protocols.[20,22,32-37] Unfortunately, 80% of all patients given adjuvant treatment have shown no direct benefit of this therapy, either because they would not have developed a recurrence anyway, even without therapy (overtreatment problem) or they have a recurrence in spite of therapy (response problem), although in the latter group the recurrence might have been delayed. Therefore an important goal for the future remains the determination of selection criteria for demonstrating a response to adjuvant therapy, for example, tests for thymidylate synthase,[38-40] preoperative CEA,[41] or cytokines in bone marrow or blood.[42,43]

In conclusion, the recommended standard adjuvant treatment of 5-FU plus LEV for 1 year can be im-

proved, as shown by the 10% gain in overall survival, by adding FA to the treatment protocol, which can be done with acceptable toxicity and cost. INF-α, in contrast, increases costs and toxicity significantly without achieving any therapeutic benefit.

REFERENCES

1. NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990;264:1444-1450.
2. Windle R, Bell P, Shaw D. Five year results of a randomized trial of adjuvant 5-fluorouracil and levamisole in colorectal cancer. Br J Surg 1987;74:569-572.
3. Moertel C, Fleming T, MacDonald J. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990;322:352-358.
4. Köhne-Wömpner C, Schmoll H. Chemotherapeutic strategies in metastatic colorectal cancer: An overview of current clinical trials. Semin Oncol 1992;19:105-125.
5. Danenberg P, Lockshin A. Fluorinated pyrimidines as tight-binding inhibitors of thymidylate synthetase. Pharmacol Ther 1981;13:69-90.
6. Rustum Y, Trave F, Zakrzewski S. Biochemical and pharmacological basis for potentiation of 5-fluorouracil action by leucovorin. NCI Monogr 1987;5:165-170.
7. Wadler S. The role of immunotherapy in colorectal cancer. Semin Oncol 1991;18(1 Suppl 1):27-38.
8. Nichols PH, Ward U, Ramsden CW, Primrose JN. The effect of 5-fluorouracil and alpha interferon and 5-fluorouracil and leucovorin on cellular anti-tumour immune responses in patients with advanced colorectal cancer. Br J Cancer 1994; 70:946-949.
9. Slaton J, Perrotte P, Inoue K, et al. Interferon-alpha-mediated down-regulation of angiogenesis-related genes and therapy of bladder cancer are dependent on optimization of biological dose and schedule. Clin Cancer Res 1999;5:2726-2734.
10. Eigler F, Gabbert H, Herfarth C, et al. Interdisziplinäre Leitlinie zur Therapie des Kolonkarzinoms. Forum Dtsch Krebsgesellschaft 1999;14:132-138.
11. Hermanek P. Tumors of the gastrointestinal tract and the pancreas: Histopathology, staging and prognosis. Anticancer Res 1999;19:2393-2396.
12. Link K, Aigner K, Peschau K, et al. Concentration and time dependence of the toxicity of fluorinated pyrimidines to HT 29 colorectal carcinoma cells. Cancer Chemother Pharmacol 1988;22:58-62.
13. Machover D, Schwarzenberg L, Goldschmidt E, et al. Treatment of advanced colorectal and gastric adenocarcinomas with 5-FU combined with high-dose folinic acid: A pilot study. Cancer Treat Rep 1982;66:1803-1807.
14. Link KH, Staib L, Kreuser ED, Beger HG. Adjuvant treatment of colon and rectal cancer: Impact of chemotherapy, radiotherapy, and immunotherapy on routine postsurgical patient management. Forschungsgruppe Onkologie Gastrointestinaler Tumoren (FOGT). Recent Results Cancer Res 1996;142:311-352.
15. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-481.
16. Bauer P, Köhne K. Evaluation of experiments with adaptive interim analysis. Biometrics 1994;50:1029-1041.
17. Moertel C, Fleming T, MacDonald J, et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: A final report. Ann Intern Med 1995;122: 321-326.
18. O'Connell M. Surgical Adjuvant Therapy of Colorectal Cancer. Dallas, Tex.: American Society of Clinical Oncology (Educational Book), 1994.
19. Hagmüller E, Lorenz D, Sturm J, et al. Long-term survival after surgical therapy of T4 colorectal carcinomas. Zentralbl Chir 1995;120:815-820.
20. Mamounas E, Rockette H, Jones J, et al. Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B vs. Dukes' C colon cancer: Results from four NSABP adjuvant studies (C-01, C-02, C-03, C-04). In Proceedings of the Thirty-Second Annual Meeting of the American Society of Clinical Oncology. Philadelphia, 1996, p 204.
21. Erlichman C, Marsoni S, Seitz J, et al. Event free and overall survival is increased by FUFA in resected B colon cancer: A pooled analysis of randomized trials. In Proceedings of the Thirty-Third Annual Meeting of the American Society of Clinical Oncology. Denver, 1997, p 280a.
22. Marsoni S. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer—International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet 1995;345:939-944.
23. Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer and bowel project protocol C-03. J Clin Oncol 1993;11:1879-1887.
24. Wadler S, Schwartz E, Goldmann L, et al. Fluorouracil and recombinant alpha-2a-interferon: An active regimen against advanced colorectal carcinoma. J Clin Oncol 1989;7:1769-1775.
25. Frasci G, Leone F, Monaco M, et al. 5-Fluorouracil-interferon-alpha 2b adjuvant treatment of Dukes' C colorectal cancer. Dis Colon Rectum 1994;37:643-650.
26. Prange H. Interferon-alpha—Zum Problem der persistierenden Neurotoxizität, Dtsch Ärztebl 1994;91(Heft 49):A3420-A3427.
27. Wolmark N, Bryant J, Smith R, et al. Adjuvant 5-fluorouracil and leucovorin with or without interferon alfa-2a in colon carcinoma: National Surgical Adjuvant Breast and Bowel Project protocol C-05. J Natl Cancer Inst 1998;90:1810-1816.
28. Staib L, Gutsche B, Link KH, Beger HG. Immune monitoring during adjuvant chemoimmunotherapy (in preparation).
29. Riethmüller G, Schneider-Gädicke E, Schlimok G, et al. Randomised trial of monoclonal antibody for adjuvant therapy of resected Dukes' C colorectal carcinoma. Lancet 1994;343: 1177-1183.
30. Riethmüller G, Holz E, Schlimok G, et al. Monoclonal antibody therapy for resected Dukes' C colorectal cancer: Seven-year outcome of a multicenter randomized trial. J Clin Oncol 1998;16:1788-1794.
31. Weiss F. Withdrawal of Panorex (Edrecolomab) [letter]. Leiden, The Netherlands: Centocor BV, August 7, 2000.
32. Francini G, Petrioli R, Lorenzini L, et al. Folinic acid and 5-fluorouracil as adjuvant chemotherapy in colon cancer. Gastroenterology 1994;106:899-906.
33. O'Connell MJ, Laurie JA, Kahn M, et al. Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. J Clin Oncol 1998; 16:295-300.
34. Haller D, Catalano P, Macdonald J, Mayer R. Fluorouracil (FU), leucovorin (LV) and levamisole (LEV) adjuvant therapy for colon cancer: Five-year final report of INT-0089. In Proceedings of the Thirty-Fourth Annual Meeting of the American Society of Clinical Oncology. Los Angeles, 1998, p 256a.

35. Wolmark N, Rockette H, Mamounas E, et al. The relative efficacy of 5-FU + leucovorin (FU-LV) 5-FU + levamisole (FU-LEV), and 5-FU + leukovorin + levamisole (FU-LV-LEV) in patients with Dukes' B and C carcinoma of the colon: First report of NSABP C-04. In Proceedings of the Thirty-Second Annual Meeting of the American Society of Clinical Oncology. Philadelphia, 1996, p 205.
36. Scheithauer W, Kornek GV, Marczell A, et al. Combined intravenous and intraperitoneal chemotherapy with fluorouracil + leucovorin vs fluorouracil + levamisole for adjuvant therapy of resected colon carcinoma. Br J Cancer 1998;77:1349-1354.
37. Zaniboni A, Labianca R, Marsoni S, et al. GIVIO-SITAC 01: A randomized trial of adjuvant 5-fluorouracil and folinic acid administered to patients with colon carcinoma—long term results and evaluation of the indicators of health-related quality of life. Gruppo Italiano Valutazione Interventi in Oncologia. Studio Italiano Terapia Adiuvante Colon. Cancer 1998;82: 2135-2144.
38. Johnston PG, Fisher ER, Rockette HE, et al. The role of thymidylate synthase expression in prognosis and outcome of adjuvant chemotherapy in patients with rectal cancer. J Clin Oncol 1994;12:2640-2647.
39. Lenz HJ, Danenberg KD, Leichman CG, et al. p53 and thymidylate synthase expression in untreated stage II colon cancer: Associations with recurrence, survival, and site. Clin Cancer Res 1998;4:1227-1234.
40. Kornmann M, Link KH, Lenz HJ et al. Thymidylate synthase is a predictor for response and resistance in hepatic artery infusion chemotherapy. Cancer Lett 1997;118:29-35.
41. Fleischer K, Möller P, Link KH, Staib L. CEA in contrast to p53 is associated with response to adjuvant chemoimmunotherapy in colorectal cancer. In Encke A, Rothmund M, Hartel W, eds. Chirurgisches Forum 2000 für Experimentelle und Klinische Forschung. Berlin-Heidelberg-New York: Springer-Verlag, 2000, pp 1-5.
42. Hochtlen VW, Gruber R, Bodenmuller H, et al. Occult epithelial tumor cells detected in bone marrow by an enzyme immunoassay specific for cytokeratin 19. Int J Cancer 1997;70: 396-400.
43. Greenson JK, Isenhart CE, Rice R, et al. Identification of occult micrometastases in pericolic lymph nodes of Duke's B colorectal cancer patients using monoclonal antibodies against cytokeratin and CC49. Correlation with long-term survival. Cancer 1994;73:563-569.

Endoscopic Transanal Resection Provides Palliation Equivalent to Transabdominal Resection in Patients With Metastatic Rectal Cancer

Herbert Chen, M.D., Bruce D. George, F.R.C.S., Howard S. Kaufman, M.D., F.A.C.S., Mohammad B. Malaki, Neil J. McC. Mortensen, F.R.C.S., Michael G.W. Kettlewell, F.R.C.S.

Patients with metastatic rectal cancer precluding curative low anterior resection (LAR) or abdominoperineal resection (APR) can require palliation for impending obstruction. LAR or APR is frequently not optimal because of the associated operative morbidity. Lesser procedures such as diverting colostomy require patients to live with a permanent stoma. Endoscopic transanal resection (ETAR) has been used for excision of rectal lesions. To determine whether ETAR provides palliation equivalent to LAR or APR, we reviewed the outcomes of 49 patients with rectal adenocarcinoma and unresectable liver metastases who required palliative intervention between January 1989 and July 1996. Of these 49 patients, 24 underwent ETAR; the intraluminal tumor was resected using the urologic resectoscope to achieve a hemostatic, patent lumen. The outcomes of these patients were compared to those of the other 25 patients who had palliative LAR, APR, or a Hartmann procedure during the same period. The median distance of the tumors from the anal verge was similar (5 cm; range 1 to 15 cm). ETAR patients had a higher percentage of poorly differentiated tumors (35% vs. 6%, $P = 0.034$) and higher preoperative alkaline phosphatase values (478 ± 75 mg/dl vs. 231 ± 24 mg/dl; $P < 0.015$), suggesting more aggressive disease and greater hepatic tumor burden, respectively. Despite these differences, overall survival and time spent outside the hospital were similar in the two groups. The median number of debulking procedures required in the 24 ETAR patients was two (range 1 to 17). Resections in the 25 LAR/APR patients included LAR in 20, APR in two, and Hartmann procedures in three. There was a trend toward more stomas in the LAR/APR group (28% vs. 17%). More important, morbidity was significantly higher in the LAR/APR patients (24% vs. 4%; $P = 0.049$). In conclusion, ETAR is a safe alternative for the palliation of incurable rectal tumors. Compared to transabdominal resection, ETAR provides equivalent palliation as measured by survival and proportion of the patient's life spent outside the hospital, with a lower stoma rate and significantly less morbidity. Therefore, in select patients with metastatic rectal cancer, ETAR is an important palliative option. (J GASTROINTEST SURG 2001;5:282-286.)

KEY WORDS: Rectal cancer, endoscopy, palliation, colon resection

Operative resection by low anterior resection (LAR) or abdominoperineal resection (APR) remains the standard for curative treatment of rectal adenocarcinoma. Unfortunately, some patients present with widely metastatic disease precluding curative resection. Such patients with stage IV disease often have symptoms such as rectal bleeding or impending obstruction that necessitate palliation. Palliative LAR or APR is frequently not optimal because of the associated operative morbidity, especially in elderly patients.[1] Other surgical options include diverting colostomy, which requires patients to live with a permanent stoma for their limited life expectancy, and transanal resection for smaller primary lesions.

Endoscopic transanal resection (ETAR) using the urologic resectoscope has been described for the management of select benign and malignant lesions of the rectum.[2-9] During this minimally invasive procedure,

From the Departments of Surgery, University of Wisconsin Medical School (H.C.), Madison, Wis.; The John Radcliffe Hospital (B.D.G., M.B.M., N.J.M.M., and M.G.W.K.), Oxford, England; and The Johns Hopkins Medical Institutions (H.S.K.), Baltimore, Md.
Presented at the Forty-First Annual Meeting of The Society for Surgery of the Alimentary Tract, San Diego, Calif., May 21-24, 2000.
Reprint requests: Herbert Chen, M.D., Department of Surgery, University of Wisconsin Medical School, H4/750 Clinical Science Center, 600 Highland Ave., Madison, WI 53792.

intraluminal tumor is resected under direct vision by a surgeon using electrocautery to achieve a hemostatic, patent rectal lumen. To determine whether ETAR provides palliation equivalent to that of LAR or APR, we reviewed the outcomes of 49 patients requiring palliation of rectal cancer.

MATERIAL AND METHODS

From January 1989 to July 1996, 49 consecutive patients with rectal adenocarcinoma and unresectable liver metastases presented to the colorectal unit at The John Radcliffe Hospital. All required palliative operative intervention for their primary lesions. Indications for surgery were obstruction, bleeding, and tenesmus. Patients with rectal pain were excluded because pain due to sacral infiltration was usually treated with radiation therapy. Inpatient and outpatient medical records were retrospectively reviewed. Data were also obtained from the hospital patient administration computer system and/or by contact with the patient's general practitioner. Survival information was obtained from these sources as well as from the Registrar of Deaths.

The technique of surgical palliation was determined by the surgeon. Of these 49 patients, 24 underwent ETAR by means of a 36 F modified urologic resectoscope with continuous glycine solution irrigation as previously described.[2,9] Briefly, the operations were performed under general or spinal anesthesia. The resectoscope was inserted through the anus. After filling of the rectum with 1.5% glycine irrigation at low pressure, resection was performed with a cutting loop. In stenosing tumors, it was usually possible to identify the site of the lumen by the presence of liquid stool. Occasionally, a soft guidewire was required. Resection usually started at the lower edge of the tumor working cephalad and laterally. Throughout the procedure, the effluent irrigating fluid containing tumor fragments was funneled into a urologic collecting tray and sent for pathologic evaluation. Palliative LAR, APR, or a Hartmann procedure was performed in the other 25 patients. The outcomes of the two groups were then compared. Measured end points included operative morbidity, survival, and percentage of remaining lifetime spent out of the hospital.

Statistical analysis was performed with SPSS software (SPSS Inc.) Analysis of variance and chi-square test were used where appropriate. Survival data were analyzed by the Kaplan-Meier method with log-rank test. Statistical significance was defined as $P < 0.05$.

RESULTS

Patient Data

The mean age of all 49 patients was 69 ± 2 years and 75% were male. There was no difference in mean age and sex distribution between ETAR and LAR/APR patients (Table I). However, there was a significant difference in preoperative alkaline phosphatase values between the two groups. Whereas LAR/APR patients had a mean alkaline phosphatase value of 231 ± 24 mg/dl, ETAR patients had a mean value of 478 ± 75 mg/dl ($P = 0.015$). Alkaline phosphatase has been shown to be the most accurate parameter for predicting survival in patients with unresectable liver metastases from colorectal cancer and neuroendocrine tumors, and may reflect hepatic tumor burden.[10-12] Both groups had rectal tumors at similar distances from the anal verge (median 5 cm in both patient populations). However, ETAR patients had a higher percentage of poorly differentiated tumors (35% vs. 6%; $P = 0.034$).

Operations

Of the 24 patients undergoing ETAR, most required palliative intervention multiple times during their limited life span. The mean number of ETARs performed in these patients was 2.9 ± 0.7. The median number of ETARs performed per patient was two (range 1 to 17). Among the 25 LAR/APR pa-

Table I. Patient and tumor data

	ETAR	LAR/APR	*P* value
No. of patients	24	25	—
Age (mean ± SEM)	69 ± 2 yr	68 ± 2 yr	NS
% Male	76%	75%	NS
Preoperative alkaline phosphatase (mean ± SEM)	478 ± 75 mg/dl	231 ± 24 mg/dl	0.015
Tumor distance from anal verge (median)	5 cm	5 cm	NS
Poorly differentiated tumor	35%	6%	0.034

ETAR = endoscopic transanal resection; LAR = low anterior resection; APR = abdominoperineal resection; SEM = standard error of the mean; NS = not significant.

Table II. Patient outcomes

	ETAR	LAR/APR	*P* value
No. of patients	24	25	—
Mortality (30-day)	4%	0%	NS
Morbidity	4%	24%	0.049
Perforation	1%	0%	
Anastomotic leak	N/A	12%	
Myocardial infarction	0%	4%	
Pneumonia	0%	4%	
Small bowel obstruction	0%	4%	
Stomas/diversion necessary	17%	28%	NS
Mean time as hospital inpatient	30 ± 6 days	37 ± 6 days	NS
Percentage of remaining lifetime spent outside of the hospital (days)	85%	81%	NS

ETAR = endoscopic transanal resection; LAR = low anterior resection; APR = abdominoperineal resection; NS = not significant; N/A = not applicable.

tients, 20 (80%) underwent LAR, two (8%) underwent APR, and three (12%) had a Hartmann procedure. Two patients who initially underwent LAR required subsequent fecal diversion for anastomotic leaks, and another patient in this group underwent a second operation for a postoperative small bowel obstruction.

Mortality and Morbidity

Thirty-day mortality consisted of one patient in the ETAR group who died in hospice care. Morbidity was significantly lower in the ETAR group when compared to the LAR/APR group (4% vs. 24%; $P = 0.049$) (Table II). In the ETAR group, one patient had an intra-abdominal perforation that required operative fecal diversion. Among the LAR/APR patients, three had anastomotic leaks. Two of these three patients required operative diversion for treatment. Other complications in the LAR/APR group included myocardial infarction in one patient, pneumonia in one patient, and small bowel obstruction requiring laparotomy and lysis of adhesions in one patient.

Outcomes

Three variables were measured to roughly determine quality of life: number of patients requiring stomas, number of days spent as an inpatient (for surgery, chemotherapy, radiation, and/or physical therapy), and the percentage of the patient's remaining life spent outside of the hospital (see Table II). Four patients (17%) in the ETAR group required a stoma at some point in their management. In the LAR/APR group, seven patients (28%) required stomas: five as part of the initial procedure (APR or Hartmann) and two for treatment of postoperative anastomotic leaks. There was no statistical difference in stoma rates. Patients in the ETAR group spent a mean number of 30 ± 6 days as inpatients compared to 37 ± 6 days for the LAR/APR patients (P = NS). Patients in both groups spent similar percentages of their remaining life outside of the hospital (ETAR 85% vs. LAR/APR 81%; P = NS).

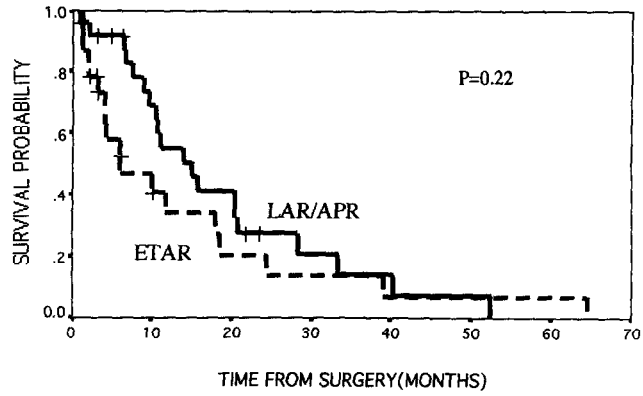

Fig. 1. Survival of patients with metastatic rectal adenocarcinoma after palliation with endoscopic transanal resection *(ETAR)* versus low anterior resection *(LAR)*, abdominoperineal resection *(APR)*, or Hartmann procedure.

Survival

Survival was analyzed by the Kaplan-Meier method (Fig. 1). ETAR patients had median and mean survivals of 6 and 15 months, respectively, whereas

LAR/APR patients had median and mean survivals of 14 and 19 months, respectively. There were no statistical differences in overall survival between the ETAR and LAR/APR groups.

DISCUSSION

ETAR is a viable option for treatment of many rectal lesions. In this report we have shown that ETAR provides equivalent palliation for patients with symptomatic rectal adenocarcinoma and unresectable liver metastases compared to LAR, APR, or Hartmann procedure. ETAR was also associated with a lower morbidity rate and a trend toward less frequent need for fecal diversion. ETAR has many advantages over traditional transabdominal resection. ETAR is minimally invasive and ideal for elderly patients who are high risk for aggressive surgery.[1] It can be performed without general anesthesia. Furthermore, ETAR avoids the need for a colostomy, which can be burdensome in patients with a limited life expectancy.

The use of ETAR for rectal lesions was first described in 1979.[13] We have previously reported our experience with 120 patients who underwent 232 ETARs for rectal cancer.[9] The complication rate was 19%, including bleeding (n = 17), pelvic sepsis (n = 7), stricture (n = 5), rectovaginal fistula (n = 4), and perforation (n = 1). The 5-year survival in this group was 13.7%. Others have also reported successful experiences with ETAR for rectal tumors with low complication rates.[3-7] In fact, ETAR has recently been used to treat postoperative colorectal strictures following LAR with stapled anastomoses.[8]

The role of local palliative procedures, such as ETAR, in patients with incurable rectal carcinoma has been debated. Initial studies indicated that resecting the primary tumor could prolong the survival of patients with unresectable liver metastases.[14] However, more recent data, summarized by Baigrie and Berry,[15] suggest that resection of the primary tumor offers little or no survival advantage in patients with liver metastases. Therefore, in such patients with incurable disease, palliation of the symptoms from the primary lesion is the goal.

There are no studies prospectively comparing treatment options for patients with symptomatic rectal cancers and liver metastases. Options other than ETAR include open resection, radiation therapy, diverting colostomy, and minimally invasive techniques such as laser treatment and colonic stents. Some retrospective studies suggest that ETAR may be more effective with regard to palliation when compared to open resection and radiotherapy.[3-7] Laser treatment and colonic stents have recently been more commonly employed as palliative interventions, and have yet to be compared to ETAR.[16,17] Tack et al.[16] recently reported on 10 patients with advanced rectal cancer who had a combination of laser treatment and placement of a self-expanding nitinol stent. Although stent placement was successful in nine patients, one deployment was complicated by a sigmoid perforation, requiring surgery. Others have reported problems with early stent occlusion and stent migration.[18,19] Furthermore, stents can be quite costly, especially if multiple deployments are needed.

Although our data suggest that ETAR provides equivalent palliation to transabdominal resection, this study does have flaws. Most transabdominal resections were performed by one surgeon and most ETARs by another. Thus surgeon bias played a strong role in patient selection. Furthermore, this was not a randomized trial. Patients who were thought to be less "fit" were not considered candidates for transabdominal resection. Furthermore, patients who had more aggressive disease, as manifested by higher alkaline phosphatase levels indicating greater hepatic tumor burden and by more poorly differentiated tumors, frequently were only offered ETARs. Despite these differences, ETAR patients had less morbidity and had almost equivalent survival.

We do not recommend ETAR for all rectal tumors with unresectable liver metastases. Our impression is that ETAR palliates symptoms of obstruction, tenesmus, and bleeding well. Radiation therapy is used principally for patients with sacral pain. Asymptomatic patients with rectal tumors and extensive liver metastases would not be treated by ETAR at our institution. In our current practice, all patients are assessed preoperatively by CT of the abdomen and pelvis, and by endorectal ultrasound. For partially obstructing rectal tumors, the decision to use open resection or ETAR depends on the overall condition of the patient and the location of the tumor. A stenosing upper rectal cancer in a patient with low-volume liver disease would probably be treated by LAR. A low, fixed rectal tumor would probably be treated by ETAR. Based on the results of this study, all surgeons in our department have now adopted this practice pattern.

CONCLUSION

We have shown in this study that ETAR is a safe, viable alternative for the palliation of incurable rectal tumors. Compared to transabdominal resection, ETAR provides equivalent palliation as measured by survival and the proportion of the patient's life spent outside the hospital, with a possibly lower overall stoma rate and

significantly less morbidity. Therefore, in select patients with incurable stage IV rectal cancer, ETAR is an important option for surgical palliation.

REFERENCES

1. Lewis AA, Khoury GA. Resection for colorectal cancer in the very old: Are the risks too high? Br Med J 1988;296:459-461.
2. Berry AR, Souter RG, Campbell WB, Mortensen NJ, Ketlewell MGW. Endoscopic transanal resection of rectal tumours—a preliminary report of its use. Br J Surg 1990;77: 134-137.
3. Gaya J, Obrador A, Ozonas M, de Sala E. Use of the urologic resectoscope in rectal pathology. Endoscopy 1983;15:2260-2262.
4. Irwin RJ. Resectoscopic transanal resection of extensive rectal adenomas. Aust N Z J Surg 1984;54:375-377.
5. Weese JL, Bruskewitz RC. Endoscopic transanal resection of rectal carcinomas using the urologic resectoscope. Dis Colon Rectum 1984;27:123-125.
6. Kurt KR, Pitts WR, Speer D, Vaughan ED. Palliation of carcinoma of the rectum and pararectum using the urologic resectoscope. Surg Gynecol Obstet 1988;166:60-62.
7. Ottery FP, Bruskewitz RC, Weese JL. Endoscopic transanal resection of rectal tumors. Cancer 1986;57:563-566.
8. Hunt TM, Kelly M. Endoscopic transanal resection (ETAR) of colorectal strictures in stapled anastomoses. Ann R Coll Surg Engl 1994;76:121-122.
9. Dickson AJ, Savage AP, Mortensen NJ, Kettle MG. Long-term survival after ETAR of rectal tumors. Br J Surg 1993; 80:1401-1404.
10. Lahr CJ, Soong SJ, Cloud G, Smith JW, Urist MM, Balch CM. A multifactorial analysis of prognostic factors in patients with liver metastases from colorectal carcinomas. J Clin Oncol 1983;1:720-726.
11. Rougier P, Milan C, Lazorthes F, Fourtanier G, Partensky C, Baumel H, Faivre J. Prospective study of prognostic factors in patients with unresected hepatic metastases from colorectal cancer. Foundation Francaise de Cancerologie Digestive. Br J Surg 1995;10:1397-1400.
12. Chen H, Hardacre JM, Uzar A, Cameron JL, Choti MA. Isolated liver metastases from neuroendocrine tumors: Does resection prolong survival? J Am Coll Surg 1998;187:88-93.
13. Zinkin LD, Katz LD, Rosin JP. A method of palliation for obstructive carcinoma of the rectum. Surg Gynecol Obstet 1979;148:427-428.
14. Stearns MW Jr, Binkley GE. Palliative surgery for cancer of the rectum and colon. Cancer 1954;7:1016-1019.
15. Baigrie RJ, Berry AR. Management of advanced rectal cancer. Br J Surg 1994;81:343-352.
16. Tack J, Gevers A, Rutgeerts P. Self-expandable metallic stents in the palliation of rectosigmoidal carcinoma: A follow-up study. Gastrointest Endosc 1998;48:267-271.
17. Coco C, Cogliandolo S, Riccioni ME, Ciletti S, Marino-Consentino L, Coppola R, Picciocchi A. Use of a self-expanding stent in the palliation of rectal cancer recurrences. A report of three cases. Surg Endosc 2000;14:708-711.
18. Spinelli P, Dal Fante M, Mancini A. Self-expanding mesh stent for endoscopic palliation of rectal obstructing tumors: A preliminary report. Surg Endosc 1992;6:72-74.
19. Rey JF, Romanczyk T, Greff M. Metal stents for palliation of rectal carcinoma: A preliminary report on 12 patients. Endoscopy 1995;27:501-504.

Repeat Hepatic Cryotherapy for Metastatic Colorectal Cancer

Mathew H. Chung, M.D., Wei Ye, M.S., Kenneth P. Ramming, M.D., Anton J. Bilchik, M.D., Ph.D.

This study evaluated the risks and benefits of repeat hepatic cryotherapy for recurrent, unresectable hepatic metastases from colorectal carcinoma. Review of a prospective database identified 195 patients who underwent hepatic cryotherapy for metastatic colorectal carcinoma during a 7-year period. Of the 14 patients who underwent successful repeat cryotherapy for recurrences confined to the liver, 86% had Duke's stage D colorectal carcinoma at initial diagnosis. The median age of the 14 patients was 58 years (range 41 to 77 years). The median number of hepatic metastases was three at the first cryotherapy and two at the second cryotherapy. At a median follow-up of 71 months, the mean survival times from original diagnosis, first cryotherapy, and second cryotherapy were 53, 42, and 19 months, respectively. At the most recent follow-up, eight patients (57%) have died of their disease, four (29%) are alive with disease, and two (14%) have no evidence of disease. The mean interval between the first and second cryotherapies was 23 months. The complication rates after the first and second cryotherapies were 7% and 14%, respectively. One patient developed a wound dehiscence after the first cryotherapy. Following the second cryotherapy, one patient had a small bowel obstruction and another had a pleural effusion. There was no perioperative mortality. Repeat cryotherapy for recurrent, unresectable hepatic metastases from colorectal cancer is safe and improves survival. However, a prospective trial is needed to validate the efficacy of systemic therapy and to better define the indications for repeat hepatic cryotherapy. (J GASTROINTEST SURG 2001;5:287-293.)

KEY WORDS: Cryotherapy, hepatic metastasis, colorectal cancer, recurrence

The resection of isolated liver metastases from colorectal cancer is potentially curative with a 5-year survival of 16% to 45%.[1] However, the prognosis for those patients with unresectable hepatic metastases is dismal with a median survival ranging from 5 to 14 months; 5-year survivors are rare.[2] Therefore many novel approaches have been developed to treat patients with unresectable colorectal liver metastases. Cryosurgical ablation of liver metastases can prolong survival in carefully selected patients.[3,4] Unfortunately, between 60% and 90% of patients undergoing liver resection or hepatic cryosurgery will have recurrent disease. In a small group of these patients, recurrence is confined to the liver.[5,6]

Repeat hepatic resection is safe and associated with improved disease-free and overall survival in patients whose recurrences are limited to the liver.[1,2,5,7-9] However, the role of repeat hepatic cryotherapy for colorectal metastases is unclear and controversial.[10] There is only one published report of repeat cryotherapy for recurrent metastases from colorectal cancer.[11] In the present study we analyzed our hepatic database to determine the morbidity and outcome of repeat hepatic cryotherapy in patients with metastatic colorectal carcinoma. In addition, we identified the prognostic impact of variables that might be used to select candidates for repeat hepatic cryotherapy.

PATIENTS AND METHODS

We reviewed our computerized database of patients treated at the John Wayne Cancer Institute and

From the John Wayne Cancer Institute, Santa Monica, Calif. (M.H.C., W.Y., and A.J.B.), and Century City Hospital Cancer Center, Century City, Calif. (K.P.R. and A.J.B.).
Supported in part by grant T32 CA 09689 from the National Cancer Institute and by funding from the Rogovin-Davidow Foundation, Los Angeles, Calif.
Presented at the Forty-First Annual Meeting of The Society for Surgery of the Alimentary Tract, San Diego, Calif., May 21-24, 2000.
Reprint requests: Mathew H. Chung, M.D., John Wayne Cancer Institute, 2200 Santa Monica Blvd., Santa Monica, CA 90404. e-mail: chungm@jwci.org

Century City Cancer Center to identify all those undergoing hepatic cryotherapy for unresectable metastases from colorectal carcinoma between August 1992 and August 1999. Of 195 patients undergoing hepatic cryosurgery during this 7-year period, 20 were considered for repeat cryotherapy of presumably isolated liver recurrences. All of these patients underwent an extensive preoperative workup that included clinical examination, serum laboratory tests, chest radiography, and computed tomography (CT) of the abdomen/pelvis with 5 to 7 mm cuts through the liver. Positron emission tomography (PET) was used if the results of other imaging studies were suspicious but not definitive. Patients were candidates for repeat cryotherapy if the liver metastases were unresectable based on their location or distribution, and if complete destruction of all visible lesions seemed feasible. Excluded were patients with diffuse infiltrative disease or large bilobar lesions (≥50% of liver volume), in whom complete ablation of hepatic lesions might induce hepatic failure. The number of hepatic lesions was not an exclusion criterion.

At the time of operation, thorough exploration was performed with the aid of intraoperative ultrasound to exclude extrahepatic disease and confirm hepatic metastasis. This exploration revealed extensive hepatic disease and/or extrahepatic disease in six patients, who therefore did not undergo repeat cryotherapy. The remaining 14 patients had isolated but unresectable liver metastasis and underwent repeat cryotherapy.

Cryotherapy was performed with an AccuProbe system (Cryomedical Sciences Inc., Rockville, Md.), which delivers liquid nitrogen to a triple-lumen insulated trocar-tipped probe that is placed in the lesion either by palpation or under ultrasound guidance. Freezing was achieved at a temperature of −190° C and maintained until the entire tumor and at least a 1 cm rim of normal liver tissue was frozen. Iceball formation was monitored with intraoperative ultrasound. Multiple probes were used to cryoablate large (≥5 cm) tumors and/or to ablate multiple lesions simultaneously. Partial double freeze/thaw cycles were used for large tumors and those tumors close to major vasculature.

Intraoperative events (operating time, estimated blood loss), perioperative complications, and hospital stay were recorded. Patients were followed up every 3 to 6 months with serial clinical examinations, laboratory assessments, chest radiography, and CT scans of the abdomen/pelvis with fine cuts through the liver. Follow-up was stopped only if the patient died.

Review of the hepatic database was supplemented as necessary by review of hospital charts, office charts, and patient interviews. Data for demographics, clinical course, pathology, surgical and adjuvant therapy, and outcome were recorded. Survival was calculated according to the methods of Kaplan and Meier. The log-rank test was used to compare differences in survival distributions among subsets of patients. A P value of <0.05 was considered significant.

RESULTS

Seven men and seven women underwent repeat cryotherapy for hepatic metastases from colorectal carcinoma. Their median age was 58 years (range 41 to 77 years). Median follow-up was 49 months (range 21 to 95 months) from resection of the primary tumor, 41 months (range 15 to 82 months) from the first cryotherapy, and 18 months (range 8 to 42 months) from the second cryotherapy.

Of the 14 primary lesions, five were in the right colon, four were in the left colon, and five were in the rectum. Twelve patients (86%) had synchronous liver metastases at presentation. The median number of initial hepatic lesions was three (range 2 to 6). The mean size of the largest hepatic lesion in each patient was 5 cm (range 2 to 12 cm). Initial hepatic metastases were in the right lobe in six cases, central in five cases, and bilobar in three cases.

The median disease-free interval before the recurrence of hepatic metastases was 18 months. The mean interval between the first and second cryosurgeries was 23 months. Of the 14 patients, 12 (86%) had hepatic recurrence at a site of previous cryosurgery. The median number of recurrent hepatic lesions in each patient was 2.3 (range 1 to 6). The mean size of the largest hepatic recurrence in each patient was 5.9 cm (range 3 to 12 cm).

Nine patients underwent other surgeries for recurrences both in the liver and elsewhere (Table I). Three patients had a third hepatic cryosurgery, three patients had pulmonary metastasectomy, two patients had resection of abdominal wall recurrences, and one patient had a retroperitoneal metastasectomy. In addition, nine patients underwent placement of a hepatic artery infusion pump during or after the first cryotherapy. All patients received adjuvant systemic chemotherapy.

Operating time, blood loss, and duration of hospital stay were similar after initial and repeat cryotherapies (Table II). The median hospital stay was 8 days following the repeat hepatic cryotherapy. Complications requiring intervention were not common after either surgery. One patient (7.1%) had wound dehiscence and an ischemic colon following the first cryotherapy. After repeat cryotherapy, one patient had a small bowel obstruction and another had sympto-

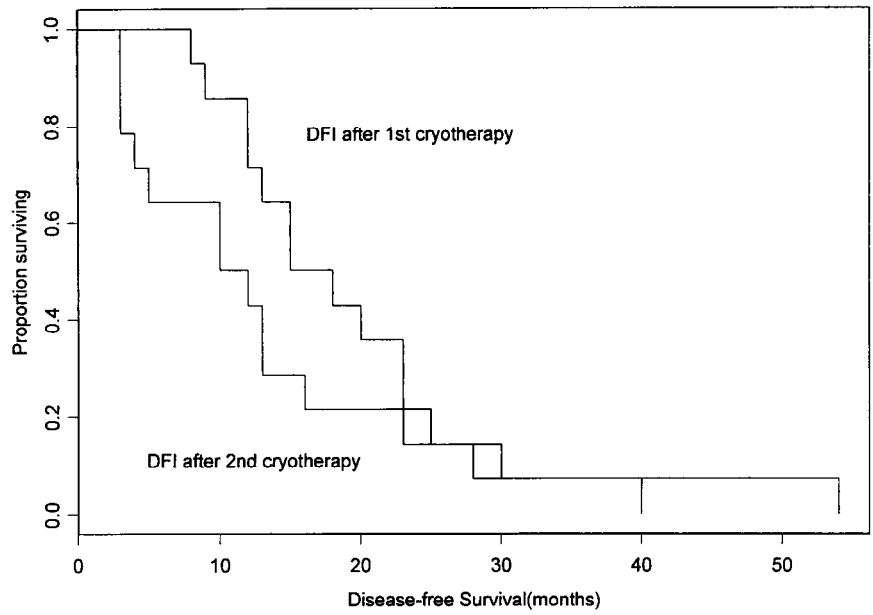

Fig. 1. Disease-free interval *(DFI)* after first and second hepatic cryosurgeries ($P = 0.15$).

Table I. Data on 14 patients undergoing second hepatic cryotherapy

		First cryosurgery			Second cryosurgery					
Age/ sex	Duke's stage	Size (cm)	No. of lesions	DFI (mo)	Size (cm)	No. of lesions	DFI (mo)	Adjuvant therapy	Additional surgery	Status/follow-up (mo)
75/F	D	8	2	30	5	2	23	S/H	3rd cryotherapy	AWD/83
66/M	D	6	2	8	4	6	3	S/H		DOD/49
59/F	D	4	6	18	3	3	12	S/H		DOD/45
56/M	D	5	4	23	6	2	40	S	Lung	DOD/68
67/F	D	5	4	12	8	4	3	S	3rd cryotherapy	DOD/21
77/F	C	12	1	13	10	1	28	S/H		AWD/57
57/F	D	3	4	25	3	2	13	S/H	3rd cryotherapy	NED/57
54/M	D	9	2	9	8	2	10	S	Abdomen	DOD/24
74/M	D	4	2	20	10	1	3	S/H		DOD/29
71/M	D	3	2	15	3	2	4	S	Abdomen	DOD/23
49/F	C	2	2	15	6	1	16	S/H	Lung	AWD/47
42/M	D	5	3	23	6	1	5	S/H		AWD/37
43/F	D	2	4	12	4.5	4	10	S/H	Lung	AWD/30
52/M	D	2	3	54	4	1	13	S	Retroperitoneal	NED/46

DFI = disease-free interval; S = systemic chemotherapy; H = hepatic regional chemotherapy; NED = no evidence of disease; AWD = alive with disease; DOD = died of disease.

matic pleural effusion requiring thoracentesis. There was no in-hospital or 30-day mortality.

At a median follow-up of 21 months after repeat hepatic cryotherapy, eight patients have died of their disease, four are alive with disease, and two are free of disease after repeated resection/cryotherapy (see Table I). The median overall survival times following resection of the primary, initial hepatic cryotherapy, and repeat hepatic cryotherapy were 53, 42, and 19 months, respectively. The median disease-free intervals following resection of the primary, initial hepatic cryotherapy, and repeat hepatic cryotherapy were 0, 18 months, and 12 months, respectively. Disease-free intervals following the first and subsequent hepatic cryotherapies are shown in Fig. 1. Comparison of disease-free survival and overall survival after repeat hepatic cryotherapy is shown in Fig. 2.

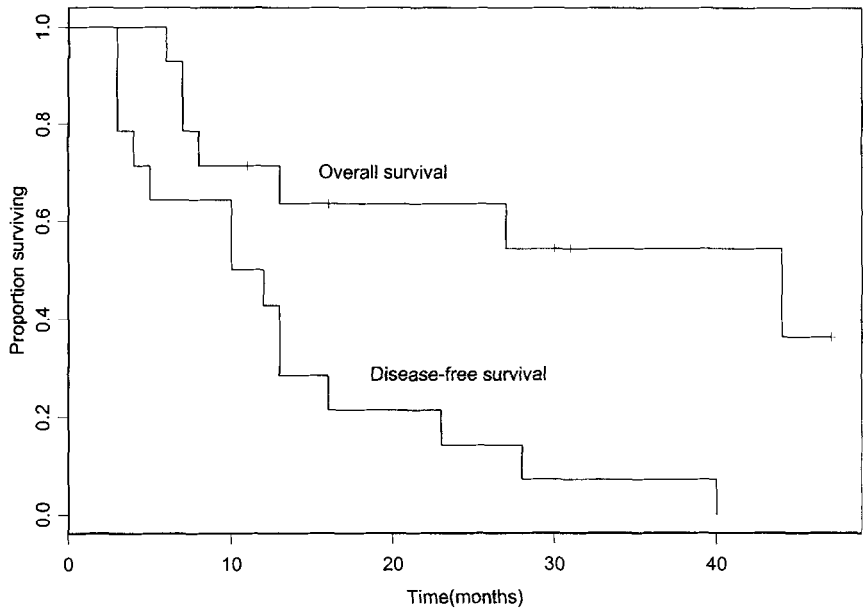

Fig. 2. Disease-free and overall survival following repeat hepatic cryotherapy ($P < 0.05$).

Table II. Intraoperative events and perioperative course

	First cryotherapy	Second cryotherapy
Operative time (min)	241 ± 63	282 ± 54
Blood loss (ml)	823 ± 310	758 ± 245
Length of stay (days)	7 ± 3	8 ± 3
Complications requiring intervention	1 (7.1%)	2 (14.3%)
Deaths	0	0

Table III. Predictors of outcome for repeat hepatic cryotherapy

Parameter	Value	Disease-free interval after second cryotherapy	Overall survival after second cryotherapy
Age	>55 yr vs. ≤55 yr	0.4016	0.5714
Sex	M/F	0.1183	0.5679
Duke's stage	D vs. C	0.4954	0.8019
Size of largest lesion*	>5 cm vs. ≤5 cm	0.4627	0.7033
No. of lesions*	≥4 vs. <4	0.0270†	0.0962
Bilobar involvement*	Yes/No	0.2578	0.2729
Regional chemotherapy	Yes/No	0.7875	0.1367
Disease-free interval after first cryotherapy	≥12 mo vs. <12 mo	0.1528	0.0673

*Tumor characteristics at first cryotherapy.
†$P < 0.05$ (log-rank test).

Parameters analyzed as potential predictors of outcome included demographics (age, sex), Duke's stage of disease at original presentation, characteristics of the first liver metastases (size, number of lesions, unilobar vs. bilobar disease), regional chemotherapy via hepatic artery infusion pump, and disease-free interval after the first cryotherapy. These were evaluated by univariate analysis using the log-rank test. Only the number of lesions at first hepatic cryotherapy predicted disease-free interval following the second cryotherapy ($P < 0.05$). None of the parameters predicted overall survival (Table III).

DISCUSSION

An estimated 130,200 new cases of colorectal cancer will be diagnosed in the United States this year.[12] Of all patients who are resected for cure, between one third and one half will have a recurrence. Nearly 70% of these patients will have liver involvement and will ultimately die of their disease.[9,13] Surgical resection represents the only chance for cure in those patients with isolated hepatic metastases and/or recurrences.[2,5,14,15] Operative morbidity and mortality in tertiary centers are acceptable and 5-year survival ranges from 25% to 40% for those undergoing complete resection.[16] Unfortunately most patients undergoing curative resection will have a recurrence.[1,2,5-9,13-15]

Repeat hepatic resection of isolated liver recurrence is safe and effective,[1,2,7-9,13,14] but the role of repeat cryotherapy for unresectable hepatic recurrence is less certain. The small series reported by Seifert and Morris[11] in Australia showed that repeat cryotherapy can be performed safely with minimal morbidity and no mortality. In their study, blood transfusion requirements and postoperative hospital stay were almost identical to those associated with a first hepatic cryotherapy. Our data confirm that a second hepatic cryotherapy can be performed safely; operating time, intraoperative blood loss, and duration of hospital stay were similar after the first and second hepatic cryotherapies (see Table II), and complications requiring intervention were uncommon. One patient had wound dehiscence and an ischemic transverse colon after the first cryotherapy, probably resulting from poor technique at operation. In this case the abdomen was explored, colon resection and diversion were performed, and the patient was ultimately discharged home without further sequelae. Another patient developed a small bowel obstruction after repeat hepatic cryotherapy; this required exploration and lysis of adhesions. The third had a symptomatic right pleural effusion after repeat cryotherapy, which required thoracentesis. Our complication rate of 14% after repeat cryotherapy compares well with the 24% morbidity reported by Seifert and Morris,[11] and with the 15% to 50% rate of complications following repeat resection.

The principles that apply to second-time hepatic cryotherapy are the same as those used to select the first-time candidates: all known disease must be ablatable (with a 1 cm margin if possible), tumor should occupy less than half of hepatic volume, and the patient should have adequate hepatic functional reserve, no evidence of extrahepatic disease, and no serious medical comorbidity. Seifert and Morris[11] excluded patients with more than three hepatic metastases, whereas we did not exclude any patients based solely on the number of metastases. In our study the median number of tumors at the time of second cryotherapy was 2.3 (range 1 to 12).

Our aggressive approach to recurrent unresectable hepatic metastases may be justified by the absence of effective alternatives. Patients with untreated liver recurrence after liver resection have a median survival of only 4 months,[2] and most published reports of chemotherapy for liver metastases report a suboptimal response (less than 30%) and a short duration of response (less than 6 months).[17,18] The median survival in our study was 19 months after repeat hepatic cryotherapy and 42 months after the first cryotherapy. Mean actuarial survival from the time of original diagnosis was 53 months. This is comparable to the 58.7 months reported by Fong et al.[2] for patients undergoing repeat hepatic resection. In the cryosurgical series reported by Seifert and Morris,[11] mean disease-free survival and overall survival times following the second cryotherapy were 13 months and 28 months, respectively; corresponding survivals in our study were 12 and 19 months at a median follow-up of 21 months (see Fig. 2).

After completing data analysis for our study group of 14 patients, we compared their overall survival with that of the remaining 181 patients from the parent group. Fig. 3 shows the significant difference in survival following one cryotherapy versus repeat cryotherapy. Although we cannot rule out the possibility that patients who qualified for a second cryotherapy had a more favorable tumor biology, the comparison still suggests that repeat hepatic cryotherapy in a subset of patients with isolated liver recurrence can improve survival. However, it is not curative; all 14 patients in our series developed a recurrence after the second cryotherapy and nine required additional surgery. Two patients are presently free of disease, but only after multiple interventions (see Table I). We emphasize that ours was an aggressive approach; of the 14 patients, three underwent a third hepatic cryotherapy, three underwent pulmonary metastasectomy, two had abdominal wall resection, and one had retroperitoneal metastasectomy. Of interest, the last patient (see Table I, bottom row) was found to have an elevated serum level of carcinoembryonic antigen (CEA) during follow-up. CT scans of the chest/abdomen/pelvis and colonoscopy did not reveal any evidence of recurrence. Whole body PET scan, however, demonstrated activity in the left upper quadrant. Surgical exploration revealed a periaortic retroperitoneal lymphadenopathy, which was resected. Pathologic examination of the specimen confirmed metastasis. Postoperatively the patient's CEA level returned to normal.

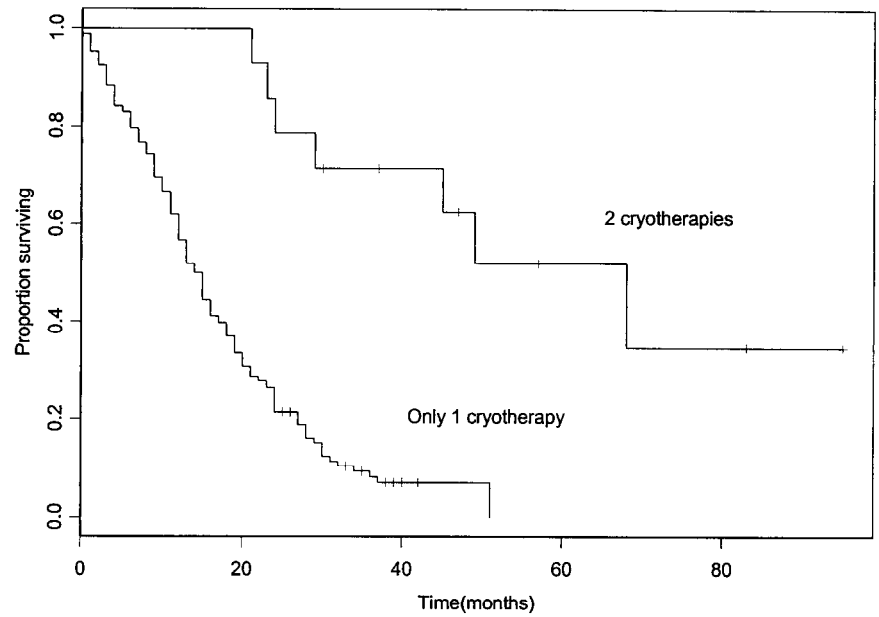

Fig. 3. Overall survival (from time of original diagnosis) of patients undergoing one versus two hepatic cryosurgeries ($P = 0.0001$).

Our data indicate a shorter disease-free interval following repeat hepatic cryotherapy (see Table II). The fact that 43% of our patients are alive at a median follow-up of 21 months from the last cryotherapy is largely due to close follow-up and aggressive surgical treatment of recurrences. A more effective systemic therapy might increase this percentage. Although nine of our patients underwent placement of a hepatic artery infusion pump, regional chemotherapy with floxuridine did not prolong the disease-free interval or improve overall survival following the second cryotherapy. In the literature, regional chemotherapy reportedly decreases the rate of local recurrence without affecting distant metastasis or survival.[19-21] All of our patients received aggressive adjuvant systemic chemotherapy—usually a 5-fluorouracil–based chemotherapy after resection of the primary tumor and irinotecan (Camptosar) at first recurrence. At the second recurrence, several patients received oxaliplatin. Regional/systemic chemotherapy did not appear to affect disease-free survival or overall survival in our study. The role of adjuvant therapy following hepatic resection or cryoablation should be investigated in a prospective trial.

Several series have examined potential parameters for selecting patients to undergo a second hepatic resection and/or cryoablation.[1,2,6,11,13,16,22] CEA levels, size of the tumor, number of lesions, bilobar involvement, and disease-free interval following the first hepatic surgery have not consistently been important in predicting outcome. We evaluated age, sex, stage of disease at presentation, tumor characteristics at first cryotherapy (size, number of lesions, bilobar involvement), regional chemotherapy via hepatic artery infusion pump, and disease-free interval after the first cryotherapy. Only the number of hepatic tumors present at the first cryotherapy was statistically significant in predicting the disease-free interval following the second cryotherapy. None of the parameters predicted overall survival following the second cryotherapy. CEA levels were not analyzed in our study because data for pre- and postoperative levels were available for only three patients.

With the recent advent of radiofrequency ablation (RFA) techniques for hepatic tumors, the role of cryosurgery is in question. Multiple studies have shown that RFA is effective and safe for the ablation of unresectable hepatic tumors.[23-25] RFA seems to be safer and less expensive than cryosurgery and can be performed via different approaches (percutaneous, laparoscopic, or at celiotomy).[26] Indeed, several patients in our series could have undergone percutaneous RFA of their liver recurrences. However, RFA is associated with longer ablation times and higher rates of local recurrence when it is used for larger tumors (>3 cm).[27] Additionally, multiple tumors cannot be ablated simultaneously with RFA technology. Therefore multiple and/or large tumors may be better ablated with cryosurgery. We have incorporated all three techniques (resection, RFA, and cryosurgery) in a management algorithm for patients with unresectable hepatic tumors.

CONCLUSION

This study is limited by its retrospective nature and by its small, highly select patient population. Even so, it offers strong evidence that repeat hepatic cryotherapy for isolated liver recurrence can be performed safely with minimal morbidity and no mortality. This aggressive approach appears to improve survival when compared to observation or medical therapy. Additionally, our survival data are comparable to survival rates associated with repeat hepatic resection. However, we caution that repeat hepatic cryotherapy is not curative; all of our patients developed a recurrence and/or progression after the second cryotherapy. Moreover, our study failed to identify reliable criteria for patient selection. A multicenter prospective trial comparing repeat cryotherapy/resection plus adjuvant systemic therapy with systemic therapy alone is necessary to determine the true efficacy of an aggressive approach for patients with recurrent hepatic metastases from colorectal carcinoma.

REFERENCES

1. Pinson C, Wright J, Chapman W, Garrard C, Blair T, Sawyers J. Repeat hepatic surgery for colorectal cancer metastatic to the liver. Ann Surg 1996;223:765-776.
2. Fong Y, Blumgart L, Cohen A, Fortner J, Brennan M. Repeat hepatic resection for metastatic colorectal cancer. Ann Surg 1994;220:657-662.
3. Korpan N. Hepatic cryosurgery for liver metastases. Long-term follow-up. Ann Surg 1997;225:193-201.
4. Dale P, Souza J, Brewer D. Cryosurgical ablation of unresectable hepatic metastases. J Surg Oncol 1998;68:242-245.
5. Stone M, Cady B, Jenkins R, McDermott W, Steele G. Surgical therapy for recurrent liver metastases from colorectal cancer. Arch Surg 1990;125:718-722.
6. Steele G, Osteen R, Wilson R, Brooks D, Mayer R, Zamcheck N, Ravikumar T. Patterns of failure after surgical cure of large liver tumors. Am J Surg 1984;147:554-559.
7. Griffith K, Sugarbaker P, Chang A. Repeat hepatic resections for colorectal metastases. Surgery 1990;107:101-104.
8. Bozzetti F, Bignami P, Montalto F, Doci R, Gennari L. Repeated hepatic resection for recurrent metastases from colorectal cancer. Br J Surg 1992;79:146-148.
9. Kin T, Nakajima Y, Kanehiro H, Hisanage M, Ohyama T, Nishio K, Sho M, Nagao M, Nakano H. Repeat hepatectomy for recurrent colorectal metastases. World J Surg 1998;22: 1087-1091.
10. Tandan VR, Harmantas A, Gallinger S. Long-term survival after hepatic cryosurgery versus surgical resection for metastatic colorectal carcinoma: A critical review of the literature. Can J Surg 1997;40:175-181.
11. Seifert J, Morris D. Repeat hepatic cryotherapy for recurrent metastases from colorectal cancer. Surgery 1999;125:233-235.
12. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. CA Cancer J Clin 2000;50:7-33.
13. Elias D, Lasser P, Hoang J, Leclere J, Debaene B, Bognel C, Spencer A, Rougier P. Repeat hepatectomy for cancer. Br J Surg 1993;80:1557-1562.
14. Lange J, Leese T, Castaing D, Bismuth H. Repeat hepatectomy for recurrent malignant tumors of the liver. Surg Gynecol Obstet 1989;169:119-126.
15. Fortner J. Recurrence of colorectal cancer after hepatic resection. Am J Surg 1988;155:378-382.
16. Adson M. Resection of liver metastases—when is it worthwhile? World J Surg 1987;11:511-520.
17. Jaffe B, Donegan W, Watson F, Spratt J. Factors influencing survival in patients with untreated hepatic metastases. Surg Gynecol Obstet 1968;127:1-11.
18. Wood C, Gillis C. Blumgart L. A retrospective study of the natural history of patients with liver metastases from colorectal cancer. Clin Oncol 1976;2:285-288.
19. Seifert J, Morris D. Prognostic factors after cryotherapy for hepatic metastases from colorectal cancer. Ann Surg 1998;228: 201-208.
20. Kemeny N, Daly J, Reichman B, Geller N, Botet J, Oderman P. Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma. A randomized trial. Ann Intern Med 1987;107:459-465.
21. Patt Y, Mavligit G. Arterial chemotherapy in the management of colorectal cancer. An overview. Semin Oncol 1991;18:478-490.
22. Weaver M, Ashton J, Zemel R. Treatment of colorectal liver metastases by cryotherapy. Semin Surg Oncol 1998;14:163-170.
23. Rossi S, Di Stasi M, Buscarini E, Cavanna L, Quaretti P, Squassante E, Garbagnati F, Buscarini L. Percutaneous radiofrequency interstitial thermal ablation in the treatment of small hepatocellular carcinoma. Cancer J Sci Am 1995; 1:73-81.
24. Siperstein A, Rogers S, Hansen P, Gitomirsky A. Laparoscopic thermal ablation of hepatic neuroendocrine metastases. Surgery 1997;122:1147-1155.
25. Curley S, Izzo F, Delrio P, Ellis L, Granchi J, Vallone P, Fiore F, Pignata S, Daniele B, Cremona F. Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies. Ann Surg 1999;230:1-8.
26. Bilchik A, Rose D, Allegra D, Bostick P, Hsueh E, Morton D. Radiofrequency ablation: A minimally invasive technique with multiple applications. Cancer J Sci Am 1999;5:356-361.
27. Bilchik A, Wood T, Allegra D, Tsioulias G, Chung M, Rose D, Ramming K, Morton D. Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms—a proposed algorithm. Arch Surg 2000;135:657-664.

Selective Internal Radiation Therapy With ^{90}Yttrium Microspheres for Extensive Colorectal Liver Metastases

Richard S. Stubbs, M.D., F.R.C.S. (Eng), F.R.A.C.S., Rebecca J. Cannan, M.Sc., Alex W. Mitchell, Ph.D.

Increasing attention has been given to treatments for colorectal liver metastases ever since hepatic resection was established as being worthwhile. Given the high proportion of patients who die of colorectal cancer with liver-only disease, it seems appropriate to be developing and investigating methods of local liver tumor ablation. Selective internal radiation therapy (SIRT) is a relatively new, not widely used, modality suitable for use even in patients with extensive liver involvement. Fifty patients with advanced, nonresectable, colorectal liver metastases were treated with SIRT between February 1997 and June 1999. Estimated liver involvement was less than 25% in 30 patients, 25% to 50% in 13, and greater than 50% in seven. A single dose of between 2.0 and 3.0 GBq of ^{90}yttrium microspheres was injected into the hepatic artery via a subcutaneous port and followed at 4-week intervals by regional chemotherapy with 5-fluorouracil. SIRT was well tolerated with no treatment-related mortality, although some treatment-related morbidity did occur including a 12% incidence of duodenal ulceration. Responses to SIRT were assessed by serial carcinoembryonic antigen (CEA) measurements and CT scans. Median CEA values 1 and 2 months after SIRT (expressed as percentage of initial CEA) were 19 and 13, respectively. Patients were assigned to one of two groups based on whether or not extrahepatic disease (EHD) developed within 6 months of SIRT. Median survival from SIRT for group 1 (EHD) (n = 26) was 6.9 months (range 1.3 to 18.8 months) and estimated survival ± standard error at 6, 12, and 18 months was 57.7 ± 3.8%, 23.1 ± 4.8%, and 0%, respectively. For group 2 (no EHD) (n = 24), median survival was 17.5 months (range 1.0 to 30.3 months) with estimated survival at 6, 12, 18, 24, and 30 months of 79.2 ± 2.9%, 66.7 ± 3.6%, 55.9 ± 3.3%, 25.2 ± 4.4%, and 16.8 ± 5.0%, respectively. This difference is statistically significant by log-rank test (P <0.010). SIRT is a highly effective and well-tolerated regional treatment for extensive colorectal liver metastases. Tumor marker data suggest that substantial destruction of liver tumors can be achieved in more than 90% of patients by a single treatment. Survival times, particularly for those who do not develop extrahepatic metastases for some time, appear to be extended. SIRT warrants further use and investigation in patients with advanced colorectal liver metastases. (J GASTROINTEST SURG 2001;5:294-302.)

KEY WORDS: Colorectal cancer, liver metastases, SIRT

The development of metastatic tumors within the liver occurs in some 50% of patients with colorectal carcinoma and is the major cause of death in those with this disease. Unlike what has been noted in patients with most other cancers, in patients with colorectal cancer the liver is frequently the only site of metastatic disease at the time of death.[1] In untreated patients, median survival from the time of diagnosis is on the order of 7.5 months with approximately 30% of patients surviving 1 year.[2]

Few meaningful treatment options seem to be available for such patients. Hepatic resection is possible in up to 15% of cases and may be curative with reported 5-year survival rates of 20% to 50%. However, the majority of patients are not suitable for hepatic resection because of the size, number, and location of their lesions, or the presence of extrahepatic disease. A number of palliative treatments have gained attention in recent years, and evidence is accumulating to suggest that these may extend life. Such treatments

From the Wakefield Gastroenterology Centre, Wakefield Hospital, Wellington, New Zealand.
Reprint requests: Mr. Richard Stubbs, Wakefield Gastroenterology Centre, Private Bag 7909, Wellington, New Zealand.

include focally destructive modalities such as cryotherapy,[3-5] radiofrequency ablation,[6] and laser ablation.[7] However, these too are only applicable to a subgroup of those with colorectal liver metastases with a small number of relatively small lesions. At the time of recognition, most patients unfortunately have extensive liver disease, either with a large number of lesions or a smaller number of large lesions. For such patients, even when the disease is confined to the liver, as is often the case, reliance must be placed on regional or systemic chemotherapy. Although the former is associated with significantly better response rates, these are still only on the order of 30% to 60% and any survival advantage is modest.[8]

Selective internal radiation therapy (SIRT) is a relatively new modality that may be valuable in this large group of patients. Whereas external-beam irradiation has found little place in the management of liver tumors because of the particularly radiosensitive nature of normal liver tissue, which limits total dosage to 30 to 35 Gy,[9-11] SIRT is a technique that allows high average doses of radiation (200 to 300 Gy) to be given to liver tumors with minimal serious effect on the nontumorous liver. The treatment entails delivery of usually a single dose of ^{90}yttrium microspheres into the hepatic artery, which by virtue of the almost exclusive arterial supply to liver tumors compared with the predominant portal supply to normal liver, results in selective tumor uptake and irradiation. High rates of response from SIRT have been reported for hepatocellular cancer and colorectal liver metastases.[12-14]

This modality has been under investigation at The Wakefield Gastroenterology Centre since February 1997 in the management of a number of types of nonresectable liver tumors including extensive colorectal metastases. In this latter context SIRT has been followed with ongoing hepatic arterial chemotherapy with 5-fluorouracil (5-FU). The purpose of this paper is to report our current experience with SIRT in the management of patients with extensive colorectal liver metastases with the intention of increasing awareness of the modality and encouraging its further investigation.

METHODOLOGY

Fifty patients (19 women and 31 men) with extensive colorectal liver metastases, who were not considered suitable candidates for either resection or cryotherapy, were treated with SIRT between February 1997 and June 1999 at The Wakefield Gastroenterology Centre. The treatment protocol was reviewed and approved by the Wellington Ethics Committee. Patients were assessed prior to treatment with CT scans of the abdomen (and pelvis if appropriate), chest x-ray examination, and standard blood tests including carcinoembryonic antigen (CEA). Although CT scans of the chest and bone scans were not routinely performed, they were done in many patients. The presence of extrahepatic disease was regarded as a relative contraindication to this treatment approach. However, in the presence of major liver disease and only minor intra-abdominal lymphadenopathy and occasionally minor or questionable lung metastases, SIRT was still considered justifiable. Life expectancy of less than 6 weeks was considered a contraindication. Only those judged fit for major abdominal surgery were considered for this treatment.

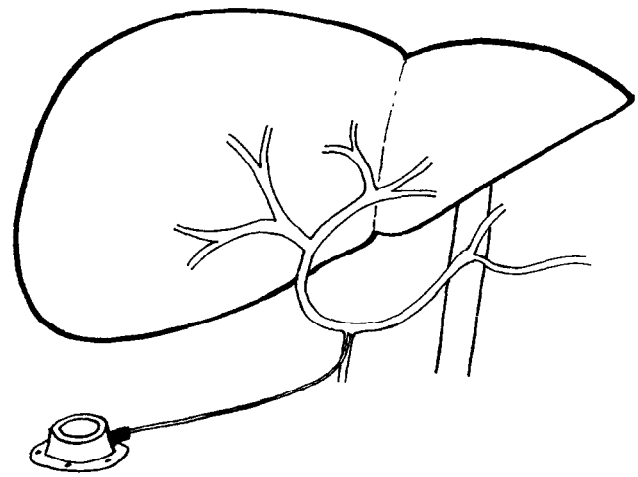

Fig. 1. Placement of hepatic artery Port-a-Cath via the gastroduodenal artery.

Laparotomy was performed for placement of a hepatic artery catheter (Port-a-Cath, Pharmacia, St. Paul, Minn.) via the gastroduodenal artery in 44 patients, using a technique we have described elsewhere[14] (Fig. 1). Briefly, cholecystectomy was carried out and particular care was taken to ligate all small vessels passing from the hepatic artery to the pancreas, stomach, and duodenum. Isolation of the vascular supply to the liver was confirmed intraoperatively by injection of 3 to 5 ml of methylene blue through the port. This technique permitted ready recognition of a dual or even triple arterial supply to the liver and when such was demonstrated, the aberrant/anomalous arteries were ligated. In 43 patients SIRT was subsequently given by administration of ^{90}yttrium resin microspheres (SIR-spheres®, Paragon Medical Ltd., Perth, Australia) into the hepatic artery via the port and was followed by hepatic artery chemotherapy (HAC) with 5-FU. In the remaining seven patients, SIR-spheres® were administered through a hepatic artery catheter placed beyond the gastroduodenal artery, via the femoral artery using a Seldinger technique, and subsequent HAC was not given.

SIRT was administered as a single treatment, under Hypnovel (Roche Products New Zealand Ltd., Aukland, New Zealand) and narcotic sedation, generally within 10 days of port placement. In those patients who received subsequent HAC, this was commenced around the time of the SIRT, such that synchronous 5-FU was received for at least 2 days after the SIRT. The dose of SIR-spheres® was titrated to the estimated extent of the disease (<25% liver replacement, 2 GBq; 25% to 50% liver replacement, 2.5 GBq; >50% liver replacement, 3 GBq) and was given over a 10-minute period, a few minutes after administration of 50 μg angiotensin II (Hypertensin, Novartis New Zealand Ltd., Aukland, New Zealand), into the hepatic artery. The SIR-spheres® were given using a special Perspex delivery apparatus, supplied by Paragon Medical Ltd. This permitted administration by pulsing of the SIR-spheres®, interspersed by flushing with sterile water.

Before the SIR-spheres® were given, two special precautions were taken. First, a "leach" test was performed in our laboratory, to confirm the stability of the SIR-spheres®, thereby ensuring that free ^{90}yttrium would not pass into the general circulation. Second, gamma scintigraphy was performed after 120 MBq of ^{99m}technetium-labeled macroaggregated albumin (^{99m}Tc-MAA; Amersham Pulmonate II, U.K., particle size 10 to 60 μm, average 35 μm) was administered into the hepatic artery either via the port or the percutaneous arterial catheter, an hour or so before the planned delivery of the SIR-spheres®. Because the particle size of the ^{99m}Tc-MAA is similar to that of the SIR-spheres® (29 to 35 μm), this scan provides an indication of the distribution of the SIR-spheres® that will be achieved and allows quantitation of any liver/lung shunt. In the event this exceeds 13%, it is unwise to proceed with SIRT because of the risk of subsequent radiation pneumonitis.[15]

In the 43 patients who received HAC, this was given continuously over 4 days with 1.0 g 5-FU per day, every 4 weeks. A portable, disposable balloon pump (Singleday Infusor PC1071, Baxter Healthcare S.A., Swinford, Ireland) was utilized and patients were maintained as outpatients for this procedure while being encouraged to pursue normal activities. The exception to this was during the initial cycle, which was given in the hospital around the time of the SIRT.

Patients were seen at 4-week intervals for repeat cycles of HAC and/or review, at which time routine blood tests including complete blood count, liver function tests, and CEA were done. Chest x-ray examination and CT scan of the liver were done every 3 months during follow-up. Tumor response was assessed both by changes in CEA and by CT scanning. CT changes within the liver were defined as follows:

Tumor response = definite reduction in size of index lesions; no enlarging or new lesions
Stable disease = no definite increase or decrease in lesion size; no new lesions
Progressive disease = definite increase in size of index lesions or appearance of new lesions

Changes in CEA were expressed as a percentage of the pre-SIRT value. Median values are quoted because the data are not normally distributed. Estimated survival was calculated by the Kaplan-Meier method, and statistical analysis was performed using the log-rank test. $P < 0.05$ was taken to indicate statistical significance.

RESULTS

The 50 patients included 31 men and 19 women whose median age was 61.4 years (range 33 to 76 years). Estimated liver involvement was less than 25% in 30 patients, between 25 and 50% in 13, and more than 50% in seven. Most patients were asymptomatic or only minimally symptomatic prior to treatment as shown by the Karnofsky scores in Table I. Only eight patients had definite evidence of extrahepatic metastatic disease at the time of SIRT, but this was generally relatively minor and not life-threatening as indicated in Table II. In 33 patients the liver metastases were present at the time of surgery for the primary site, and in 17 patients the metastases became evident at a subsequent time.

No deaths or life-threatening morbidity resulted from the surgery to place the hepatic artery Port-a-Cath or the hepatic artery catheter. Abdominal and thoracic scanning with a gamma camera following injection of ^{99m}Tc-MAA into the hepatic artery revealed a median liver/lung shunt of 0.25% (range 0 to 9.3%) and confirmed the approximate anticipated distribution of the SIR-spheres® to be administered. In 3 of the 50 patients the ^{99m}Tc-MAA scan revealed problems that required further surgery before SIRT could be safely and effectively given. In one patient the scan showed the port was accessing only the left liver, in another the catheter had become dislodged from the gastroduodenal artery, and in the third significant perfusion of the pancreas and duodenum was demonstrated. All three patients underwent additional surgery to correct the problem before receiving treatment. SIRT was administered a median of 3.2 months (range 0.5 to 71.6 months) after the diagnosis of liver metastases.

In two patients blockage of the port catheter occurred during administration of the SIR-spheres® and led to catheter "blowout" when forceful flushing was

undertaken. In the first patient the port was abandoned and SIRT was given by femoral artery catheter, and in the second urgent laparotomy was performed, the port was replaced, and SIRT was administered immediately thereafter.

Table I. Karnofsky scores of 50 patients at beginning of treatment

Score (%)	n
100	27
90	10
80	6
70	3
60	2
50	2

Table II. Sites and extent of extrahepatic disease prior to SIRT

Patient	Site and extent
1	Several lung lesions less than 1.0 cm; 6 cm right adrenal lesion
2	Solitary 1.5 cm lung lesion—excised prior to SIRT
3	Several small porta hepatis nodes less than 1 cm
4	Several small porta hepatis nodes less than 2 cm
5	2 cm recurrence in abdominal scar; early local pelvic recurrence
6	Several small lung sites and porta hepatis nodes all less than 1 cm
7	4 cm porta hepatis nodal mass—excised prior to SIRT
8	Several lung sites all less than 1 cm

Acute pain and/or nausea was experienced at the time of SIR-spheres® administration in 14 patients (28%) but was readily manageable with narcotics and antiemetics. Overall the SIRT was well tolerated and no serious in-hospital morbidity occurred. However, six patients (12%) developed an acute duodenal ulcer in the first 2 months after SIRT and the initial cycle of HAC, which may have been related to misperfusion of the duodenum by either SIR-spheres® or HAC or both. Two of these patients experienced acute upper gastrointestinal bleeding from the ulcer, one of whom required emergency surgery from which he recovered uneventfully. Patients were discharged a median of 2 days following SIRT (range 2 to 10 days). All experienced lethargy and some had anorexia for up to 5 or 6 weeks following the SIRT. No patient developed clinical evidence of radiation pneumonitis or hepatitis, and no biliary toxicity was observed as a result of the SIRT or ongoing HAC with 5-FU.

Antitumor effect was assessed by both tumor marker (CEA) and CT responses. Tumor marker (CEA) responses were dramatic (Fig. 2) and were seen in almost all patients. Three patients had normal serum CEA levels prior to treatment, and these levels remained normal throughout follow-up. These patients were not included in the following analysis. After 3 months, serum CEA levels were higher than pretreatment levels in only 2 (5.9%) of 34 patients. By 6 months, serum CEA levels were higher than pretreatment levels in 5 (20.0%) of 25 patients. At 12 months, serum CEA levels were higher than pretreatment levels in 6 (37.5%) of 16 patients. The median (range) serum CEA level, as a percentage of pre-

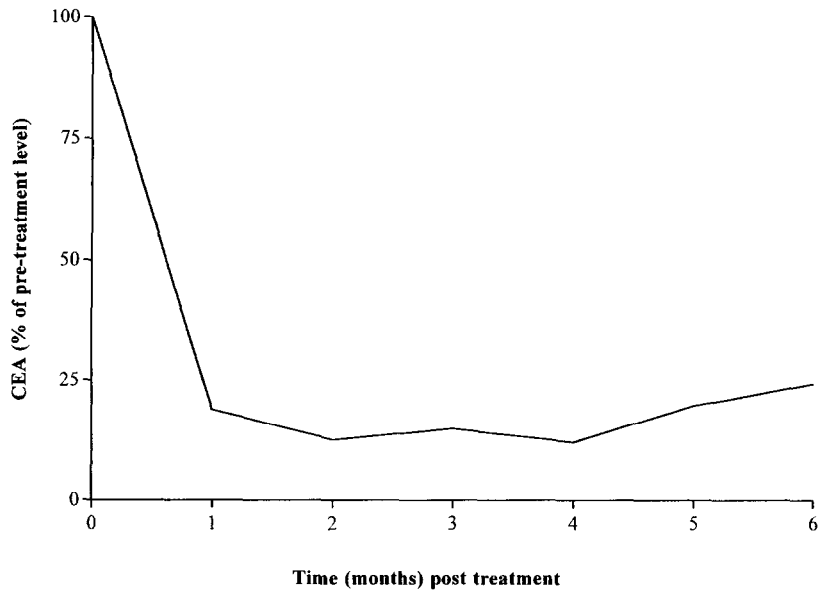

Fig. 2. Median serum CEA level following SIRT expressed as a percentage of pretreatment CEA.

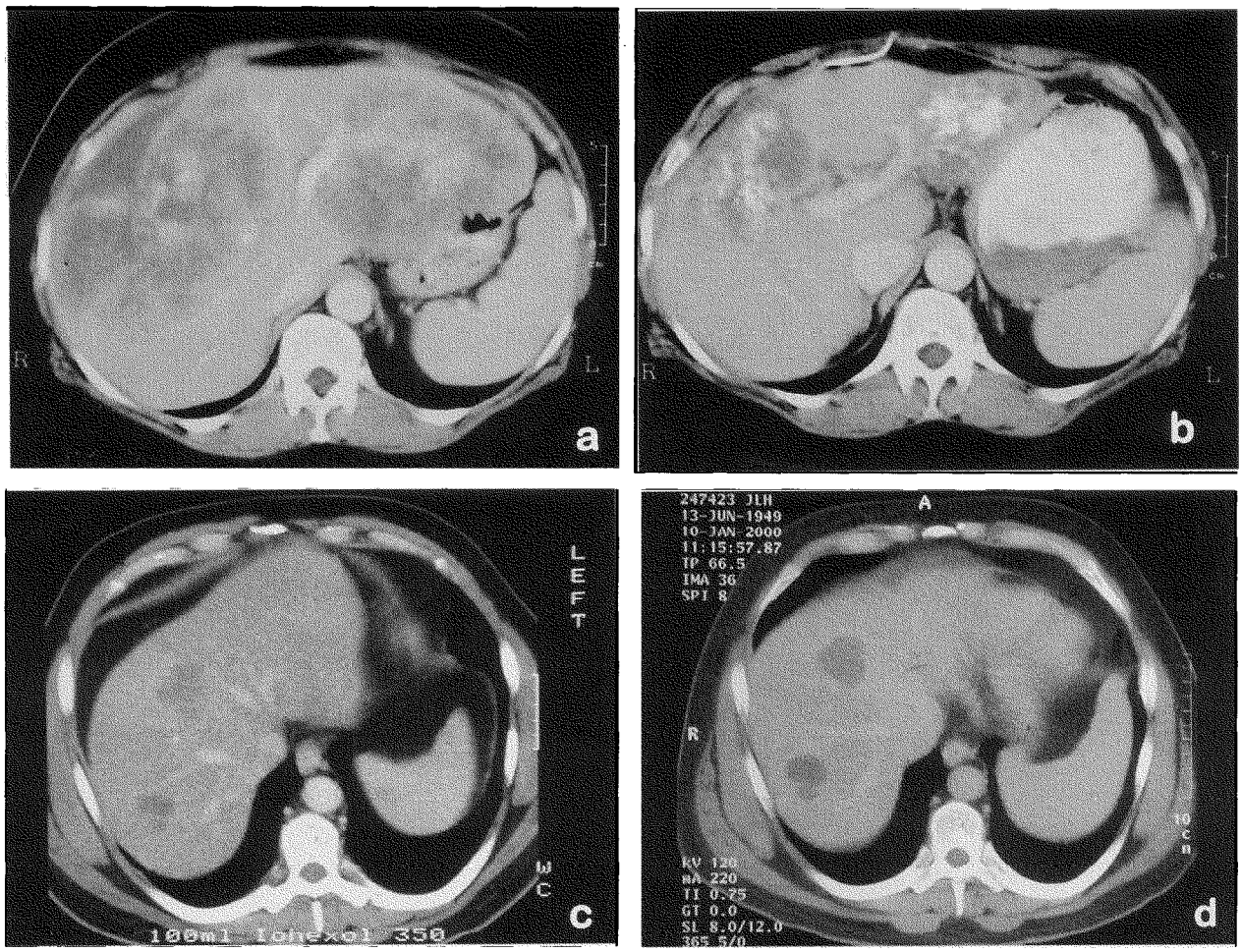

Fig. 3. CT changes after SIRT in two patients who responded well to treatment. **A** and **B**, Two large liver metastases before and 6 months after SIRT. Corresponding CEA values were 23,160 ng/ml and 2312 ng/ml, respectively. **C** and **D**, Two metastases in another patient before and 6 months after SIRT with no significant change in size but a decrease in CEA from 11.1 ng/ml to 1.2 ng/ml.

Table III. CT changes at 3 and 6 months after SIRT

	3 months	6 months
No. of patients	44	28
Reduction in tumor size	32	23
Stable disease	8	4
Increase in tumor size or new lesions	4	1

treatment levels, at 3, 6, and 12 months was 15.0% (0.3 to 135.8%), 24.3% (0.5 to 296.4%), and 24.0% (1.0 to 328.1%), respectively. HAC seemed very effective at maintaining the tumor marker response as demonstrated in Fig. 2. Significant increases in CEA levels were most commonly associated with and indicative of the development of extrahepatic disease and were uniformly seen prior to death.

Responses as judged by CT scanning 3 and 6 after SIRT are shown in Table III. Although the changes in tumor size on CT scanning are not always as impressive as the tumor marker changes, progressive liver disease was seen in only 4 (9%) of 44 patients after 3 months and in only one further patient after 6 months. Fig. 3 demonstrates the CT changes seen in two patients in whom excellent tumor marker responses were seen. Progressive disease on CT (be it liver or elsewhere) was never accompanied by a fall in CEA.

Twenty-six patients (52%), including the initial eight, already had or developed extrahepatic disease (EHD) within 6 months of receiving SIRT; they have been designated group 1. Within this group, CEA levels were rising significantly after 3 months in 16 of 20 patients for whom CEA data were available. The remaining 24 patients (48%) still had liver-only disease 6 months after SIRT and have been designated group 2. Within this group CEA was increasing significantly after 3 months in only 3 of 23 patients for whom CEA data were available. Median follow-up for

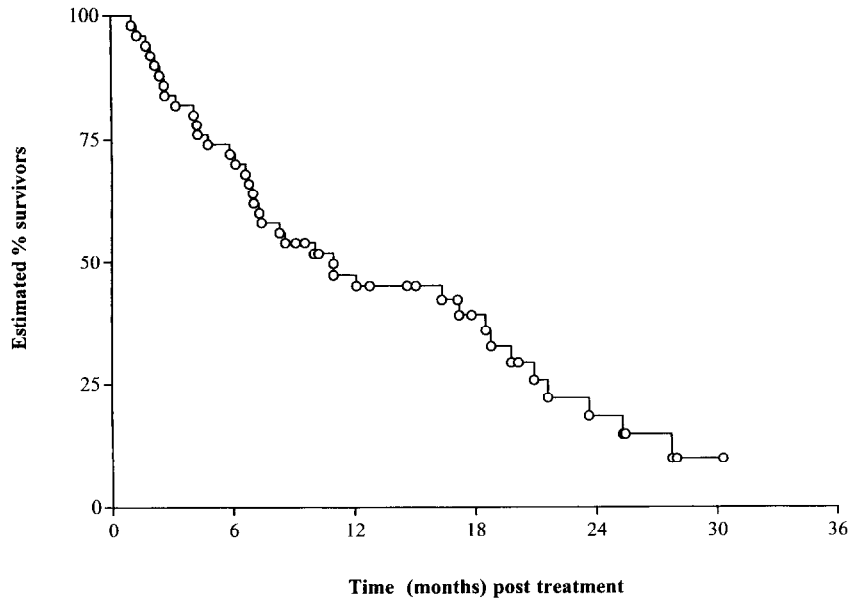

Fig. 4. Estimated survival (Kaplan-Meier method) for 50 patients after SIRT. The number of patients alive and under observation at the time of treatment and at six monthly intervals thereafter were as follows: 50, 36, 21, 12, 5, and 1.

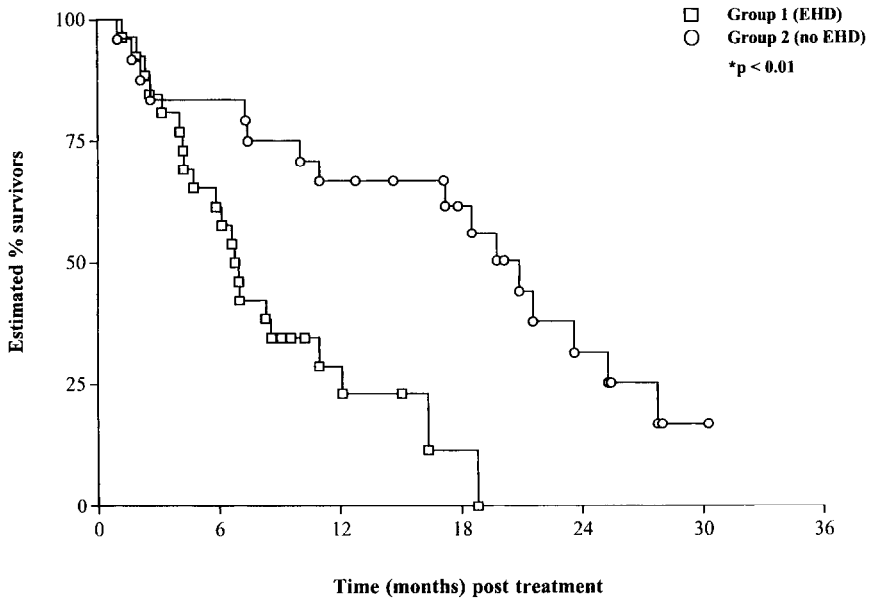

Fig. 5. Estimated survival (Kaplan-Meier method) for patients after SIRT. Group 1 includes those who already had or developed extrahepatic disease within 6 months of SIRT, and group 2 includes those in whom metastatic disease remained confined to the liver 6 months after SIRT. The number of patients alive and under observation at the time of treatment and at six monthly intervals thereafter were as follows: 26, 16, 5, 1, 0 for group 1 and 24, 20, 16, 11, 5, 1 for group 2. EHD = extrahepatic disease.

all patients was 25.5 months (range 8.6 to 37.5 months). Median survival from the time of diagnosis of liver metastases is 14.5 months (range 1.9 to 91.4 months) and from the time of treatment is 9.8 months (range 1.0 to 30.3 months). Kaplan-Meier estimated survival ± standard error for all patients after SIRT (Fig. 4) is 70 ± 2.3% at 6 months, 45.1 ± 3.0% at 12 months, 36.0 ± 3.0% at 18 months, 14.7 ± 3.3% at 24 months, and 9.8 ± 3.5% at 30 months. A comparison of the estimated survival following treatment of patients in groups 1 EHD and 2 (no EH) is shown in Fig. 5. For patients in group 1 median survival from

diagnosis of liver metastases is 11.4 months (range 1.9 to 23.0 months). Median survival after treatment is 6.9 months (range 1.3 to 18.8 months) and the estimated survival ± standard error at 6 months is 57.7 ± 3.8%, 23.1 ± 4.8% at 12 months, and 0% at 18 months. For patients in group 2 median survival from diagnosis of liver metastases is 24.7 months (range 3.0 to 91.4 months). Median survival after treatment is 17.5 months (range 1.0 to 30.3 months), and the estimated survival ± standard error at 6 months is 79.2 ± 2.9%, 66.7 ± 3.6% at 12 months, 55.9 ± 3.3% at 18 months, 25.2 ± 4.4% at 24 months, and 16.8 ± 5.0% at 30 months. These differences are statistically significant.

At the time this report was being written, 37 patients had died a median of 11.6 (range 1.9 to 91.4) months after diagnosis and 7.0 (range 1.0 to 27.8) months after SIRT. Thirty of these patients died with progressive extrahepatic disease (10 liver plus one other site, 20 liver plus two or more other sites). Only seven patients (19%) had liver-only disease.

DISCUSSION

The appearance of colorectal liver metastases has long been regarded as a harbinger of death, and a rather nihilistic approach to management has often been taken. However, there is increasing reason to suppose an aggressive approach to liver-only metastases is justifiable. Autopsy studies indicate a high proportion of those dying of colorectal cancer do so with liver-only disease,[1] and clinical observation makes it clear that colorectal liver metastases progress more quickly than those at most other sites and in most instances will determine the prognosis. Somewhat contrary to initial opinion, liver resection for resectable disease emerged through the 1980s and 1990s as a worthwhile treatment,[16] and evidence has been accumulating since the 1990s to indicate that locally ablative techniques such as cryotherapy,[3-5] radiofrequency ablation,[6] and laser destruction[7] may also be worthwhile in some circumstances. However, most patients with colorectal liver metastases have too much disease for any of these techniques to be applicable. Regional chemotherapy has been extensively investigated and offers some advantages over systemic chemotherapy, but is still not sufficiently reliable to be of unequivocal benefit.[8]

SIRT is a potential therapeutic option for such patients. High rates of local tumor response have been reported[12-14] and are confirmed by the present study. This is not surprising in view of the very high doses of radiation being achieved within tumor relative to normal liver parenchyma. Although it is not possible to be precise about the delivered absorbed doses because of the point source nature of the radiation delivered and the nonhomogeneous tumor and liver uptake, it has been calculated and reasonably validated that average tumor doses on the order of 200 to 300 Gy are being achieved.[13,17] This is in the face of average doses to unaffected liver of 15 to 50 Gy, which again because of the nonhomogeneous uptake and delivery of the radiation, does not result in clinically significant radiation hepatitis. Conventional techniques for radiation therapy are not suitable for liver metastases because total delivered doses in excess of only 30 to 35 Gy lead to potentially fatal radiation hepatitis.[9-11]

Selective tumor uptake is brought about by the particulars of tumor versus liver blood supply, whereby upwards of 95% of tumor blood supply is from the hepatic artery, whereas only perhaps 25% of normal liver blood supply is from the hepatic artery.[18,19] This selectivity can be enhanced still further by the prior administration of vasoconstrictive agents such as angiotensin II, which cause greater vasoconstriction of normal liver arterioles than tumor arterioles.[20]

Assessment of tumor response on the basis of tumor marker data indicates that even in those with extensive liver replacement, responses occur in approximately 90% of individuals. Furthermore, if as is likely to be the case, there is a linear relationship between serum CEA levels and tumor cell mass, a single dose of SIRT leads on average to destruction of 85% to 90% of hepatic tumor within 2 months. The benefit of this treatment seems to be well maintained by ongoing HAC. CT assessments support this based on the finding that fewer than 10% of patients demonstrate progression of liver tumor within 3 months of receiving SIRT. That SIRT plus HAC can achieve more than HAC or indeed systemic chemotherapy alone has not yet been conclusively shown, but the response rates reported here and by others are numerically superior to those reported for either HAC or systemic chemotherapy alone. Randomized trials are needed and will resolve this issue. The first of these has been completed in Perth, Australia, and is awaiting publication.

Survival data are both interesting and important. Considering the extent of disease in those being treated, a median survival time of 9.8 months from treatment and 14.5 months from diagnosis compares favorably with median survival times in similar but untreated patients, on the order of 7 to 10 months from diagnosis.[2,21,22] What is very clear is that the principal determinant of survival time after SIRT plus ongoing HAC is the development of extrahepatic disease. In the 48% of treated patients who still had liver-only disease after 6 months, the median survival time was 17.5 months from treatment and 24.7 months from diagnosis. It is particularly important to note that only

19% of those dying had liver-only disease, indicating that further significant advances in survival time will come only with the introduction of a treatment capable of controlling extrahepatic sites of disease. At the present time, systemic chemotherapy does not appear able to do this. There is some reason to be optimistic that new approaches to immunotherapy utilizing dendritic cell vaccines may prove able to do so.[23]

SIRT with SIR-spheres® is a relatively straightforward and safe technique, provided that careful attention to detail is given. The SIR-spheres® themselves are resin-based microspheres with a lower specific gravity than the glass microspheres used by some groups.[24,25] As a result they probably have better distribution characteristics when injected into the hepatic artery and thus may be safer and more effective. Leaching of the ^{90}yttrium from the microspheres has been a theoretical concern, leading to uptake in bone and subsequent bone marrow depression, but is not seen in practice, and the manufacture of SIR-spheres® is now sufficiently reliable to not require on-site "leach testing" prior to administration. ^{90}Yttrium is a particularly suitable isotope for medical use in this situation. As a pure beta emitter it is much simpler to handle and use than gamma or mixed beta and gamma emitters such as ^{131}iodine. In addition, its half-life of 2.7 days and maximum penetration in soft tissue of 11 mm both contribute to suitability for the purpose. The microspheres do not degrade and are of a size (29 to 35 μm) that means they are trapped in the arteriolar capillaries. Providing there is no significant arteriovenous shunt through the liver or tumor, they will not pass into the pulmonary circulation and thereby make radiation pneumonitis a possibility. ^{99m}Tc-MAA scanning prior to administration of the SIR-spheres® has been shown to be a very satisfactory technique for demonstrating such arteriovenous shunting and should always be carried out.[26] In practice the principal hazards associated with SIRT come from the potential for inadvertent perfusion of other foregut organs, particularly the duodenum, stomach, and pancreas. Even small quantities of microspheres caught in the capillary bed of the duodenal or stomach wall may lead to ulceration, bleeding, and even perforation. Again the ^{99m}Tc-MAA scan can alert the clinician to this by the demonstration of extrahepatic perfusion. The technique of port placement is particularly important to the success of the technique in terms of both safety and efficacy. We have documented this more fully elsewhere.[27] SIRT is not thought to be working through simple devascularization as this does not occur with delivery of approximately 20×10^6 spheres of an average size of 29 to 35 μm. Furthermore, effective devascularization techniques have never been shown to produce significant tumor destruction because of the rapidity of revascularization.

Given that SIRT appears so effective in destroying much of the liver tumor, it may seem tempting to utilize this therapy alone, administered via a hepatic artery catheter. Although this approach is currently taken by some groups including our own for nonresectable hepatocellular cancer,[13] we doubt that it can be delivered quite so safely in this manner in those with colorectal metastases because of the desirability of treating both sides of the liver. The ability to ligate anomalous hepatic arteries and the small vessels passing to the duodenum, stomach, and pancreas at the time of laparotomy and port placement does enhance the ability to isolate the liver prior to SIRT. Furthermore, we and others have presented evidence elsewhere that the addition of regional chemotherapy to hepatic cryotherapy seems to enhance the results in that setting,[3,5] and it seems inherently sensible to introduce a measure such as regional chemotherapy to control the residual liver tumor after SIRT.

SIRT is a novel and interesting means of delivering high-dose radiation relatively selectively and safely to patients with extensive colorectal liver metastases and has achieved high response rates and encouraging survival statistics. Further use and investigation of this approach in this group of patients who have such a poor prognosis seems warranted.

REFERENCES

1. Weiss L, Grundmann E, Torhorst, J, Hartveit F, Moberg I, Eder M, Fenoglio-Preiser CM, Napier J, Horne CHW, Lopez MJ, Shaw-Dunn RI, Sugar J, Davies JD, Day DW, Harlos JP. Haematogenous metastatic patterns in colonic carcinoma: An analysis of 1541 necropsies. J Pathol 1986;150: 195-203.
2. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. Lancet 1994;343:1405-1410.
3. Morris DL, Ross WB, Igbal J, McCall JL, King J, Clingan PR. Cryoablation of hepatic malignancy: An evaluation of tumor marker data and survival in 110 patients. GI Cancer 1996;1: 247-251.
4. Seifert JK, Junginger T, Morris DL. A collective review of the world literature on hepatic cryotherapy. J R Coll Surg Edinb 1998;43:141-154.
5. Stubbs RS, Alwan MH, Booth MWC. Hepatic cryotherapy and subsequent hepatic arterial chemotherapy for colorectal metastases to the liver. HPB Surg 1998;11:97-104.
6. Curley SA, Izzo F, Delrio P, Ellis LM, Granchi J, Vallone P, Fiore F, Pignata S, Daniele B, Cremona F. Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies. Ann Surg 1999;230:1-8.
7. Heisterkamp J, van Hillegersberg R, Ijzermans JNM. Interstitial laser coagulation for hepatic tumours. Br J Surg 1999; 86:293-304.
8. Meta-Analysis Group in Cancer. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. J Natl Cancer Inst 1996;88:252-258.

9. Ingold JA, Reed GB, Kaplan HS, Bagshaw MA. Radiation hepatitis. Am J Roentgenol Radium Ther Nucl Med 1965; 93:200-208.
10. Concannon JP, Edelmann A, Frich JC, Kunkel G. Localized "radiation hepatitis" as demonstrated by scintillation scanning. Radiology 1967;89:136-139.
11. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity from cancer treatment. Int J Radiat Oncol Biol Phys 1995;31:1237-1248.
12. Gray BN, Anderson JE, Burton MA, van Hazel G, Codde J, Morgan C, Klemp P. Regression of liver metastases following treatment with yttrium-90 microspheres. Aust N Z J Surg 1992;62:105-110.
13. Lau WY, Ho S, Leung TWT, Chan M, Ho R, Johnson PJ, Li AKC. Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of ^{90}yttrium microspheres. Int J Radiat Oncol Biol Phys 1998;40: 583-592.
14. Stubbs RS, Cannan RJ, Mitchell AW, Alwan MH. An initial experience with selective internal radiation therapy (SIRT) for non-resectable colorectal liver metastases. GI Cancer 1999;3: 135-143.
15. Leung TWT, Lau W-T, Ho SKW, Ward SC, Chow JHS, Chan MSY, Metreweli C, Johnson PJ, Li AKC. Radiation pneumonitis after selective internal radiation treatment with intraarterial ^{90}yttrium-microspheres for inoperable hepatic tumours. Int J Radiat Oncol Biol Phys 1995;33:919-924.
16. Fong Y, Blumgart LH, Cohen AM. Surgical treatment of colorectal metastases to the liver. Ca Cancer J Clin 1995;45: 50-62.
17. Ho S, Lau WY, Leung TWT, Chan M, Ngar YK, Johnson PJ, Li AKC. Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours. Eur J Nucl Med 1996;23:947-952.
18. Taylor I, Bennett R, Sherriff S. The blood supply of colorectal liver metastases. Br J Cancer 1979;39:749-756.
19. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol 1954;30:969-974.
20. Burton MA, Gray BN, Coletti A. Effect of angiotensin II on blood flow in the transplanted sheep squamous cell carcinoma. Eur J Cancer Clin Oncol 1988;24:1373-1376.
21. Cady B. Natural history of primary and secondary tumors of the liver. Semin Oncol 1983;10:127-134.
22. Finan PJ, Marshall RJ, Cooper EH, Giles GR. Factors affecting survival in patients presenting with synchronous hepatic metastases from colorectal cancer: A clinical computer analysis. Br J Surg 1985;72:373-377.
23. Chen W, Rains N, Young D, Stubbs RS. Dendritic cell-based cancer immunotherapy: Potential for treatment of colorectal cancer? J Gastroenterol Hepatol 2000;15:698-705.
24. Andrews JC, Walker SC, Ackermann RJ, Cotton LA, Ensminger WD, Shapiro B. Hepatic radioembolization with yttrium-90 containing glass microspheres: Preliminary results and clinical follow-up. J Nucl Med 1994;35:1637-1644.
25. Anderson JH, Goldberg JA, Bessent RG, Kerr DJ, McKillop JH, Stewart I, Cooke TG, McArdle CS. Glass yttrium-90 microspheres for patients with colorectal liver metastases. Radiother Oncol 1992;25:137-139.
26. Leung W, Lau WL, Ho SKW, Chan M, Leung NWY, Lin J, Metreweli C, Johnson PJ, Li AKC. Measuring lung shunting in hepatocellular carcinoma with intrahepatic-arterial technetium-99m macroaggregated albumin. J Nucl Med 1994;35: 70-73.
27. Wickremesekera J, Cannan RJ, Stubbs RS. Hepatic artery access ports: Recognising and avoiding the problems. Aust N Z J Surg 2000;70:496-502.

Effect of Matrix Metalloproteinase Inhibition on Colonic Anastomotic Healing in Rats

Teruo Kiyama, M.D., Masahiko Onda, M.D., Akira Tokunaga, M.D., David T. Efron, M.D., Adrian Barbul, M.D.

Wound strength depends on the balance between collagen synthesis and degradation; however, the role of collagen breakdown in wound healing is still not well understood. We investigated the role of matrix metalloproteinases in wound healing by using BE16627B, a matrix metalloproteinase inhibitor. Identical surgical procedures consisting of a colonic anastomosis (single-layer, inverted) and implantation of an osmotic pump in the back were performed in male Sprague-Dawley rats weighing 270 to 290 grams. The animals were randomly assigned to receive either BE16627B (n = 10) dissolved in dimethylsulfoxide and diluted with ethylene glycol at a dosage of 2.4 mg/rat/day for 3 days or the vehicle solution alone (n = 11). The solutions were administered through the surgically implanted osmotic pumps. The animals were killed 4 days after surgery, and the colonic bursting pressure (mm Hg) and hydroxyproline concentration (μg/mg wet tissue, index of collagen) were measured. The administration of BE16627B enhanced colonic anastomotic healing, as measured by the increase in the colonic bursting pressure (160 ± 12 vs. 125 ± 7 mm Hg; $P < 0.05$) and the increase in the soluble fraction of collagen (0.27 ± 0.01 vs. 0.21 ± 0.01 μg/mg wet tissue; $P < 0.01$) in the anastomosis. Histologic examination of the tissue revealed that the use of BE16627B resulted in the preservation of the multilayered colonic structure and increased the network of collagen between both ends of the colon in the thickening submucosal layer. These findings demonstrate that the inhibition of matrix metalloproteinase activity influences colonic anastomotic healing, indicating a potential mechanism for enhancing anastomotic healing. (J GASTROINTEST SURG 2001;5:303-311.)

KEY WORDS: Matrix metalloproteinases, colonic anastomosis, wound healing, collagen, collagenase

Failure of anastomotic healing is a serious complication of large bowel surgery.[1] Many factors have been shown to impair gastrointestinal healing. Local factors, including technical details and the presence of intra-abdominal sepsis, and systemic factors, such as the nutritional state of the host, have been implicated in the etiology of anastomotic leaks.[2] An increasing number of cellular and subcellular interactions between wounded cell populations and matrices has been identified as having a profound effect on wound healing.

Many components of the healing process are common to all tissues, such as the initial inflammatory response, early collagenolysis, deposition of new collagen, and eventual maturation of the scar. However, the strength of intestinal wounds increases far more rapidly than the strength of cutaneous wounds, under normal circumstances.[3] Collagenase activity increases throughout the gastrointestinal tract after transection and reanastomosis, although not as much as in cutaneous wounds.[4]

Collagenases, together with gelatinases and stromelysins, belong to the general category of matrix metalloproteinases (MMPs).[5] These enzymes contain zinc at their active site and require a neutral pH and Ca^{2+} for full activity. MMPs are secreted as inactive proenzymes and are activated proteolytically. Their activity can be inhibited by tissue MMP inhibitors.

From the Department of Surgery I, Nippon Medical School, Tokyo, Japan (T.K., M.O., and A.T.), and the Department of Surgery, Sinai Hospital and The Johns Hopkins Medical Institutions, Baltimore, Md. (D.T.E. and A.B.).
Supported by a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science.
Presented at the Forty-First Annual Meeting of The Society for Surgery of the Alimentary Tract, San Diego, Calif., May 21-24, 2000.
Reprint requests: Teruo Kiyama, M.D., Department of Surgery I, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. e-mail: kiyama@nms.ac.jp

The role of collagenases in wound healing is not fully understood, although they are rapidly induced after wounding and exhibit a distinct pattern of expression. At different times during healing, inflammatory cells, fibroblasts, keratinocytes, and endothelial cells all serve as sources of various MMPs.[6]

Successful wound healing is tantamount to the achievement of a strong and stable scar, and wound strength is determined by the amount and quality of newly synthesized and deposited collagen, as well as the degradation of preformed collagen. The balance between these two factors ultimately determines the strength and integrity of wounds during the early period of healing. Collagenase plays an important role in determining anastomotic integrity and suture-holding capacity during the first few days of healing.[7] The activity of collagenase increases significantly 3 days after colonic anastomosis, and the suture-holding capacity in the region of the anastomosis decreases by up to 80% during this period.[8,9] When sepsis is present, excess enzymes may promote dehiscence. This complication is most likely to occur 3 to 5 days after surgery.

BE16627B is an MMP inhibitor that lacks MMP isotype specificity.[10] MMP inhibitors, such as BE16627B or its analogues, have been shown to inhibit tumor progression and the growth of metastases. MMP inhibitors have also been used to improve outcome after septic shock and hemorrhage by inhibiting the role of MMPs in promoting the formation of tumor necrosis factor-alpha.[11-13] Furthermore, MMP inhibition has also been shown to decrease angiogenesis, as demonstrated in a rat corneal model.[14]

In cutaneous wound healing models, MMP inhibition enhances wound strength, even though new collagen synthesis and inflammatory responses are decreased.[15] We hypothesized that the inhibition of collagenase activity would improve colonic anastomotic healing by reducing collagenolysis and indirectly enhancing anastomotic collagen deposition. In the present study we investigated the effect of the MMP inhibitor BE16627B on rat colonic anastomotic healing.

MATERIAL AND METHODS

Animals

The experimental protocol was approved by the Institutional Animal Care and Use Committee of Nippon Medical School. Twenty-one male Sprague-Dawley rats (Nippon Clea, Tokyo, Japan), weighing 270 to 290 grams, were acclimatized to our laboratory conditions for 7 days before being used in the experiment. The animals were housed at 21° C with 12-hour light/dark cycles and allowed free access to tap water and standard rodent chow (CL-2, Nippon Clea).

Colonic Anastomosis

The animals were weighed and anesthetized by intraperitoneal injection of pentobarbital sodium (50 mg/kg of body weight) (Nembutal; Dai-Nippon Pharmaceutical Co., Tokyo, Japan). A laparotomy was performed under aseptic conditions through a lower midline incision. The distal colon was divided 2 cm proximal to the peritoneal reflection without damaging the mesenteric vascular arcade. A single-layer, inverting anastomosis was made using interrupted 6-0 Prolene sutures (Ethicon, Inc., Tokyo, Japan), and the abdominal wall was closed in two layers. A miniosmotic pump (model 1003, ALZA, Palo Alto, Calif.), preloaded as described below, was implanted in the left side of the back. The rats were then housed in individual metabolic cages.

The animals were randomly assigned to receive either BE16627B (Dr. A. Okuyama, Banyu Tsukuba Research Institute, Tsukuba, Japan) (n = 10) dissolved in dimethylsulfoxide and diluted with the same volume of ethylene glycol at a dosage of 2.4 mg/rat/day for 3 days or the vehicle solution alone (n = 11) by subcutaneous infusion via the osmotic pump. Body weight, water and food intake, and urine output were monitored daily.

Colonic Bursting Pressure

Four days after surgery, the rats were killed with a lethal dose of pentobarbital. Cardiac blood was drawn for determination of serum albumin, total protein, and urea nitrogen levels. The abdomen was opened. The anastomotic bursting pressure was measured in situ according to a previously reported procedure.[16] Briefly, a 16-gauge silicone rubber catheter was inserted via an incision into the proximal colon and held in position with 3-0 silk sutures. The rectum (distal to the anastomosis) was then ligated with a 3-0 silk suture, and normal saline solution was continuously infused through the catheter via a pump (Watson-Marlow, Cornwall, England) at a rate of 1.0 ml/min. The pressure was monitored using a disposable pressure transducer (DTX Plus, Baxter, Tokyo, Japan), simultaneously displayed on a monitor, and continuously recorded on a polygraph system (Nihon Koden, Tokyo, Japan). The peak pressure attained before rupture of the anastomosis was recorded as the bursting pressure.

Soluble and Insoluble Fractions of Collagen and α-Amino Nitrogen

After bursting, the anastomotic segment (comprising a 1 cm length of bowel centered at the anastomosis) was excised, cleared of surrounding mesentery and

fat, and rinsed with saline solution. Half of each anastomosis was used for staining with hematoxylin and eosin, and azan stain (*azo*carmine-*ani*lin blue). The latter stain shows collagenous fibers as well as mucous substances in various shades of blue, allowing them to be distinguished from the reddish-stained nuclei and cytoplasmic components. The other half of each anastomosis was stored at −20° C for up to 24 hours until the hydroxyproline content, which was used as an index of anastomotic collagen, could be determined.

The collagen was fractionated into soluble and insoluble fractions.[17] Briefly, the colon segments were weighed while wet and minced into fragments smaller than 1 mm. The salt-soluble fraction was extracted by placing the fragments in sodium chloride at a concentration of 0.15 mol/L in a Tris buffer (pH 7.2) for 72 hours. After centrifugation and decanting of the salt solution, the acid-soluble collagen was similarly extracted from the residual colon fragments using acetic acid at a concentration of 0.5 mol/L for 72 hours. The acid-soluble fraction was also decanted and stored for analysis. The salt- and acid-soluble extracts were evaporated to dryness at 110° C. Each of the soluble collagen extracts and the residual colon fragments (representing insoluble collagen) were hydrolyzed in 6N hydrochloric acid, and the hydroxyproline content was determined spectrophotometrically using the method described by Woessner.[18] α-Amino nitrogen, an index of the total protein content, was also measured in the ample hydrolysates according to a previously described method.[19]

Statistics

All data are expressed as means ± standard error of the mean (SEM). Statistical comparisons were made using the unpaired Student's *t* test and the StatView II statistical package (Abacus Concepts, Berkeley, Calif.).

RESULTS

All animals appeared healthy throughout the experiment, and no deaths or abscesses were noted. Animals in both groups demonstrated an initial decrease in body weight on the first postoperative day. However, the body weight of the BE16627B animals began to increase thereafter, whereas the body weight of the vehicle-infused animals continued to decrease until the second postoperative day (Fig. 1). Postoperatively, the BE16627B group gained significantly more weight than the control group on days 2 through 4 (Table I).

Food intake on day 2 was higher in the rats that received BE16627B than in the control rats (13.7 ± 3.2

Table I. Metabolic parameters

Group	Body weight (day 0, g)	Δ Body weight (day 0-4, g)	Food intake (g/day)	Water intake (ml/day)	Urine output (ml/day)
BE16627B	276 ± 3	13.6 ± 3.1*	14.8 ± 1.5	15.7 ± 1.3	34.0 ± 1.5
Control	277 ± 2	−1.1 ± 2.8	12.7 ± 1.6	12.9 ± 1.0	31.5 ± 2.3

Mean ± SEM.
*P <0.005.

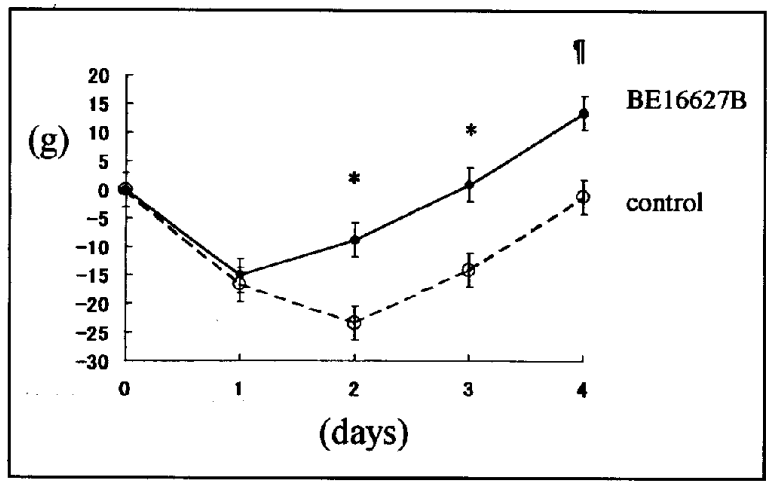

Fig. 1. Changes in body weight after surgery in BE16627B-treated rats (n = 10) and control rats (n = 11) (mean ± SEM; * = P <0.05; ¶ = P <0.005).

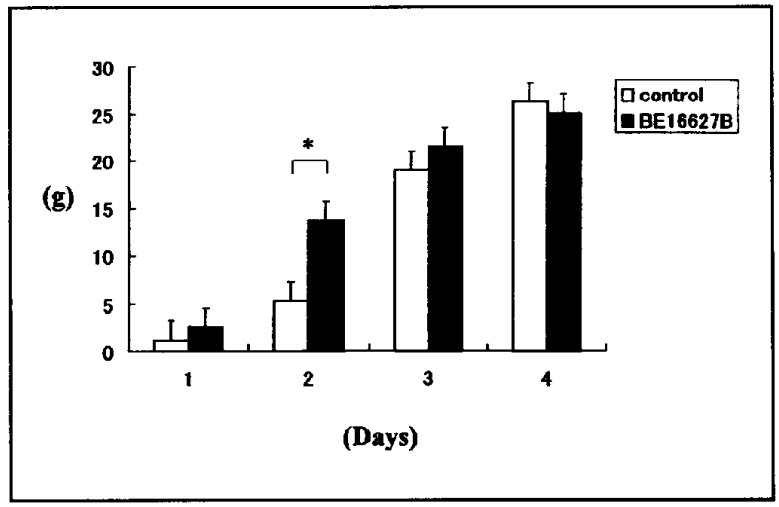

Fig. 2. Daily chow intake after surgery in BE16627B-treated rats (n = 10) and control rats (n = 11) (mean ± SEM; *P = <0.05).

Table II. Nutritional parameters (blood chemistry)

Group	Total protein (g/dl)	Albumin (g/dl)	Urea nitrogen (mg/dl)
BE16627B	5.7 ± 0.1	4.0 ± 0.1	20.6 ± 1.1
Control	5.6 ± 0.1	3.9 ± 0.1	20.5 ± 0.7

Mean ± SEM.

Table III. Anastomotic hydroxyproline and α-amino nitrogen content

Group	Soluble collagen (μg/mg wet tissue)	Insoluble collagen (μg/mg wet tissue)	α-Amino nitrogen (μmol/mg wet tissue)
Control	0.21 ± 0.01	1.89 ± 0.07	90.8 ± 3.1*
BE16627B	0.27 ± 0.01†	1.77 ± 0.07	83.0 ± 1.9

Mean ± SEM.
*P <0.05.
†P <0.001.

vs. 5.3 ± 1.4 g/day, P <0.05; Fig. 2), but no other differences between the two groups were noted in terms of mean food intake, water consumption, or urine output (see Table I). No differences in serum albumin, total protein, or urea nitrogen levels were observed between the two groups (Table II).

The bursting pressure of the anastomotic segment was significantly higher in the BE16627B group than in the control group (160 ± 12 vs. 125 ± 7 mm Hg; P <0.05). The soluble fraction of collagen in the anastomotic segment was also significantly higher in the BE16627B group, but the insoluble fraction of collagen was the same for both groups. The total protein level, measured as the α-amino acid content, was significantly reduced in the BE16627B group (Table III).

Macroscopic inspection revealed that the suture ties along the anastomosis were visible in the BE16627B group, but a linear ulceration with a white necrotic tissue was present along the suture line in the control group (Fig. 3). Thickening of the bowel wall was limited to the area surrounding the suture ties in the BE16627B group, and the network of blood vessels in the serosa was visible. In the control group, however, the area adjacent to the anastomosis had thickened, making the network of blood vessels in the serosa difficult to observe.

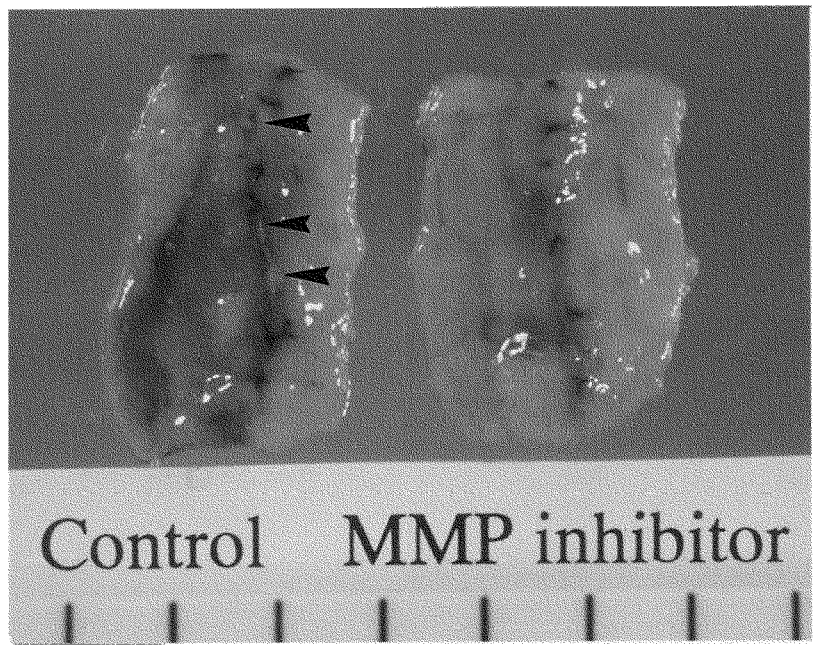

Fig. 3. Macroscopic views of colonic anastomoses 4 days after surgery. The anastomosis of the control rat shows a linear ulceration with a white necrotic tissue (arrow) and a thickened bowel wall. The anastomosis of the BE16627B-treated rat shows no defect in the mucosa, and the blood vessel network is visible on the serosal side.

The histologic examination using hematoxylin and eosin staining revealed that both ends of the bowel were attached by a thick submucosal layer in the BE16627B group and by thin, nonstructural granulation tissue in the control group (Fig. 4). In the BE16627B group, the multilayered structure of the bowel was well preserved; mucosa with glands covered the region of the anastomosis, the submucosa was thick, and blood vessels were seen in the submucosa and subserosa. In the control group, the granulation tissue was well established and had replaced the structure of the bowel; a single layer of epithelium covered the absent mucosa on the granulation tissue, and both ends of the bowel were attached by a thin, nonstructural granulation and covered with fibrous tissue on the serosa.

Collagen (Azan) staining revealed that the number of collagen fibers in the submucosal layer had increased only at the anastomotic site in the BE16627B group. In the control group, however, the number of fibers increased at the anastomotic site, as well as along the adjacent regions of the bowel (Fig. 5). In the BE16627B group, the thickening of the submucosa was limited, as approximately 20 mucosal glands and both ends were attached in a layer-to-layer fashion, especially the collagen fibers in the thickened submucosal layer. In the control group, the region of submucosal thickening extended for approximately 40 mucosal glands, and both ends were attached by a small portion of collagen fibers in the submucosa. The number of collagen fibers in the adjacent regions of the bowel was also higher.

DISCUSSION

The data obtained in these experiments demonstrate that BE16627B, an inhibitor of MMPs, enhances colonic anastomotic healing as measured by increases in both anastomotic bursting pressure and the soluble fraction of collagen in the anastomotic segment. The chow intake on day 2 recovered to more than 50% of the mean daily chow intake in the BE16627B group and to less than 25% of the mean daily intake in the control group, accounting for the larger increase in body weight on days 2 to 4 in the BE16627B group. Because MMP inhibitors have been reported to inhibit the production of tumor necrosis factor-alpha during sepsis and hemorrhage, BE16627B may also induce early recovery from surgical insults and stimulate appetite.

The colonic bursting pressure is determined primarily by the following two factors: the net amount

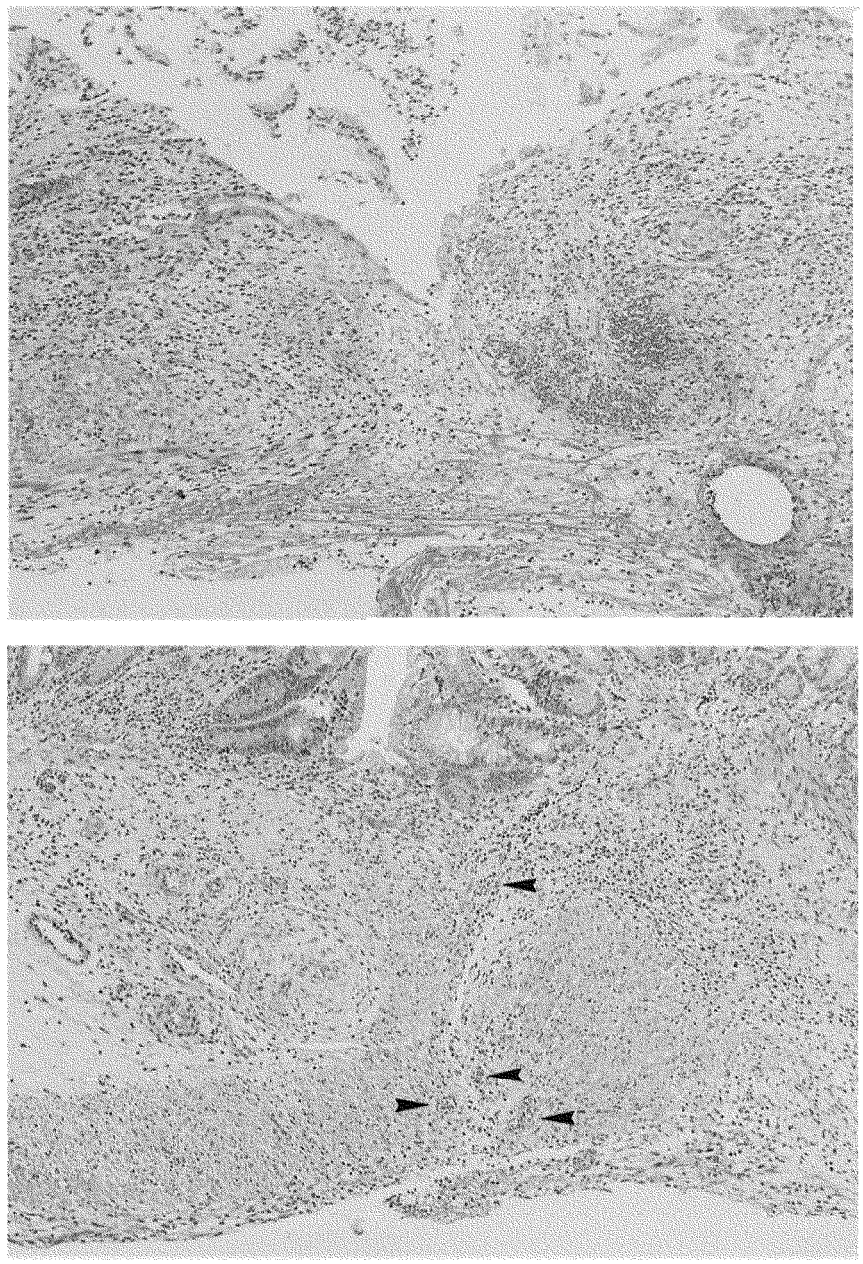

Fig. 4. Histologic appearance of the anastomosis in a control rat **(A)** and a BE16627B-treated rat **(B).** In the control rat, the anastomosis has been replaced by granulation tissue covered by a single layer of epithelium. In the BE16627B-treated rat, the multilayered architecture of the bowel has been well preserved, including the presence of glands in the mucosa, the thickening of the submucosal layer, and proper muscle, serosa, and blood vessels (arrow). (Hematoxylin & eosin stain, ×200.)

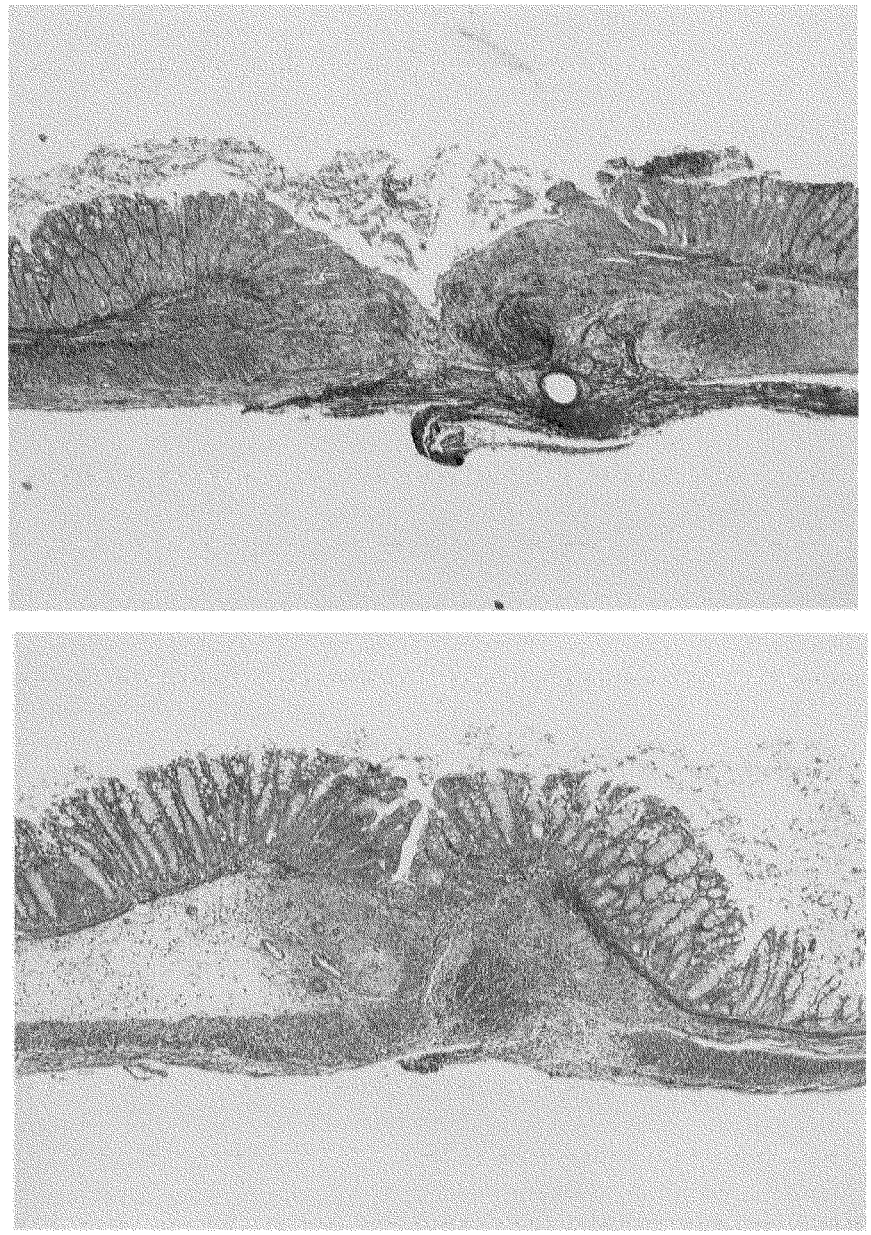

Fig. 5. Histologic appearance of the anastomosis in a control rat **(A)** and a BE16627B-treated rat **(B).** In the control rat, a large number of collagen fibers are present in the submucosal layer of the adjacent regions of the colon, but the ends of the bowel are attached only by a thin granulation tissue. In the BE16627B-treated rat, a large number of collagen fibers are present only at the site of the anastomosis, and the ends of the bowel are attached mainly by a thickened submucosal layer. (Azan stain, ×500.)

of wound collagen deposition and the cross-linking of this collagen. Net collagen deposition, in turn, depends on collagen turnover and is a reflection of collagen synthesis minus collagen breakdown. Soluble collagen consists of a salt-soluble fraction, which may represent actively synthesized collagen, and an acid-soluble fraction, which may represent fibers that have been depolymerized, translocated, and reutilized in collagen synthesis. Our experimental data suggest that the soluble fraction of collagen deposition is responsible for the attachment of both anastomotic ends and the increase in mechanical strength of the anastomotic segment in the BE16627B group. Insoluble collagen, which is polymerized, accounts for almost 90% of the collagen at the anastomotic site. The insoluble collagen fraction did not differ between the two groups in our study. Collagenase activities of peritoneal fluids on zymography also did not differ between the two groups on day 4 (data not shown). The dosage of BE16627B used in this study was 2.4 mg/rat/day for 3 days. This dosage is less than the dosage of 0.5 to 2 mg/mouse/day used in a previous study that demonstrated the inhibition of human tumor growth as well as lung colonization.[10] BE16627B alone might not be sufficient to completely inhibit the activity of MMP. Alternatively, the MMP activity might have recovered on day 4 because the BE16627B inhibition was reversed by the onset of dialysis.[10] In the present study, the total protein level was significantly higher in the control group than in the BE16627B group. The total protein level also increased in colonic anastomosis with intra-abdominal sepsis, although the concentration of insoluble collagen decreased.[17] BE16627B may decrease the infiltration of inflammatory cells as well as collagen degradation.

Collagen (Azan) staining showed that both ends of the bowel were attached by a larger number of collagen fibers in the thick submucosal region of the BE16627B group. In the control group, the anastomosis of the bowel was replaced by granulation tissue with numerous collagen fibers in the submucosal layer of the colon, but both ends of the bowel were attached by a small collagen network in a thin granulation tissue. The increased deposition of collagen in the BE16627B group may be responsible for the higher bursting pressure.

The gastrointestinal tract has a multilayered architecture and a large microorganism content in its lumen. In addition, the serosa influences the sealing of the suture line. The gastrointestinal tract also has a unique vascular supply.[2] All of these factors contribute to the healing of colonic anastomoses. The mucosal component of gastrointestinal anastomoses is repaired by the migration and hyperplasia of epithelial cells, which cover the granulation tissue of the wound, thereby sealing the defect and creating a barrier to the luminal contents.[20] This sealing can be completed in as little as 3 days if the layers of the bowel wall are directly apposed.[21] In the control group, a single layer of epithelial cells covered the granulation tissue on day 4. Delayed epithelization results in a more profound and prolonged inflammatory process, which contributed to the much larger total protein concentration in the anastomotic segment of the control rats. The increase in the total protein concentration in the control rats may indicate the deposition of an extracellular matrix, which is critical for mechanical strength and is influential in regulating cellular gene expression and phenotypic differentiation.[22,23] Histochemical staining showed a dilatation of the arterioles in the submucosal and subserosal layers in the BE16627B group, but only the capillary vessels were dilated in the control group. Although MMP inhibitors have been reported to inhibit angiogenesis, the preservation of the multilayered structure may suggest vascular communication in the BE16627B group.

CONCLUSION

Our findings suggest that the inhibition of MMP activity can influence colonic anastomotic healing, indicating a potential mechanism for enhancing anastomotic healing. The preservation of a multilayered structure in the anastomotic region may help to maintain the collagen network in the submucosal layer, thereby increasing the mechanical strength of the anastomosis.

We are grateful to Dr. A. Okuyama, Banyu Pharmaceutical Company, for providing the BE16627B and for his helpful advice.

REFERENCES

1. Schrock TR, Deveney CW, Dunphy JE. Factor contributing to leakage of colonic anastomoses. Ann Surg 1973;177:513-518.
2. Thornton FJ, Barbul A. Healing in the gastrointestinal tract. Surg Clin North Am 1997;77:549-573.
3. Cronin K, Jackson DS, Dunphy JE. Changing bursting strength and collagen content of the healing colon. Surg Gynecol Obstet 1968;126:747-753.
4. Hawley PR, Faulk WP, Hunt TK, Dunphy JE. Collagenase activity in the gastro-intestinal tract. Br J Surg 1970;57:896-900.
5. Shingleton WD, Hodges DJ, Brick P, Cawston TE. Collagenase: A key enzyme in collagen turnover. Biochem Cell Biol 1996;74:759-775.
6. Stricklin GP, Li L, Nanney LB. Localization of mRNAs representing interstitial collagenase, 72-kda gelatinase, and TIMP in healing porcine burn wounds. J Invest Dermatol 1994;103:352-358.

7. Chowcat NL, Savage FJ, Lewin MR, Boulos PB. Direct measurement of collagenase in colonic anastomosis. Br J Surg 1990;77:1284-1287.
8. Jonsson K, Jiborn H, Zederfeldt B. Breaking strength of small intestinal anastomoses. Am J Surg 1983;145:800-803.
9. Hogstrom H, Haglund U. Postoperative decrease in suture holding capacity in laparotomy wounds and anastomosis. Acta Chir Scand 1985;151:533-535.
10. Naito K, Kanbayashi N, Nakajima S, et al. Inhibition of growth of human tumor cells in nude mice by a metalloproteinase inhibitor. Int J Cancer 1994;58:730-735.
11. Gearing AJ, Beckett P, Christodoulou M, Churchill M. Processing of tumour necrosis factor-alpha precursor by metalloproteinases. Nature 1994;370:555-557.
12. Solorzano CC, Ksontini R, Pruitt JH, Auffenberg T. A matrix metalloproteinase inhibitor prevents processing of tumor necrosis. Shock 1997;7:427-431.
13. Wang P, Ba ZF, Galardy RE, Chaudry IH. Administration of a matrix metalloproteinase inhibitor after hemorrhage. Shock 1996;6:377-382.
14. Galardy RE, Groelny D, Foellmer HG, Fernandez LA. Inhibition of angiogenesis by the matrix metalloprotease inhibitor N-[2R-2(hydroxamidocarbonylmethyl)-4-methylpentanoyl]-L-tryptophan methylamide. Cancer Res 1994;54:4715-4718.
15. Witte MB, Kiyama T, Barbul A, et al. Metalloproteinase inhibitors and wound healing: A novel enhancer of wound strength. Surgery 1998;124:464-470.
16. Kiyama T, Efron DT, Tantry U, Barbul A. Effect of nutritional route on colonic anastomotic healing in the rat. J GASTROINTEST SURG 1999;3:441-446.
17. Kiyama T, Onda M, Tokunaga A, Yoshiyuki T, Barbul A. Effect of early postoperative feeding on the healing of colonic anastomoses in the presence of intra-abdominal sepsis in rats. Dis Colon Rectum 2000;43(Suppl):S54-S58.
18. Woessner J. The determination of hydroxyproline in tissue and protein samples containing small proportions of this amino acid. Biochem Biophys 1961;93:440-446.
19. Kiyama T, Witte M, Thornton FJ, Barbul A. The route of nutrition support affects the early phase of wound healing. JPEN 1998;22:276-279.
20. Graham MF, Blomquist P, Zederfeldt B. The alimentary canal. In Cohen IK, Dieglemann RF, Lindblad WJ, eds. Wound Healing: Biochemical and Clinical Aspects. Philadelphia: WB Saunders, 1992, pp 433-449.
21. Ellison GW. Wound healing in the gastrointestinal tract. Semin Vet Med Surg (Small Anim) 1989;4:287-293.
22. Raghow R. The role of extracellular matrix in postinflammatory wound healing and fibrosis. FASEB J 1994;8:823-831.
23. Saarialho-Kere UK, Kovacs SO, Pentland AP, Olerud JE, Welgus HG. Cell-matrix interactions modulate interstitial collagenase expression by human keratinocytes actively involved in wound healing. J Clin Invest 1993;92:2858-2866.

Laparoscopy With Laparoscopic Ultrasound for Pretreatment Staging of Hepatocellular Carcinoma: A Prospective Study

Marco Montorsi, M.D., Roberto Santambrogio, M.D., Paolo Bianchi, M.D., Enrico Opocher, M.D., Gian Paolo Cornalba, M.D., Giovanni Dapri, M.D., Luigi Bonavina, M.D., Massimo Zuin, M.D., Mauro Podda, M.D.

Laparoscopy with laparoscopic ultrasound (L-LUS) has proved to be superior to conventional CT imaging in the staging of hepatocellular carcinoma (HCC). The aim of our prospective study was to evaluate the efficacy of L-LUS as compared with currently available imaging techniques (spiral CT or Lipiodol CT) in patients with HCC and liver cirrhosis. From January 1998 to May 2000, 70 consecutive patients (50 men and 20 women; mean age 67 ± 7 years) were enrolled. Liver cirrhosis was related to chronic hepatitis C virus infection in 55, hepatitis B virus infection in seven, and alcohol abuse in eight patients. Preoperative diagnostic workup included the following: 70 ultrasound examinations of the liver, 23 CT scans after Lipiodol arteriography, and 53 spiral CT scans. A single lesion was found in 39 patients, two lesions in 20 patients, and three lesions in 11 patients. L-LUS was performed in all patients under general anesthesia using a two- to three-trocar technique. The examination was completed in 68 patients (97%); in two cases extensive adhesions prevented the L-LUS examination. L-LUS yielded additional information in 39 patients (57%). New histologically proved HCC lesions were detected in 14 patients (in the same liver segment in 4 cases and in different liver segments in 10 cases), and an adrenal metastasis was seen in one patient. In 23 patients, benign nodules were identified as regenerative macronodules, low-grade dysplastic nodules, or small hemangiomas. In 10 patients, correct localization of the primary lesion was detected by L-LUS in comparison with the preoperative liver location. In our experience, L-LUS is a safe and reliable procedure. It provides superior information (intraoperative histologic confirmation) for the diagnosis and pretreatment staging of HCC in patients with cirrhosis when compared with current radiologic imaging techniques. (J GASTROINTEST SURG 2001;5:312-315.)

KEY WORDS: Hepatocellular carcinoma, liver cirrhosis, laparoscopic ultrasound, radiofrequency interstitial thermal ablation

Notwithstanding recent refinements in imaging techniques for patients with liver cirrhosis and hepatocellular carcinoma (HCC), preoperative diagnostic studies such as ultrasound examination, spiral CT, Lipiodol CT, and magnetic resonance imaging (MRI) still have some limitations in the assessment of the number and exact location of hepatic nodules.[1] The current standard for accurate staging of hepatic tumors prior to surgical resection involves laparotomy and intraoperative ultrasound examination of the liver.[2]

Laparoscopy with laparoscopic ultrasound (L-LUS) provides information similar to that obtained by means of intraoperative ultrasound[3] and can identify lesions that are undetectable by preoperative imaging techniques.[4] Furthermore, L-LUS also allows performance of ultrasound-guided biopsy[5] and interstitial therapies such as ethanol injection, cryoablation, or radiofrequency thermal ablation in the same session.[6-9] We report herein our experience with L-LUS in the preoperative assessment of patients with HCC

From the Istituto di Chirurgia Generale e Oncologia Chirurgica (M.M. and L.B.), Ospedale Maggiore, IRCCS; the Clinica Chirurgica (R.S., P.B., E.O., and G.D.); the Cattedra di Medicina Interna (M.Z. and M.P.); and the Unità di Radiologia Diagnostica Interventistica (G.P.C.), Ospedale San Paolo, University of Milan, Milan, Italy.
Supported in part by a grant from Unità di Ricerca FIRC "Prevenzione, diagnosi e terapia del carcinoma epatico."
Presented in part at the Forty-First Annual Meeting of The Society for Surgery of the Alimentary Tract, San Diego, Calif., May 21-24, 2000.
Reprint requests: Marco Montorsi, M.D., Ospedale San Paolo-Via A. di Rudinì, 8 20142 Milano, Italy. e-mail: marco.montorsi@unimi.it

and liver cirrhosis who were potential candidates for invasive treatment, resection, or interstitial therapies.

METHODS

Clinical Material

Patients with a single HCC nodule or multinodularity (up to three lesions with at least one nodule ≤50 mm) in liver cirrhosis who were candidates for surgical resection or interstitial therapy treatment were enrolled in the study. The exclusion criteria were tumor size greater than 5 cm, the presence of more than three nodules, a complete portal thrombosis, and/or coexisting severe liver disease (Child's C cirrhosis). Predetermined criteria for interstitial therapies were outlined in a previous work.[9]

Technical Notes

The ultrasound scanner used was an Aloka SSD 500 B-mode system (Aloka Co., Ltd., Tokyo, Japan). The laparoscopic ultrasound probe had a rigid shaft, 10 mm in diameter and 50 cm in length. A 7.5 MHz linear-array transducer was side mounted near the tip of the shaft. The length of the transducer surface was 38 mm, which produced an image approximately 4 cm in length and 6 cm in depth. The probe and the cable were sterilized by immersion in 2% glutaraldehyde solution. All examinations were performed by a surgeon trained in ultrasound techniques.[10]

The development of laparoscopic ultrasound scanning techniques of the liver was based on the standard intraoperative ultrasound examination performed during laparotomy.[11,12] With the patient under general anesthesia, after establishing a pneumoperitoneum by a percutaneous or open (Hasson) technique, a 10 mm trocar was inserted through an umbilical incision. An initial laparoscopic exploration of the peritoneal cavity was performed and a second 10 mm trocar was inserted at the right hypochondrium or flank between the anterior and midaxillary line. In this regard, a preoperative evaluation of the inferior limit of the liver is of great importance to avoid placing the port site too near the scanning area, thereby preventing adequate contact between the transducer and the liver surface. Once the laparoscopic ultrasound examination of the liver was completed, a third optional 10 mm trocar was selected based on the number of lesions to be treated and their location. These access sites allowed complete visualization of the entire organ. Biopsy of suspected malignant liver nodules was routinely performed through alternate trocar sites using an automatic disposable 18-gauge biopsy needle (Temno, Bauer Medical International SA, Santo Domingo). Prior to L-LUS examination, all patients were subjected to standard external liver ultrasonography and spiral CT or post-Lipiodol CT. Post-treatment follow-up included ultrasound examination of the liver every 3 months and a spiral CT every 6 months.

RESULTS

Between February 1996 and May 2000, 70 patients with HCC and liver cirrhosis were enrolled in the study. There were 50 men and 20 women, whose mean age was 67 ± 7 years (range 51 to 79 years). Fifty-five patients had cirrhosis due to hepatitis C, seven had cirrhosis due to hepatitis B, and the remaining eight had alcoholic cirrhosis. Forty-seven patients were Child-Pugh class A and 23 were class B. Before treatment, all patients underwent an ultrasound examination of the liver and either Lipiodol CT (23 patients) or dual-phase spiral CT allowing the hepatic arterial phase and portal venous phase of hepatic enhancement to be imaged separately (53 patients); in six patients both Lipiodol CT and spiral CT were performed.

Thirty-nine patients had a solitary lesion, 20 patients had two lesions, and 11 patients had three lesions. The mean diameter of the tumors, measured by preoperative ultrasound, was 30 ± 12 mm (range 13 to 50 mm).

In all 70 patients, a complete laparoscopic ultrasound examination was attempted. In two patients (3%) the presence of extensive adhesions prevented intraoperative scanning of the liver. Therefore 68 of 70 patients had a complete laparoscopic study and were suitable for the final evaluation (97% feasibility rate). In another 10 patients multiple adhesions required surgical dissection to allow an effective laparoscopic ultrasound evaluation (14%). In 14 patients L-LUS and ultrasound-guided biopsy took 38 ± 5 minutes to perform, whereas in the remaining 54 patients L-LUS with some additional therapeutic measures (ethanol injection, radiofrequency, or laparoscopic liver resection) took 67 ± 26 minutes.

Histologically, 63 of the 68 primary liver tumors were shown to be HCC, whereas two cases were peripheral cholangiocarcinoma and three were high-grade dysplastic nodules; therefore L-LUS and ultrasound-guided biopsy changed the presumptive preoperative diagnosis of HCC and liver cirrhosis in five patients (7%).

L-LUS provided additional information in 39 patients (57%) (more than one additional item of information in each patient); new HCC nodules were detected in 14 patients (in the same liver segment in 4 cases and in different liver segments in 10 cases). An adrenal metastasis was seen in one patient. All of these

Table I. Correlation between L-LUS detection of new malignant hepatic nodules and number or diameter of primary lesions identified on preoperative imaging

	New malignant nodules (L-LUS)	
	Absent	Present
No. of primary lesions*		
One lesion (39 cases)	34	5 (13%)
Two or more lesions (29 cases)	20	9 (31%)
Diameter (mm) of primary lesions†	28 ± 12	37 ± 15

L-LUS = laparoscopy with laparoscopic ultrasound.
*$P = 0.0124$.
†$P = 0.0398$.

Table II. Surgical procedures performed following L-LUS examination

Procedure	No. of patients
Laparoscopic ultrasound–guided biopsy	6
Hepatic resection	8*
Laparoscopic hepatic resection plus radiofrequency	2
Laparoscopic "one-shot" ethanol injection	8
Laparoscopic radiofrequency	42†
Laparoscopic radiofrequency plus ethanol injection	4

*Laparoscopic surgical resection in one patient.
†In two patients, a percutaneous radiofrequency procedure was performed for extensive adhesions.

nodules were histologically proved. Thus L-LUS identified new malignant lesions in 22% of cases. These new hepatic nodules had a mean diameter of 14 ± 8 mm; a statistically significant correlation between these new nodules and the number and the diameter of the primary lesions was found (Table I). Moreover, in 23 patients, some additional benign nodules were identified as regenerative macronodules, low-grade dysplastic nodules, or small hemangiomas. On the basis of L-LUS findings, the patients underwent a subsequent therapeutic procedure as described in Table II.

DISCUSSION

Multiplicity of neoplastic lesions and a high recurrence rate are major problems complicating the curative treatment of patients with HCC and liver cirrhosis. The prognosis of HCC might be improved by increasing the detection rate and selecting the appropriate treatment for multiple lesions. Although surgical resection is still considered the treatment of choice for small HCC lesions occurring in patients with liver cirrhosis and good hepatic function,[13] it showed a high rate of recurrence.[14] This accounts for the increased use of both alternative ablative therapies[15] and L-LUS, which allowed a thorough evaluation of the liver and abdominal cavity with additional information for complete neoplastic staging prior to the definitive treatment.

In the present study 15 (22%) of 68 patients evaluated by L-LUS revealed new malignant hepatic lesions. Prelaparoscopic diagnostic workup with extracorporeal ultrasound and Lipiodol or spiral CT was considered the best procedure available. In any case, small satellite nodules were found that had gone undetected with both of these imaging techniques. Of the 68 patients evaluated by L-LUS, 39 were considered to have a solitary HCC before L-LUS, but in five of these patients (13%) new malignant nodules were identified. However, only one (6%) of 16 patients in whom the main tumor was considered to be solitary and 2 cm or less in diameter had multicentric HCC. Most of these new nodules were very small (no larger than 1 cm in diameter) with a mean diameter of 14 ± 8 mm. In our experience, L-LUS modified the original planned procedures in 12 of these 15 patients; five patients were subjected to laparoscopic exploration only, four patients required additional thermoablation, and three patients had an ethanol injection for distant satellite nodules. In the remaining three patients, the new malignant lesion was close to the primary nodule and was therefore treated with the planned segmental hepatic resection.

In the cirrhotic liver, various types of hepatocytic nodular lesions including regenerative nodules or

hemangiomas could be detected.[16,17] Nonetheless, it is difficult to judge whether a nodular lesion with a diameter of approximately 10 mm is HCC based on the ultrasonographic image alone. Histologic diagnosis of new nodules was reported by means of resection, enucleation, or thick-needle biopsy.[2]

Because small HCC lesions are generally histologically well differentiated and sometimes very difficult to diagnose in small specimens, we preferred to not use fine-needle biopsy. New, very small hyperechoic nodules were not biopsied, particularly if they were located in liver segments that are difficult to reach; the nodules with this ultrasound pattern had a very low risk of being cancerous.[2-5] These patients were subjected to a strict follow-up program with ultrasound and spiral CT.

Although all forms of ultrasonography are operator dependent and present a significant "learning curve," we believe that most hepatobiliary surgeons, particularly those with experience in extracorporeal and intraoperative ultrasound imaging, can expect to embrace this method with a minimum of additional training.[12,18] When compared with intraoperative ultrasound at laparotomy, some limitations of the laparoscopic technique still exist. The angle and the direction of ultrasound scanning under laparoscopy are limited by the position of the laparoscopic ports. Thus some difficulties can be encountered during examination of the superior and posterior segments (IVA, VII, and VIII): this problem can be dealt with by filling the upper abdomen with sterile saline solution to create an acoustic window and/or by using a flexible probe. Learning the technique for laparoscopic ultrasound–guided interventional procedures could be somewhat more difficult laparoscopically, but readily attainable after exposure to several cases.[5] The technique of LUS alone failed to differentiate benign from malignant nodules and required a laparoscopic ultrasound–guided biopsy in most cases.

In conclusion, L-LUS provides all the features that are lacking with the current preoperative imaging techniques—that is, greater accuracy and better definition of the location of the lesions relative to the liver anatomy. In our experience, it has greatly contributed to the accurate staging of HCC in liver cirrhosis and has aided in intraoperative decision making. Furthermore, in the same session it was possible to perform different therapeutic procedures such as ethanol injection or radiofrequency and segmental liver resection.[19] We suggest using this procedure in all patients who are candidates for a laparotomy and liver resection or in those candidates for thermal ablation in whom the percutaneous approach is deemed very difficult or dangerous.

REFERENCES

1. Solbiati L, Cova L, Ierace T, Marelli P, Dellanoce M. Liver cancer imaging: The need for accurate detection of intrahepatic disease spread. J Comput Assist Tomogr 1999;23:S29-S37.
2. Kokudo N, Bandai Y, Imanishi H, et al. Management of new hepatic nodules detected by intraoperative ultrasonography during hepatic resection for hepatocellular carcinoma. Surgery 1996;119:634-640.
3. Tandan VR, Asch M, Margolis M, Page A, Gallinger S. Laparoscopic vs. open intraoperative ultrasound examination of the liver: A controlled study. J GASTROINTEST SURG 1997;1:146-151.
4. John TG, Greig JD, Crosbie JL, Miles WFA, Garden OJ. Superior staging of liver tumors with laparoscopy and laparoscopic ultrasound. Ann Surg 1994;220:711-719.
5. Ido K, Nakazawa Y, Isoda N, et al. The role of laparoscopic US and laparoscopic US-guided aspiration biopsy in the diagnosis of multicentric hepatocellular carcinoma. Gastrointest Endosc 1999;50:523-526.
6. Cuschieri A, Bracken J, Boni L. Initial experience with laparoscopic ultrasound-guided radiofrequency thermal ablation of hepatic tumours. Endoscopy 1999;31:318-321.
7. Ido K, Isoda N, Kawamoto C, et al. Laparoscopic microwave coagulation therapy for solitary hepatocellular carcinoma performed under laparoscopic ultrasonography. Gastrointest Endosc 1997;45:415-420.
8. Lezoche E, Paganini AM, Feliciotti F, et al. Ultrasound-guided laparoscopic cryoablation of hepatic tumors: Preliminary report. World J Surg 1998;22:829-836.
9. Montorsi M, Santambrogio R, Bianchi P, et al. Radiofrequency interstitial thermal ablation (RITA) of hepatocellular carcinoma (HCC) in liver cirrhosis: Role of the laparoscopic approach. Surg Endosc (in press).
10. Santambrogio R, Montorsi M, Bianchi P, et al. Common bile duct exploration and laparoscopic cholecystectomy: Role of intraoperative ultrasonography. J Am Coll Surg 1997;185:40-48.
11. Machi J. Intraoperative and laparoscopic ultrasound. Surg Oncol Clin North Am 1999;8:205-226.
12. Machi J, Schwartz JH, Zaren HA, Noritomi T, Sigel B. Technique of laparoscopic ultrasound examination of the liver and pancreas. Surg Endosc 1996;10:684-689.
13. Philosophe B, Greig PD, Hemming AW, et al. Surgical management of hepatocellular carcinoma: Resection or transplantation? J GASTROINTEST SURG 1998;2:21-27.
14. Sarasin FP, Giostra E, Mentha G, Hadengue A. Partial hepatectomy or orthotopic liver transplantation for the treatment of resectable hepatocellular carcinoma? A cost-effectiveness perspective. Hepatology 1998;28:436-442.
15. Lencioni R, Bartolozzi C. Nonsurgical treatment of hepatocellular carcinoma. Cancer J 1997;10:17-23.
16. Borzio M, Borzio F, Croce AM, et al. Ultrasonography-detected macroregenerative nodules in cirrhosis: A prospective study. Gastroenterology 1997;112:1617-1623.
17. Hytiroglou P, Theise ND. Differential diagnosis of hepatocellular nodular lesions. Semin Diagn Pathol 1998;15:285-299.
18. Lo CM, Lai ECS, Liu CL, Fan ST, Wong J. Laparoscopy and laparoscopic ultrasonography avoid exploratory laparotomy in patients with hepatocellular carcinoma. Ann Surg 1998;4:527-532.
19. Siperstein A, Garland A, Engle K, et al. Laparoscopic radiofrequency ablation of primary and metastatic liver tumors. Technical considerations. Surg Endosc 2000;14:400-405.

The Hippurate Ratio as an Indicator of Functional Hepatic Reserve for Resection of Hepatocellular Carcinoma in Cirrhotic Patients

Alan W. Hemming, M.D., M.Sc., Steven Gallinger, M.D., M.Sc., Paul D. Greig, M.D., Mark S. Cattral, M.D., M.Sc., Bernard Langer, M.D., Bryce R. Taylor, M.D., Zulfikarali Verjee, B.Sc., Ph.D., Esther Giesbrecht, M.Sc., Yoshiko Nakamachi, R.N., Katryn N. Furuya, M.D.

Predicting the ability of the cirrhotic liver to withstand resection remains a challenge for the surgeon. This study evaluates the use of the hippurate ratio, a novel assessment of glycine conjugation of paraaminobenzoic acid by the liver, as a preoperative indicator of functional hepatic reserve. Between 1998 and 2000, sixty-one cirrhotic patients were prospectively assessed for hepatic resection using the hippurate ratio, indocyanine green retention at 15 minutes (ICG R-15), and other standard measures of liver function. Twenty-six patients were excluded as candidates for resection on the basis of inadequate functional hepatic reserve. Patients excluded from resection had significantly higher ICG R-15 values (29% ± 9% vs. 16% ± 12%, $P = 0.001$), higher Child-Pugh scores (5.9 ± 0.9 vs. 5.3 ± 0.4, $P = 0.01$), and lower hippurate ratios (30% ± 14% vs. 45% ± 15%, $P = 0.005$). There was a significant correlation between the hippurate ratio and ICG R-15. Other indicators of liver function such as factor V, factor VII, albumin, bilirubin, prothrombin time, and transaminases were no different between patients who did and those who did not undergo resection. Of the 35 patients resected, there were seven (20%) who developed varying degrees of liver failure with three perioperative deaths (8.5%). Patients who had some degree of liver failure had significantly lower hippurate ratios than patients who had no liver failure (29% ± 10% vs. 48% ± 14%, $P = 0.002$). There was no difference in ICG R-15 values between patients who had liver failure and those who did not. The hippurate ratio offers information on hepatocellular reserve that is not provided by other measures of liver function and may allow better selection of cirrhotic patients for liver resection. (J GASTROINTEST SURG 2001;5:316-321.)

KEY WORDS: Liver function, cirrhosis, liver resection, hepatocellular carcinoma, indocyanine green, paraminobenzoic acid

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and is responsible for more than one million deaths annually.[1] Without treatment the prognosis is dismal.[2] Partial hepatic resection is generally accepted as the treatment of choice for HCC if resection is possible, with transplantation reserved for a specific subset of patients with both poor liver function and limited disease.[3] Unfortunately, most cases of HCC are first seen at a size or stage that is too advanced to allow transplantation, while at the same time the presence of cirrhosis and decreased hepatocellular function makes hepatic resection a higher risk endeavor in cirrhotic than in noncirrhotic patients. Current operative mortality for hepatic resection in noncirrhotic patients is reported to range from 0% to 3%,[4,5-7] whereas operative mortality even in well-selected cirrhotic patients is 10% to 15%.[8-11] The ability of the surgeon to ac-

From the Department of Surgery (A.W.H.), University of Florida, Gainesville, Fla.; and the Department of Surgery (S.G., P.D.G., M.S.C., B.L., and B.R.T.), University of Toronto, and the Divisions of Pediatric Laboratory Medicine (Z.V. and E.G.), Gastroenterology, and Nutrition (Y.N. and K.N.F.), The Hospital for Sick Children, and the Department of Pediatrics and Pharmacology (K.N.F.), University of Toronto, Toronto, Ontario, Canada.

Supported by a grant from the Physician's Services Incorporated Foundation, Ontario, Canada.
Presented at the Forty-First Annual Meeting of The Society for Surgery of the Alimentary Tract, San Diego, Calif., May 21-24, 2000.
Reprint requests: Alan W. Hemming, M.D., University of Florida, Center for Hepatobiliary Disease, P.O. Box 100286, Gainesville, FL 32610. e-mail: hemmiaw@mail.surgery.ufl.edu

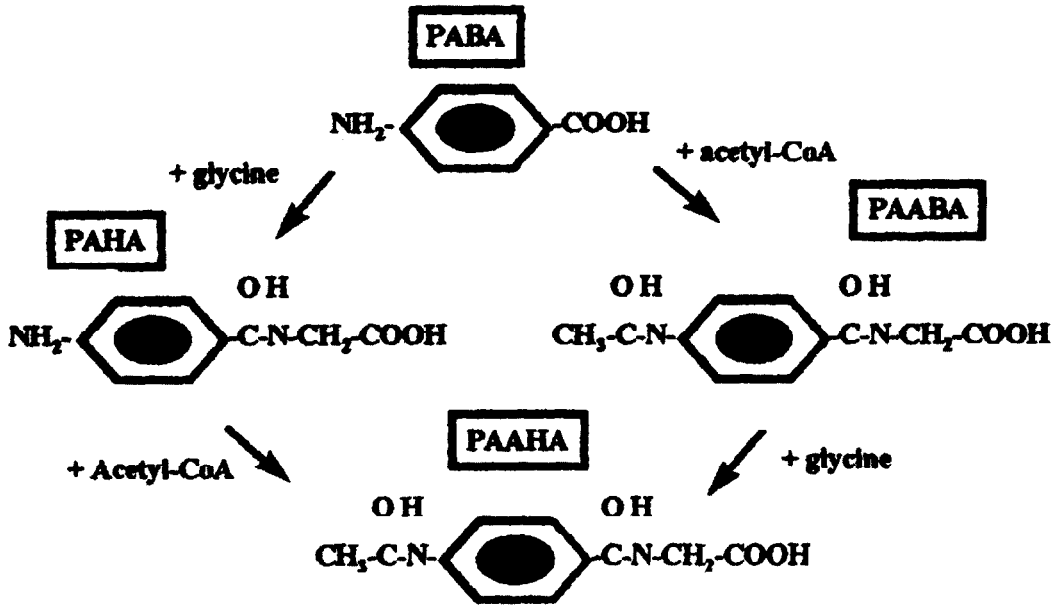

Fig. 1. Hepatic metabolism of para-aminobenzoic acid (PABA). PAHA = para-aminohippuric acid; PAABA = para-acetamidobenzoic acid; PAAHA = para-acetamidohippuric acid.

curately estimate hepatocellular reserve prior to liver resection in the cirrhotic patient has been notoriously unreliable. A variety of methods have been developed to estimate preoperative liver function in the cirrhotic patient with perhaps the most experience with indocyanine green (ICG) clearance.[11-13] ICG clearance is a relatively time-consuming, expensive, and labor-intensive test, however, and has not been widely adopted in Western centers. A widely available, economical, less labor-intensive test of liver reserve would be a useful addition to the preoperative assessment of patients with HCC and cirrhosis who are being considered for resection.

Para-aminobenzoic acid (PABA) is readily absorbed from the gastrointestinal tract and is extensively metabolized in the liver by phase II conjugation reactions independent of the cytochrome p450 system[14,15] to form three major metabolites. PABA is either glycine conjugated to form para-aminohippuric acid (PAHA) or undergoes acetylation to form para-acetamidobenzoic acid (PAABA). Para-acetamidohippuric acid (PAAHA) is then formed through acetylation of PAHA or through glycine conjugation of PAABA (Fig. 1). This study assesses glycine conjugation of PABA by the liver as a novel assessment of liver function in patients with HCC who are being considered for hepatic resection.

PATIENTS AND METHODS

All patients with HCC who were referred for resection over a 24-month period from 1998 to 2000 were assessed prospectively. All patients initially underwent surgical assessment and were considered candidates for resection based on review of imaging studies, clinical evaluation, and baseline liver function tests that included aspartate aminotransferase, alanine aminotransferase, prothrombin time, albumin, bilirubin, and alkaline phosphatase. Patients who were not thought to be surgical candidates based on initial evaluation did not undergo further liver function assessment and are not addressed in this study. Sixty-one patients considered possible candidates for resection were then assessed with additional tests of liver function that included factor V and VII levels, indocyanine green retention at 15 minutes (ICG R-15), and determination of the hippurate ratio after oral administration of PABA. Patients ranged from 26 to 79 years of age (mean 53 years). Male-to-female ratio was 2:1. Underlying liver disease was hepatitis B in 45% of patients, hepatitis C in 40% of patients, and alcohol related in 15%. Patients who had ICG R-15 values above 30% or tumors that would require extensive resection which ICG R-15 values indicated would exceed functional hepatic reserve[16] were not offered resection.

Indocyanine Green Clearance

A baseline venous blood sample was drawn followed by intravenous bolus administration of ICG, 0.5 mg/kg. Blood samples were then drawn at 2, 5, 10, 15, 20, 30, and 45 minutes. Blood samples were centrifuged and the serum was analyzed using a spec-

trophotometer at a wavelength of 805λ, and the optical density (OD) was recorded. The baseline serum sample was used for calibration. The logs of outside densities were then plotted against time. ICG R-15 was extrapolated from the obtained curve as $OD_{15min}/OD_{0min} \times 100\%$.

Hippurate Ratio

After a 4-hour fast, a baseline venous blood sample was drawn. A second sample was drawn 30 minutes after oral administration of PABA at a dosage of 5.0 mg/kg to a maximum dose of 170 mg. Samples were analyzed using a modification of the high-pressure liquid chromatographic (HPLC) method of Yung-Jato et al.[17] After solid-phase extraction, patient samples (50 μl) were injected onto an HPLC Supelco LC-18 column (Sigma-Aldrich, St. Louis, Mo.) with a mobile phase of acetonitril:methanol:50 mmol/L phosphate buffer, pH 3.15 (2:8:90 by volume). A flow rate of 1.2 ml/min was used to achieve complete separation with ultraviolet spectrophotometric detection at 290λ. Quantification was performed by comparing peak height ratios of PABA and its metabolites to internal standards. PABA and its metabolites were expressed as molar concentrations and the hippurate ratio was derived from the formula:

$$\text{Hippurate ratio} = \frac{\text{PAHA(M)} + \text{PAAHA(M)}}{\text{PAHA(M)} + \text{PAAHA(M)} + \text{PABA(M)} + \text{PAABA(M)}} \times 100\%$$

Patients underwent liver resection using standard liver resection techniques.[3] Perioperative blood transfusion (intraoperative plus blood transfused in the first 24 hours post resection), fresh-frozen plasma requirements, and complications were recorded. Liver failure was defined as the development of encephalopathy, ascites requiring sustained diuretics or paracentesis to control, or coagulopathy unresponsive to vitamin K that required fresh-frozen plasma administration for an international normalization ratio (INR) of more than 2.0 after the first 24 hours post resection.

Statistical analysis was performed using SPSS 9.0 software (SPSS Inc., Chicago, Ill.). Parametric statistical analysis included Pearson's r and student's t tests. Nonparametric analysis included chi-square or Fisher's exact test when appropriate. Alpha was specified as $P < 0.05$. Results are reported as mean ± 1 standard deviation when not otherwise specified.

RESULTS

After assessment, there were 26 patients who had ICG R-15 values above 30% or tumors that would require a degree of resection which ICG R-15 values indicated would exceed functional hepatic reserve. Thirty-five patients eventually underwent hepatic resection. Resections performed are shown in Table I. Mean operating time was 4 ± 1.5 hours with a median perioperative blood transfusion of 1 unit of packed red cells (range 0 to 20 units). Patients who were not offered resection on the basis of inadequate hepatocellular reserve had significantly higher ICG R-15 values (29% ± 9% vs. 16% ± 12%, $P = 0.001$), higher Child-Pugh scores (5.9 ± 0.9 vs. 5.3 ± 0.4, $P = 0.01$), and lower hippurate ratios (30% ± 20% vs. 45% ± 15%, $P = 0.005$). There was a significant correlation ($P = 0.01$) between the hippurate ratio and ICG R-15 (Fig. 2). Other indicators of liver function such as factor V, factor VII, albumin, bilirubin, prothrombin time, and transaminases were no different between patients who did and did not undergo resection.

Table I. Types of liver resections performed

Resection	Number
Right lobe	6
Left lobe	4
Right trisegmentectomy	3
Left trisegmentectomy plus inferior vena cava resection	1
Left lateral segmentectomy	4
Left lateral segment + segment 6	1
Segments 7 + 8	1
Segments 7 + 8 with right hepatic vein graft	1
Segments 5 + 6	4
Segments 6 + 7	1
Segments 4b + 5	1
Segment 8	1
Segment 6	2
Segment 5	1
Segment 4	4
TOTAL	35

There were three postoperative deaths from complications of liver failure for an operative mortality rate of 8.5%. An additional four patients had evidence of liver failure for an overall liver failure rate of 20% (Table II).

Patients who had liver failure had significantly lower hippurate ratios than patients who did not have liver failure (29% ± 10% vs. 48% ± 14%, $P = 0.002$). There was no significant difference in ICG R-15 values between patients who developed liver failure and those who did not (21% ± 8% vs. 15% ± 8%, $P = 0.08$). Preoperative prothrombin time, bilirubin, transaminases, albumin, factor V, factor VII, and Child-Pugh score were not predictive of postoperative liver failure. Perioperative blood transfusion requirements were not predictive of the development of

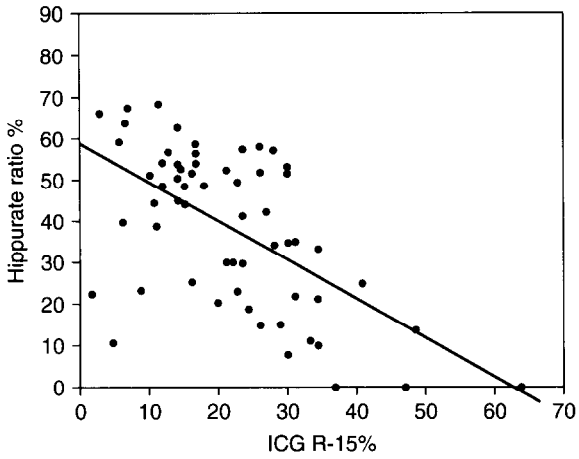

Fig. 2. The hippurate ratio showed a significant correlation with ICG R-15 ($P = 0.01$).

Table II. Liver failure in cirrhotic patients undergoing hepatic resection

Patient	Complication
1	Liver failure/sepsis/death on postoperative day 8
2	Liver failure/bleeding/sepsis/death on postoperative day 12
3	Liver failure/encephalopathy/death on postoperative day 27
4	Encephalopathy, persistent ascites, prolonged coagulopathy
5	Persistent ascites, prolonged coagulopathy
6	Persistent ascites
7	Persistent ascites

liver failure overall but were significantly higher in the patients who eventually died of liver failure than in the patients who survived their operations (9 ± 9 units vs. 1 ± 1 unit, $P = 0.01$).

DISCUSSION

Liver resection in cirrhotic patients has a higher operative mortality than in noncirrhotic patients, primarily because of the increased risk of liver failure when operating in the setting of impaired liver function. The Child-Pugh classification system has been demonstrated to correlate with a higher risk of operative mortality[18,19] with Child's A patients being at lowest risk for liver failure; however, in general only Child's A or early Child's B patients are offered resection. Standard liver function tests have not been useful in selecting patients for resection within the group of patients with Child's A cirrhosis, with the exception of elevated transaminase levels indicating active hepatitis, which is associated with poor outcome after liver resection.[20] Operative mortality for hepatic resection even in well-selected cirrhotic patients is approximately five times as high as in noncirrhotic patients.[7,8,10,21,22] The availability of a test of hepatocellular reserve that could identify patients who would not tolerate hepatic resection would obviously be helpful to the surgeon. Although there have been many attempts to identify such a test, including MEGX[23] (a lidocaine metabolite), galactose clearance,[24] the redox tolerance index,[25] and cytochrome C oxidase activity,[26] no single test has gained widespread acceptance. The most widely used test to date has been ICG clearance, which according to most reports provides useful information for selecting patients who will tolerate resection.[12,13,27] ICG clearance has not been widely adopted in the West, however, largely because it is a test that is expensive, labor-intensive, and time consuming to perform. The hippurate ratio, which measures glycine conjugation of PABA by the liver, is relatively simple to perform and may offer some advantages over ICG clearance. Glycine conjugation is dependent on hepatocyte mitochondrial function, and decreased glycine conjugation has experimentally been shown to be related to a decrease in hepatocyte mitochondrial adenosine triphosphate.[28,29] The hippurate ratio has not been assessed previously in the setting of hepatic resection but has been shown to correlate with liver function both in chronic liver disease and in the setting of fulminant hepatic failure.[30] In the present study the hippurate ratio clearly correlated with ICG clearance and showed a decrease in glycine conjugation in patients selected as having inadequate hepatocellular reserve for resection by ICG-R15. Additionally, patients who underwent liver resection with adequate hepatic reserve as indicated by ICG R-15 but who subsequently developed liver failure had significantly lower hippurate ratios than patients who did not have liver failure. There was no difference in ICG R-15 values between patients who developed liver failure and those who did not, which suggests that the hippurate ratio may be a more discriminating test of hepatocellular reserve than is ICG R-15. However, the sample size of the study was relatively small, which does not allow us to draw a definitive conclusion regarding the superiority of one test over the other. As has been reported in previous studies,[12] standard tests of liver function including transaminases, prothrombin time, bilirubin, albumin, as well as factor V and VII levels were not helpful in predicting postoperative liver failure. Blood transfusion requirements that were not predictive of overall liver failure, however, were significantly higher in patients who eventually died of complications of liver failure than in patients who had

a successful outcome. In this prospective study, the number of patients was not sufficient to determine whether poor liver function, as manifested by either high ICG R-15 values or a low hippurate ratio, and blood loss were independent factors that contributed to postoperative liver failure or whether poor liver function causes increased operative blood loss. However, in a retrospective study, Nonami et al.[31] reported that both poor liver function assessed by ICG R-15 and operative blood loss were independent predictors of death after hepatic resection in the cirrhotic patient stressing the importance of meticulous technique and methods of minimizing blood loss during hepatic resection.

This is the first study to evaluate the use of the hippurate ratio, a measure of glycine conjugation by the liver, to assess hepatic functional reserve in the setting of hepatic resection in the cirrhotic patient. The hippurate ratio may offer better discrimination of the ability of the liver to withstand hepatic resection than the current standard, ICG clearance. The use of the hippurate ratio to select specific patients for resection will require further assessment with a larger number of patients before a definitive conclusion of its utility can be reached; however, initial evaluation appears promising.

REFERENCES

1. Loetze MFJ, Carr B. Hepatobiliary neoplasms. In Devita VT, ed. Cancer: Principles and Practice of Oncology. Philadelphia: JB Lippincott, 1993, pp 883-914.
2. Barbara L, Benzi G, Gaiani S, Fusconi F, Zironi G, Siringo S, Rigamonti A, Barbara C, Grigioni W, Mazziotti A, et al. Natural history of small untreated hepatocellular carcinoma in cirrhosis: A multivariate analysis of prognostic factors of tumor growth rate and patient survival. Hepatology 1992;16:132-137.
3. Hemming AW, Greig PD, Langer B. Current surgical management of primary hepatocellular carcinoma. Adv Surg 1999;32:169-192.
4. Bradley AL, Chapman WC, Wright JK, Marsh JW, Geevarghese S, Blair KT, Pinson CW. Surgical experience with hepatic colorectal metastasis. Am Surg 1999;65:560-566; discussion 566-567.
5. Elias D, Cavalcanti de Albuquerque A, Eggenspieler P, Plaud B, Ducreux M, Spielmann M, Theodore C, Bonvalot S, Lasser P. Resection of liver metastases from a noncolorectal primary: Indications and results based on 147 monocentric patients. J Am Coll Surg 1998;187:487-493.
6. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. Ann Surg 1999;230:309-318; discussion 318-321.
7. Hemming AW, Sielaff TD, Gallinger S, Cattral MS, Taylor BR, Greig PD, Langer B. Hepatic resection of noncolorectal nonneuroendocrine metastases. Liver Transpl 2000;6:97-101.
8. Philosophe B, Greig PD, Hemming AW, Cattral MS, Wanless I, Rasul I, Baxter N, Taylor BR, Langer B. Surgical management of hepatocellular carcinoma: Resection or transplantation? J GASTROINTEST SURG 1998;2:21-27.
9. Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. Ann Surg 1993;218:145-151.
10. Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. Ann Surg 1999;229:790-799; discussion 799-800.
11. Lau H, Fan ST, Ng IO, Wong J. Long term prognosis after hepatectomy for hepatocellular carcinoma: A survival analysis of 204 consecutive patients. Cancer 1998;83:2302-2311.
12. Hemming AW, Scudamore CH, Shackleton CR, Pudek M, Erb SR. Indocyanine green clearance as a predictor of successful hepatic resection in cirrhotic patients. Am J Surg 1992;163:515-518.
13. Shimada M, Takenaka K, Fujiwara Y, Gion T, Shirabe K, Yanaga K, Sugimachi K. Risk factors linked to postoperative morbidity in patients with hepatocellular carcinoma. Br J Surg 1998;85:195-198.
14. Koren G, Weizman Z, Forstner G, MacLeod SM, Durie PR. Altered PABA pharmacokinetics in cystic fibrosis. Implications for bentiromide test. Dig Dis Sci 1985;30:928-932.
15. Laufer D, Cleghorn G, Forstner G, Ellis L, Koren G, Durie P. The bentiromide test using plasma p-aminobenzoic acid for diagnosing pancreatic insufficiency in young children. The effect of two different doses and a liquid meal. Gastroenterology 1991;101:207-213.
16. Kubota K. Ultrasonography: Intraoperative. In Livraghi T, Buscarini L, eds. Diagnosis and Treatment of Hepatocellular Carcinoma. London: Greenwich Medical Media, 1997, p 114.
17. Yung-Jato LL, Durie PR, Soldin SJ. Liquid-chromatographic measurement of p-aminobenzoic acid and its metabolites in serum. Clin Chem 1988;34:2235-2238.
18. Nagasue N, Kohno H, Tachibana M, Yamanoi A, Ohmori H, El-Assal ON. Prognostic factors after hepatic resection for hepatocellular carcinoma associated with Child-Turcotte class B and C cirrhosis. Ann Surg 1999;229:84-90.
19. Paquet KJ, Gad HA, Lazar A, Koussouris P, Mercado MA, Heine WD, Jachman-Jahn V, Ruppert W. Analysis of factors affecting outcome after hepatectomy of patients with liver cirrhosis and small hepatocellular carcinoma. Eur J Surg 1998;164:513-519.
20. Kubo S, Nishiguchi S, Shuto T, Tanaka H, Tsukamoto T, Hirohashi K, Ikebe T, Wakasa K, Kuroki T, Kinoshita H. Effects of continuous hepatitis with persistent hepatitis C viremia on outcome after resection of hepatocellular carcinoma. Jpn J Cancer Res 1999;90:162-170.
21. Fong Y, Salo J. Surgical therapy of hepatic colorectal metastasis. Semin Oncol 1999;26:514-523.
22. Bismuth H, Chiche L. Comparison of hepatic resection and transplantation in the treatment of liver cancer. Semin Surg Oncol 1993;9:341-345.
23. Ercolani G, Grazi GL, Calliva R, Pierangeli F, Cescon M, Cavallari A, Mazziotti A. The lidocaine (MEGX) test as an index of hepatic function: Its clinical usefulness in liver surgery. Surgery 2000;127:464-471.
24. Zoedler T, Ebener C, Becker H, Roeher HD. Evaluation of liver function tests to predict operative risk in liver surgery. HPB Surg 1995;9:13-18.
25. Mori K, Ozawa K, Yamamoto Y, Maki A, Shimahara Y, Kobayashi N, Yamaoka Y, Kumada K. Response of hepatic mitochondrial redox state to oral glucose load. Redox tolerance test as a new predictor of surgical risk in hepatectomy. Ann Surg 1990;211:438-446.
26. Ueda J, Mori K, Sakai Y, Tanaka A, Katayama T, Maki A, Shimahara Y, Yamaoka Y, Ozawa K. Noninvasive evaluation of cytochrome c oxidase activity of the liver. Its prognostic value for hepatic resection. Arch Surg 1994;129:303-308.

27. Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. Br J Surg 1997; 84:1255-1259.
28. Krahenbuhl L, Reichen J, Talos C, Krahenbuhl S. Benzoic acid metabolism reflects hepatic mitochondrial function in rats with long-term extrahepatic cholestasis. Hepatology 1997;25: 278-283.
29. Gregus Z, Fekete T, Halaszi E, Klaassen CD. Does hepatic ATP depletion impair glycine conjugation in vivo? Drug Metab Dispos 1996;24:1347-1354.
30. Furuya KN, Durie PR, Roberts EA, Soldin SJ, Verjee Z, Yung-Jato L, Giesbrecht E, Ellis L. Glycine conjugation of para-aminobenzoic acid (PABA): A quantitative test of liver function. Clin Biochem 1995;28:531-540.
31. Nonami T, Nakao A, Kurokawa T, Inagaki H, Matsushita Y, Sakamoto J, Takagi H. Blood loss and ICG clearance as best prognostic markers of post-hepatectomy liver failure. Hepatogastroenterology 1999;46:1669-1672.

BOUND VOLUMES

Bound volumes are available to subscribers only. The hardbound volume of six issues of the 2001 *Journal of Gastrointestinal Surgery* must be ordered by October 1, 2001, from Quality Medical Publishing, Inc., 11970 Borman Dr., Suite 222, St. Louis, MO 63146. Payment of $75 in U.S. funds must accompany all orders.

Bosentan, an Endothelin Antagonist, Augments Hepatic Graft Function by Reducing Graft Circulatory Impairment Following Ischemia/Reperfusion Injury

Rocco Ricciardi, M.D., Bradley K. Schaffer, M.D., Shimul A. Shah, M.D., Steven H. Quarfordt, M.D., Barbara F. Banner, M.D., Suzanne M. Wheeler, B.S., Susan E. Donohue, B.S., William C. Meyers, M.D., Ravi S. Chari, M.D.

Endothelin is a potent hepatic vasoconstrictor. We evaluated the role of an endothelin antagonist in hepatic ischemia/reperfusion injury. Bosentan, a novel endothelin receptor antagonist, was infused directly into the portal vein prior to cold ischemia and immediately on reperfusion, in five porcine livers. Five other pigs underwent routine liver harvest and reperfusion without bosentan treatment. Hepatic vascular resistance and liver tissue blood flow, as measured by thermistor flow probes, were determined following reperfusion. Hepatocellular damage was assessed through hepatic venous levels of sorbitol dehydrogenase and lactate dehydrogenase. Endothelial cell damage was determined in sections immunostained for factor VIII. Graft function was determined through oxygen consumption, bile production, and response to bile acid challenge. Organs treated with bosentan demonstrated lower vascular resistance and enhanced tissue blood flow ($P < 0.05$) as compared to untreated organs. Portal vein inflow to hepatic tissue was significantly enhanced (4.4-fold) in the bosentan-treated organs ($P < 0.05$). No difference was observed in hepatocellular damage. Pathology scores for factor VIII immunohistochemical staining were 2.3-fold higher in the bosentan-treated livers as compared to untreated livers ($P < 0.05$). The bosentan-treated livers also demonstrated enhanced oxygen consumption, increased bile production, and augmented biliary response to a bile acid challenge ($P < 0.05$). These results indicate that administration of bosentan before and after ischemia/reperfusion reduces hepatic circulatory disturbances, diminishes endothelial cell damage, and augments hepatic graft function. (J GASTROINTEST SURG 2001;5:322-329.)

KEY WORDS: Ischemia, liver, reperfusion, function, endothelin, blood flow

Ischemia/reperfusion injury (I/R) continues to pose a perplexing problem to all transplant specialists. During liver transplantation, I/R is known to negatively affect the function of the liver through alterations in energy production and usage, cellular integrity, signaling mechanisms, and hepatic tissue circulation. Data detailing the circulatory impairment that occurs following I/R demonstrate both a macrocirculatory and microcirculatory perfusion failure.[1,2] The microcirculatory failure following I/R is characterized by decreased sinusoidal perfusion and referred to as the "no-reflow" phenomenon.[1,3] On a larger scale, the macrocirculatory perfusion failure includes decreased hepatic tissue blood flow to peripheral tissues and reduced portal vein inflow to the hepatic parenchyma.[2] Given that liver function is intimately linked to hepatic blood flow,[4,5] much research has focused on reducing the postreperfusion circulatory impairment.

A number of vasoactive mediators have been implicated in the pathogenesis of hepatic postreperfusion circulatory failure, including nitric oxide, endothelins, and carbon monoxide. Recently, attention has focused mainly on the role of endothelins in propagating the described circulatory impairments. This attention is due to data demonstrating upregulation

From the Department of Surgery, University of Massachusetts Medical School, Worcester, Mass.
Presented at the Forty-First Annual Meeting of The Society for Surgery of the Alimentary Tract, San Diego, Calif., May 21-24, 2000.
Reprint requests: Ravi S. Chari, M.D., Department of Surgery, University of Massachusetts Medical School, 55 Lake Avenue, North, Worcester, MA 01655. e-mail: ChariR@ummhc.org

of the endothelin message within 6 hours of cold ischemia in the rat kidney.[6] Further studies revealed increased endothelin levels in hepatic venous blood on reperfusion[7,8] in small and large animal livers. A recent report further implicated endothelins in mediating the no-reflow phenomenon in rat hepatic sinusoids,[9] a process that was abrogated by hepatic nitric oxide production.

Collectively these observations implicate endothelins in hepatic circulatory failure following I/R; thus we undertook a study to evaluate the effect of endothelins on (1) macrocirculatory perfusion failure, (2) cellular damage, and (3) graft function. To perform these studies, an endothelin receptor antagonist, bosentan, was infused into the large animal liver *before* and *after* I/R. Administration of bosentan reduced hepatic circulatory disturbances, lessened endothelial cell damage, and augmented hepatic graft function. Clinically, administration of an endothelin antagonist may improve postreperfusion graft function.

METHODS

Animal Preparation

All procedures and protocols were approved by the University of Massachusetts animal review board, IACUC. Donor Yorkshire pigs weighing 35 to 40 kg were used for these experiments. Animals were sedated with a mixture (1.0 ml/kg) of telazol, ketamine, and xylazine. The concentrations of the components were as follows: telazol, 150 mg/ml (Ft. Dodge Animal Health, Ft. Dodge, Iowa); ketamine, 50 mg/ml (Ft. Dodge Animal Health); and xylazine, 10 mg/ml (Phoenix Pharmaceuticals Inc., St. Joseph, Mo.). Animals were endotracheally intubated and anesthesia was provided by inhalation isoflurane (1.5%). The femoral vein and artery were cannulated for intravenous infusions and continuous blood pressure monitoring, respectively.

Liver Preparation

Through a midline laparotomy, the cystic duct was ligated without removing the gallbladder, and a 14 Fr cannula (Sherwood Medical, St. Louis, Mo.) was inserted into the common bile duct. The hepatic artery and portal vein were isolated. The chest was opened through a median sternotomy and the suprahepatic vena cava was isolated. Following infusion of 20,000 units of intravenous heparin, a 21 Fr perfusion cannula (Medtronic Biomedicus, Eden Prairie, Minn.) was placed in the right external jugular vein and directed toward the suprahepatic vena cava. Next, 1000 ml of blood was drained into the perfusion circuit reservoir[10] at a rate of 300 ml/min. While the blood was being drained, the hepatic artery (8 Fr) and the portal vein (17 Fr) were cannulated. During drainage of blood, the systemic blood pressure was maintained above 80 mm Hg. The liver was perfused in situ with three liters of Euro-Collins solution (Fresenius USA, Ogden, Utah) (2 liters portal vein; 1 liter hepatic artery), then cooled to 4° C with iced saline solution. Euro-Collins solution was used instead of University of Wisconsin solution in order to reduce experimental costs and because of the nature of the injury that occurs during shorter periods of cold ischemia. It is estimated that the conditions produced by preserving an organ in Euro-Collins solution for 6 hours are similar to conditions following 24 hours' preservation in University of Wisconsin solution.[11] During Euro-Collins infusion, the inferior vena cava was vented in the chest. The infrahepatic vena cava was ligated and the liver was removed with all cannulas in place. A 32 Fr drainage cannula was placed in the suprahepatic vena cava during cold storage.

Graft Reperfusion

The liver was maintained at 4° C for 2 hours. After cold ischemia, Euro-Collins solution was washed from the graft using room temperature saline solution (1 liter portal vein; 1 liter hepatic artery). The graft was then connected to the perfusion circuit as previously described.[10] The circuit had a total blood volume of 1000 ml. A Plexus membrane oxygenator heat exchanger (Shiley Inc., Irvine, Calif.) warmed the blood to 37° C. The liver was perfused slowly through the portal vein and hepatic artery. Initial inferior vena cava outflow, approximately 300 ml, was discarded to prevent Euro-Collins contamination into the system. The portal vein flow reached 550 to 700 ml/min (0.50 to 0.75 ml/g liver/min) and the hepatic artery, perfused with additional nonpulsatile flow, reached 100 to 200 ml/min (0.16 to 0.2 ml/g liver/min).[10] Blood gas values (pH and partial pressures of oxygen and carbon dioxide) were monitored every 30 minutes both proximal and distal to the liver. Portal pressures remained below 15 mm Hg, whereas hepatic artery pressures remained below 150 mm Hg during reperfusion. The partial pressure of oxygen before blood entered the liver was maintained above 95 mm Hg.

Experimental Protocol

Bosentan (lot 704001) was obtained from F. Hoffmann-La Roche Ltd. (Basel, Switzerland). Fifty milligrams of bosentan was dissolved in saline solution (250 ml) and administered directly into the portal vein for 15 minutes prior to cold ischemia and again 15 minutes following early reperfusion in five pigs. The

bosentan dose was extrapolated from previous experimental data.[12-14] The dosing of bosentan (before harvest and after reperfusion) is based on previous data indicating the timing of endothelin production. Bosentan was administered prior to harvest (to antagonize endogenous endothelin production) and following reperfusion (to antagonize the known endothelin upregulation that occurs during cold ischemia). In five other pigs (250 ml), saline was administered without bosentan (untreated). No other differences in study protocol existed between the bosentan and the untreated group.

Determination of Hepatic Circulatory Impairment

To evaluate the effect of bosentan on hepatic circulatory impairment, hepatic vascular resistance and liver tissue blood flow were determined in all grafts. Hepatic vascular resistance was calculated by means of the following equation:

Portal vein pressure (mm Hg) − vena cava pressure (mm Hg)/portal blood flow (ml/min)

Portal venous pressure was determined with a 16-gauge 24-inch catheter inserted into the portal vein cannula that was directed toward the liver hilum during reperfusion. Inferior vena cava pressure was determined through a similar cannula inserted into the outflow tract of the liver. Both catheters were connected to standard pressure transducers and monitored every hour during reperfusion.

Liver tissue blood flow was determined with thermistor flow probes (Thermal Technologies Inc., Cambridge, Mass.) directly inserted into each of the four lobes of the porcine liver. Flows were recorded following 30 minutes of reperfusion, a time required for the organ to achieve thermal equilibrium. To determine the relative inflows from the hepatic artery versus the portal vein, one vessel was clamped and lobar tissue blood flow subsequently recorded. The vessel was then reperfused and blood flows were redetermined in the same lobe. These maneuvers allowed detection of the relative importance of the portal vein and hepatic artery to lobar tissue blood flow.

Determination of Hepatocellular Damage

Cellular function and damage were estimated through determinations of peak venous levels of lactate dehydrogenase (LDH) and sorbitol dehydrogenase activity (SDH), two indicators of hepatocellular damage.[15,16] Determinations of SDH are particularly useful markers of hepatocyte injury in the large animal liver.[17] LDH and SDH activities were measured in hepatic venous blood samples every 30 minutes following reperfusion. Spectrophotometric assay kits (Sigma, St. Louis, Mo.) were used in the analyses. Peak hepatic venous levels were calculated for each graft and standardized to total serum protein.

Determination of Endothelial Cell Damage

To evaluate endothelial cell damage, wedge biopsies were obtained at the end of reperfusion from both the left and right hepatic lobes. Biopsies were cleanly excised with a scalpel. Tissues were formalin fixed, paraffin embedded, and stained with hematoxylin and eosin. Additional sections cut at 4 microns were immunostained using anti–factor VIII antibody (Dako, Glostrup, Denmark) on an automated immunostainer (Bio-Tek, Burlington, Vermont).

Positive Control. Several biopsies from the normal in situ liver were also taken to ensure normal immunostaining of the in situ liver prior to experimentation.

Specimen Analysis. A pathologist (B.F.B.), blinded as to specimen treatment, evaluated all slides. The slide sections were scanned and evaluated for normal histology or changes of zonal ischemia, apoptotic bodies, micro- and macrovesicular steatosis, and sinusoidal dilatation. Positive staining of endothelium in the portal veins was noted as a built-in control. Because of the distinct lobular structure, central veins surrounded by interconnecting portal triads were easily seen. Five such lobules with a clear relationship of portal triad to central vein were selected and arbitrarily divided into zones 1, 2, and 3 (as defined by Rappaport) for evaluation of immunostaining. Immunostaining was called positive when a distinct dark brown color was present, corresponding to flat endothelial cells, along the sinusoidal walls. Positive sinusoidal staining was graded as follows: 0 = no staining; 1 = positive staining in less than half the sinusoids in the zone; 2 = positive staining in more than half the sinusoids. Scores for the five areas selected were averaged for each zone per slide and recorded.

Analysis of Graft Function

Graft function was determined through oxygen consumption, biliary production, and biliary production following bile acid stimulation.[10] To estimate graft oxygen consumption, arterial blood gases from the portal vein and vena cava were obtained every 30 minutes. A model 1640 blood gas analyzer (Instrumentation Laboratory, Lexington, Mass.) was used to

analyze the samples. Oxygen consumption was calculated using the standard equation:

(Portal vein O_2 saturation − vena cava O_2 saturation) × (1.34) × (hemoglobin) × (portal vein flow/min + hepatic artery flow/min) ÷ (liver weight [g])

Mean oxygen consumption was calculated starting at 30 minutes of reperfusion until the end of the experiment.

Baseline biliary flow data were monitored in the unstimulated state. After 2 hours of reperfusion, a time previously determined to be necessary for optimal reestablishment of normal bile secretory mechanisms,[10] hepatic grafts received biliary stimulation with taurocholate (Sigma) (5952 μmol/15 min). Taurocholate was infused into the portal vein of the graft for 15 minutes. Unstimulated and taurocholate-stimulated bile was collected every 15 minutes and measured in a graduated cylinder. Recorded values include maximal biliary production prior to taurocholate infusion and following the bile acid infusion.

Data Analysis

Statistical significance was determined by means of Student's *t* tests. A P value <0.05 was considered significant.

RESULTS

Evaluation of Hepatic Circulatory Impairment

Hepatic vascular resistance was calculated every hour during reperfusion. Hepatic vascular resistance for untreated organs was 0.021 ± 0.001 mm Hg min/ml. In the bosentan-treated group, vascular resistance was significantly lower, 0.015 ± 0.0004 mm Hg min/ml ($P<0.05$). Hepatic vascular resistance remained relatively constant from the beginning to the end of the reperfusion period.

Liver tissue blood flow was determined with thermistor flow probes following 30 minutes of reperfusion. In untreated organs, liver tissue blood flow was 25.0 ± 4.6 ml/100 g/min. This postreperfusion tissue blood flow is approximately one-half the preharvest blood flow values, although total organ blood flow are maintained constant.[2] The bosentan-treated organs demonstrated significantly higher liver tissue blood flow, 59.0 ± 5.7 ml/100 g/min, as compared to untreated organs ($P<0.05$) (Fig. 1).

Differences in vascular inflow were also noted between the two groups. Following I/R, when portal vein inflow was impaired (80%) in untreated organs, liver tissue blood flow to the hepatic parenchyma decreased from 33.0 to 22.4 ml/100 g/min (decrease by 32% ± 9%). In the bosentan-treated organ, a similar disruption of portal vein inflow produced a significantly greater reduction in liver tissue blood flow from 61.0 to 14 ml/100 g/min (decrease by 77% ± 7%) ($P<0.05$). Although disruption of hepatic artery inflow decreased hepatic tissue blood flow to the hepatic parenchyma, there was no difference in this change between untreated and bosentan-treated organs.

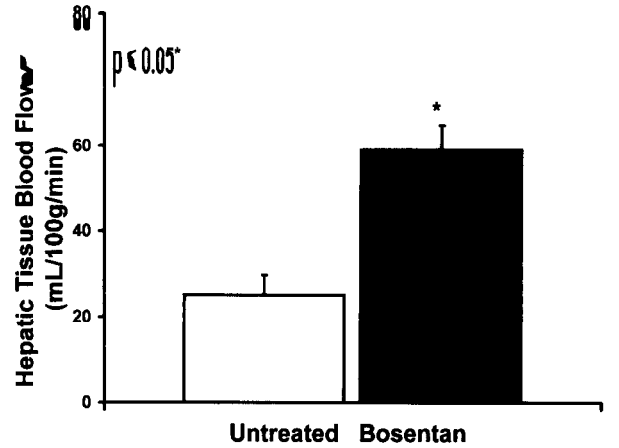

Fig. 1. Effect of bosentan on hepatic tissue blood flow following ischemia/reperfusion injury. Data represent mean hepatic tissue blood flow ± standard error of the mean in five untreated organs and five bosentan-treated organs.

Evaluation of Hepatocellular Damage

Hepatocellular damage markers, LDH and SDH, were measured before harvest and every 30 minutes after reperfusion in the hepatic venous blood. Comparisons of LDH and SDH levels in the organ prior and following I/R demonstrated sharp increases in enzyme activities. LDH increased from 14.6 ± 5 U/mg protein prior to I/R to 45.8 ± 7 U/mg protein in all livers following I/R. SDH similarly increased from 23.5 ± 8 U/mg protein prior to I/R to 1332 ± 185 U/mg protein in all livers following I/R. No difference in maximal postreperfusion LDH levels was noted between untreated livers (41.8 ± 5 U/mg protein) and bosentan-treated livers (49.8 ± 14 U/mg protein). Similarly, no difference in maximal postreperfusion SDH levels was noted between untreated livers (1052 ± 164 U/mg protein) and bosentan-treated livers (1613 ± 285 U/mg protein).

Evaluation of Endothelial Cell Damage

Following 3 hours of reperfusion, pathology specimens were obtained from the left and right lobes and immunostained for factor VIII. Prior to cold

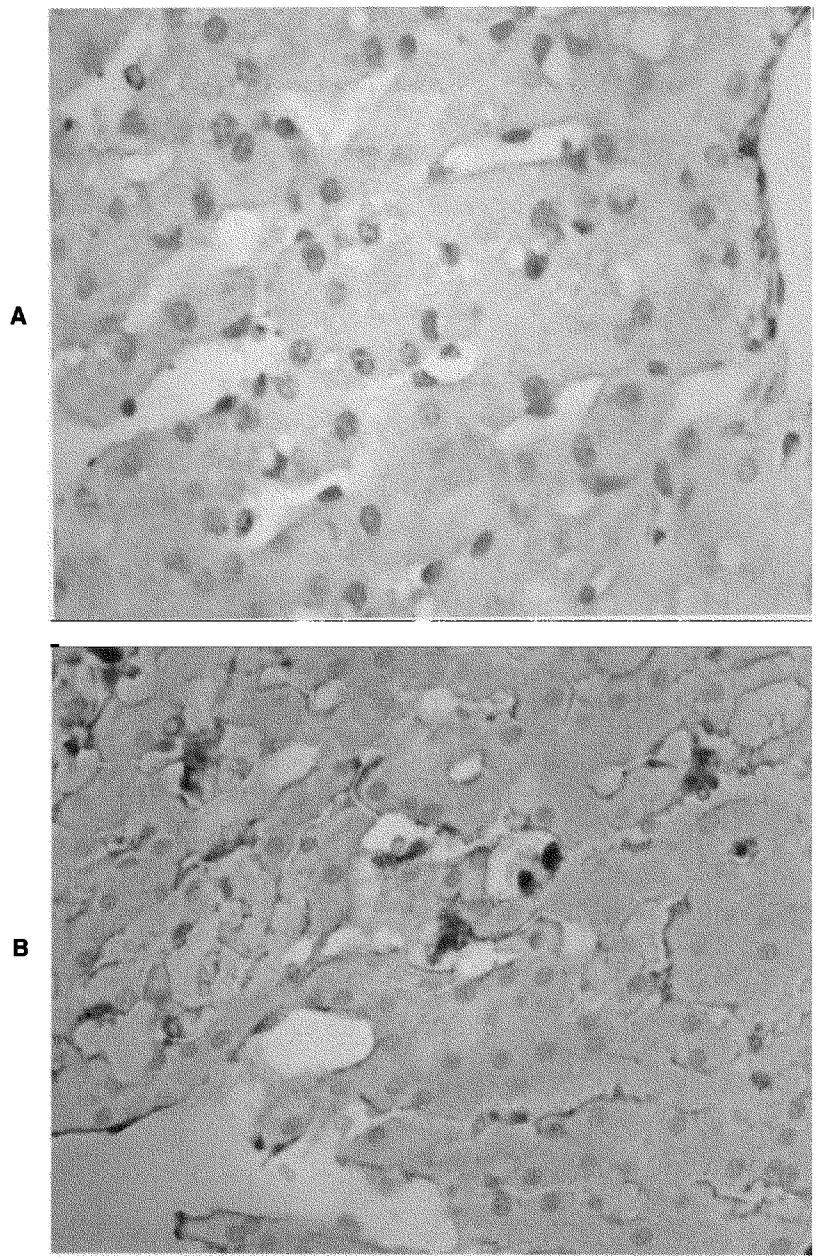

Fig. 2. A, Biopsy specimen from an untreated organ. Factor VIII immunostain revealed lack of positive immunostaining everywhere (score 0) except the central vein. (×400.) **B,** Biopsy specimen from a bosentan-treated organ. Factor VIII immunostain revealed brown positive stain along the sinusoids (score 2). (×400.)

ischemia, in both groups, pathology scores for factor VIII immunostaining were 1.9 ± 0.05 (top score = 2.0). I/R produced endothelial cell rounding and displacement from the basement membrane, resulting in a decrease in factor VIII pathology scores to 0.36 ± 0.07. Untreated liver postreperfusion biopsy scores for factor VIII immunostaining were 0.23 ± 0.09. Fig. 2, *A* shows a biopsy specimen taken from an untreated organ after 3 hours of reperfusion. The bosentan-treated organs demonstrated significantly higher immunostain scores, 0.54 ± 0.11 ($P < 0.05$). Fig. 2, *B* demonstrates a biopsy taken from a bosentan-treated organ after 3 hours of reperfusion.

Evaluation of Graft Function

Graft function was determined through hepatic oxygen consumption and biliary production with and without bile acid stimulation. After the first 30 minutes of reperfusion, hepatic oxygen consumption remained stable. In the untreated organ, hepatic oxygen consumption was 0.5 ± 0.1 ml/100 g/min. The bosentan-treated organ demonstrated significantly higher oxygen consumption, 0.9 ± 0.1 ml/100 g/min ($P < 0.05$) following I/R (Fig. 3).

The cold-reperfused liver demonstrates reduced biliary production following I/R, and requires 1 to 2 hours of reperfusion to return to normal.[10] Maximal biliary production following I/R was 1.0 ± 0.1 ml/15 minutes in the untreated liver and 1.7 ± 0.3 ml/15 minutes in the bosentan-treated organ ($P < 0.05$) (see Fig. 3). Two hours after I/R, all reperfused livers were challenged with 5952 μmol/15 minutes of taurocholate via the portal vein. With bile acid infusion, biliary production was markedly increased in both the untreated organ and the bosentan-treated organ. Yet biliary production was significantly higher in response to the bile acid challenge in the bosentan-treated organ (7.4 ± 0.4 ml/15 minutes) as compared to the untreated organ (3.5 ± 0.6 ml/15 minutes) ($P = 0.003$).

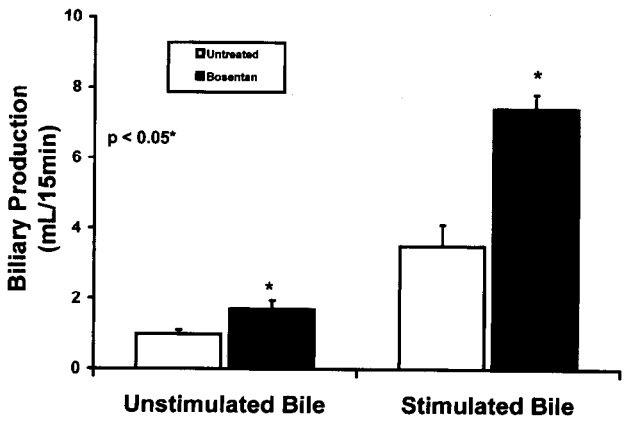

Fig. 3. Effect of bosentan on graft biliary production after ischemia/reperfusion injury, both unstimulated and following stimulation with taurocholate. Data represent mean biliary flows (± standard error of the mean) in five untreated organs and five bosentan-treated organs.

DISCUSSION

In the present study, the effect of an endothelin receptor antagonist, bosentan, on hepatic circulation, cell damage, and graft function was evaluated following I/R. The data reveal that grafts treated with bosentan demonstrated lower hepatic vascular resistance, enhanced liver tissue blood flow, and improved portal vein inflow following I/R. Although no change in hepatocellular damage was noted, endothelial cell damage was reduced in the bosentan-treated livers. Bosentan grafts also demonstrated enhanced oxygen consumption, increased bile flow, and augmented responses to bile acid challenge. These results indicate that administration of bosentan before and after I/R may be a useful approach to improving preservation damage and graft function of the transplanted liver.

The endothelins are a family of proteins first discovered in 1988.[18] These peptides are potent vasoconstrictors that produce prolonged pressor responses in both vascular and nonvascular tissues.[19] Although a basal release of endothelins is thought to modulate numerous vascular beds, de novo synthesis with large bursts of newly synthesized endothelins also occurs in response to various signals.[18] These signals range from chemical stimuli to hypoxic stresses. For example, induction of hypoxia to the rat arterial bed leads to a dramatic rise in endothelin message and subsequent increases in intracellular calcium.[20] These intracellular changes lead to vasoconstriction and a sharp rise in vascular pressures.

Endothelins have been localized in many tissues including the lungs, kidneys, heart, peripheral vasculature, and liver. Given the ubiquity in which endothelins are found, these peptides have been implicated in a variety of disease processes including cardiovascular, inflammatory, and transplantation pathophysiologies. A number of drugs have been developed aimed at blocking endothelin binding to its receptor.[21] The agent used in the present study, bosentan, is an orally active, nonselective endothelin receptor antagonist.[22] This compound has already undergone evaluation in human studies of pulmonary hypertension[23] and congestive heart failure,[24] demonstrating no significant toxic effects as compared to placebo. In the liver, bostentan has been shown to reduce hepatic injury secondary to endotoxemia in mice,[12] lessen portal pressures in a rat model of cirrhosis,[13] and reduce the hepatic microcirculatory damage of I/R in the canine

liver.[14] No study has, however, evaluated the effect of bosentan on hepatic macrocirculation and function following I/R.

Previous data from our laboratory have demonstrated significant alterations in hepatic tissue blood flow (macrocirculation) following I/R. The reperfused large animal liver is characterized by enhanced hepatic resistance, reduced liver tissue blood flow, and decreased portal vein inflow to the hepatic parenchyma.[2] In the present study, a significant decrease in hepatic resistance was noted with bosentan treatment. Livers perfused with bosentan also demonstrated enhanced liver tissue blood flow and augmented portal vein inflow to the hepatic parenchyma. The lobar tissue blood flow of the bosentan-treated organs almost returned to that expected for a normal in situ liver.[2]

The observed improvements in the macrocirculation of bosentan-treated organs corresponds to previous data demonstrating similar improvements in the microcirculation of reperfused livers treated with endothelin antagonists.[25,26] A significant decrease in leukocyte endothelial cell interactions in hepatic acini was noted on reperfusion in rat livers treated with an endothelin antagonist prior to ischemia. The same study also demonstrated improved sinusoidal blood flow and attenuated microvascular perfusion failure as evaluated by intravital microscopy.[25] Given the improvements in micro- and macrocirculatory perfusion with endothelin receptor antagonist, endothelins likely play a key role in mediating the circulatory collapse of I/R.

Antagonism of endothelins has previously been shown to augment graft function following I/R. Infusions of endothelin receptor antagonists improves graft function in the transplanted porcine liver as measured by indocyanine green retention and enhanced serum total bile acid.[26] In addition, infusions of endothelin antagonists lead to improved survival in the reperfused dog liver following 2 hours of ischemia.[27] The data in these previous studies are similar to the results obtained in the present study. Improved graft function as evaluated by enhanced oxygen consumption, biliary production, and response to bile acid challenge was demonstrated with bosentan treatment. These functional changes in hepatic grafts during bosentan treatment may be significantly influenced by the observed dramatic changes in the vascular supply to the hepatic parenchyma. Given the significant contribution of endothelins to the pathophysiology of ischemia/reperfusion and the volume of data indicating a hepatoprotective role for endothelin receptor antagonists, clinical trials should be considered evaluating the potential benefit of these agents in transplantation.

REFERENCES

1. Clemens MG, McDonagh PF, Chaudry IH, Baue AE. Hepatic microcirculatory failure after ischemia reperfusion: Improvement with ATP-MgCL2 treatment. Am J Physiol 1985;248: H804-H811.
2. Ricciardi R, Foley DP, Quarfordt SH, et al. Cold ischemia affects regional hepatic tissue perfusion [abstr]. Hepatology 1999;30:223A.
3. Koo A, Komatsu H, Tao G, Inoue M, Guth PH, Kaplowitz N. Contribution of no-reflow phenomenon to hepatic injury after ischemia-reperfusion: Evidence for a role for superoxide anion. Hepatology 1992;15:507-514.
4. Lautt WW. The 1995 Ciba-Geigy Award Lecture. Intrinsic regulation of hepatic blood flow. Can J Physiol Pharmacol 1996;74:223-233.
5. Ricciardi R, Foley DP, Quarfordt SH, et al. Variables predict ex-vivo support organ function (submitted for publication).
6. Wilhelm SM, Simonson MS, Robinson AV, Stowe NT, Schulak JA. Cold ischemia induces endothelin gene upregulation in the preserved kidney. J Surg Res 1999;85:101-108.
7. Kawamura E, Yamanaka N, Okamoto E, Tomoda F, Furukawa K. Response of plasma and tissue endothelin-1 to liver ischemia and its implication in ischemia reperfusion injury. Hepatology 1995;21:1138-1143.
8. Nakamura S, Nishiyama R, Serizawa A, et al. Hepatic release of endothelin-1 after warm ischemia. Transplantation 1995;59: 679-684.
9. Pannen BH, Al-Adili F, Bauer M, Clemens MG, Geiger KK. Role of endothelins and nitric oxide in hepatic reperfusion injury in the rat. Hepatology 1998;27:755-764.
10. Foley DP, Vittimberga FJ, Quarfordt SH, et al. Biliary secretion of extracorporeal porcine livers with single and dual vessel perfusion. Transplantation 1999;68:362-368.
11. Southard JH, Belzer FO. Organ preservation. Annu Rev Med 1995;46:235-247.
12. Iskitt AB, Sungur A, Gedikoglu G, Oguz Guc M. The effects of bosentan, aminoguanidine and L-canavanine on mesenteric blood flow, spleen, and liver in endotoxaemic mice. Eur J Pharmacol 1999;379:73-80.
13. Sogni P, Moreau R, Gomola A, et al. Beneficial hemodynamic effects of bosentan, a mixed ET_A and ET_B receptor antagonist, in portal hypertensive rats. Hepatology 1998;28: 655-659.
14. Koeppel TA, Kraus T, Thies JC, Gebhard MM, Otto G, Post S. Effects of mixed ETA and ETB receptor antagonist (Ro-47-0203) on hepatic microcirculation after warm ischemia. Dig Dis Sci 1997;42:1316-1321.
15. Asada M, Galambos JT. Sorbitol dehydrogenase and hepatocellular injury: An experimental and clinical study. Gastroenterology 1963;44:578-587.
16. Wiesner IS, Rawnsley HM, Brooks FP, Senior JR. Sorbitol dehydrogenase in the diagnosis of liver disease. Am J Dig Dis 1965;10:147-151.
17. Jenkins SJ, Green SA, Clark PA. Clinical chemistry reference values of normal domestic animals in various age groups—as determined on the ABA-100. Cornell Vet 1982;72:403-415.
18. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988;332:411-415.
19. Randall MD. Vascular activities of the endothelins. Pharmacol Ther 1991;50:73-93.
20. Rakugi H, Tabuchi Y, Nakamura M, et al. Evidence for endothelin-1 release from resistance vessels of rats in response to hypoxia. Biochem Biophys Res Commun 1990;169:973-977.

21. Moreland S. Endothelin receptor antagonists: A brief review. Can J Physiol Pharmacol 1994;72:1469-1471.
22. Clozel M, Breu V, Gray GA, et al. Pharmacological characterization of bosentan, a new potent orally active nonpeptide endothelin receptor antagonist. J Pharmacol Exp Ther 1994; 270:228-235.
23. Williamson DJ, Wallman LL, Jones R, et al. Hemodynamic effects of Bosentan, an endothelin receptor antagonist, in patients with pulmonary hypertension. Circulation 2000;102: 411-418.
24. Sustch G, Bertel O, Richenbacher P, et al. Regulation of aldosterone secretion in patients with chronic congestive heart failure by endothelins. Am J Cardiol 2000;85:973-976.
25. Kitayama Y, Yamanaka N, Kawamura E, Kuroda N, Okamoto E. Hepatoprotective effect of the endothelin receptor antagonist TAK-044 against ischemia-reperfusion injury in the canine liver. Hepatology 1997;27:1652-1660.
26. Yamanaka N, Takaya Y, Oriyama T, et al. Hepatoprotective effect of a nonselective endothelin receptor antagonist (TAK-044) in the transplanted liver. J Surg Res 1997;70:156-160.
27. Urakami A, Todo S, Zhu Y, et al. Attenuation of ischemic liver injury by monoclonal anti-endothelin antibody, AwETN40. J Am Coll Surg 1997;185:358-364.

Randomized Comparison of Conventional and Gasless Laparoscopic Cholecystectomy: Operative Technique, Postoperative Course, and Recovery

Jens Fromholt Larsen, M.D., Per Fjstrud, M.D., Joergen U. Kristensen, M.D., Flemming Svendsen, M.D., Finn Redke, M.D., Vivi Pedersen, M.D.

The positive CO_2 pneumoperitoneum needed to create the working space for laparoscopic surgery induces cardiovascular, neuroendocrine, and renal changes. Concern about these pathophysiologic changes has led to the introduction of a gasless technique. Fifty consecutive patients with symptomatic gallstones were randomized to conventional (CLC) or gasless laparoscopic cholecystectomy (GLC), with special reference to overall patient satisfaction, technical difficulties, duration of surgery, postoperative pain, and recovery. The overall exposure of the operative field was extremely poor in the GLC group, whereas the duration of surgery, steps involved in the cholecystectomy technique, length of hospital stay, and postoperative pain score did not differ significantly. After discharge, the median time to complete relief of pain tended to be shorter in the gasless group (5 days [range 1 to 15]) vs. the conventional group (8 days [range 1 to 15]). The period to return to normal activity was shorter in the GLC group (6 days [range 1 to 15]) compared to the CLC group (8.5 days [range 1 to 15]) ($P = 0.031$). No differences were found in terms of fatigue, dizziness and nausea, and overall satisfaction with the outcome. This study demonstrates a significantly shorter convalescence after laparoscopic cholecystectomy by means of the gasless technique compared to the conventional CO_2 technique. Exposure of the operative field was less than optimal using the gasless technique. (J GASTROINTEST SURG 2001;5:330-335.)

KEY WORDS: Laparoscopic cholecystectomy, pneumoperitoneum, gasless laparoscopy, comparative study, methods

Laparoscopic surgery involves less trauma than open surgery with a reduction in postoperative pain and less pulmonary and cardiovascular dysfunction.[1] These benefits may be particularly important to patients with preexisting cardiopulmonary disease. Pneumoperitoneum achieved with high-flow insufflation of CO_2 provides good exposure of the abdominal viscera by creating a uniform dome-type cavity, which is the basis for laparoscopic operations. However, pneumoperitoneum induces complex pathophysiologic changes.[2] The main hemodynamic changes induced by CO_2 insufflation during laparoscopic cholecystectomy are well documented and consist of significant increases in mean arterial pressure, cardiac index, and systemic and pulmonary vascular resistance. Even the patient's position may cause hemodynamic changes, and the combined effects of anesthesia, head-up tilt, and insufflation may produce a 50% decrease in the cardiac index. Changes in venous circulation can also occur and may mimic abnormalities such as chronic heart failure, as shown by echocardiography.[3,4]

One major technical disadvantage of using CO_2 insufflation is it requires an airtight system. Airtight systems do not allow palpation of the intra-abdominal organs during laparoscopy, and combined laparoscopic and open procedures are difficult to handle because of the loss of pneumoperitoneum. A large number of mechanical elevators of the abdominal wall have been developed. The most widely used system is the Lap-

From the Departments of Surgical Gastroenterology (J.F.L., P.E., and J.U.K.), Anesthesia (F.S. and F.R.), and Cardiology (V.P.), Aalborg Hospital, Aalborg, Denmark.
Supported by grants from Nordjyllands Amts Forskningsråd, Aalborgs Stifts Julelotteri, and Det Obelske Familiefond.
Presented at the Forty-First Annual Meeting of The Society for Surgery of the Alimentary Tract, San Diego, Calif., May 21-24, 2000.
Reprint requests: Dr J. Fromholt Larsen, Department of Surgical Gastroenterology, Aalborg Hospital, P.O. Box 365, 9100 Aalborg, Denmark.

arolift developed by Origin Medsystems, Inc. (Menlo Park, Calif.). This system uses an intraperitoneal fan-shaped retractor and a mechanical arm providing a tenting of the abdominal wall. The Laparotensor (Lucini, Milan, Italy) provides traction of the skin and subcutaneous tissue creating a more domelike working cavity without penetrating the peritoneum. The gasless technique permits the use of unvalved trocars to perform minilaparotomy for operative purpose without compromising the working chamber, and it eliminates the pathophysiologic effects of pneumoperitoneum. However, the gasless technique has some disadvantages such as the absence of counterpressure on the intra-abdominal organs and limitation of trocar placement.[5]

Few studies have investigated and compared conventional laparoscopic and gasless techniques, and no general conclusions could be reached because of the small amount of data and conflicting results.[6-11] The aim of this study was to compare gasless (Laparotensor) and conventional laparoscopic cholecystectomy in a randomized setting paying particular attention to exposure of the operative field, technical difficulties, duration of surgery, postoperative pain, clinical course, and convalescence.

MATERIAL AND METHODS

Patients

Fifty consecutive patients with symptomatic cholecystolithiasis fulfilling the inclusion criteria were randomly allocated to one of two groups: conventional laparoscopic cholecystectomy (CLC) or gasless laparoscopic cholecystectomy (GLC). The allocation sequence was generated by random numbers using Documenta Geigy. Patients were randomly allocated by opening sealed envelopes on the day of surgery. The intervention assignments were hidden from the patients and from the nursing staff on the ward. Data were collected from December 1, 1998 to October 1, 1999. Inclusion criteria consisted of the following: age over 18 years and body mass over 30 kg/m^2. Informed written consent was obtained from all patients. Patients with acute pancreatitis, cholecystitis, cholangitis, blood diseases, rheumatic diseases, acute infectious diseases, and renal or liver diseases were excluded from the study. The study was approved by the local ethics committee.

Operations

All operations were performed by three surgeons experienced in CLC and GLC. In one group (CLC), laparoscopic cholecystectomy was performed using conventional CO_2 pneumoperitoneum at a pressure of 12 mm Hg and two 10 mm trocars and two 5 mm trocars. In the other group (GLC), two curved steel needles were inserted into the subcutaneous space and attached to a mechanical arm affixed to the operating table. A minilaparotomy (15 mm) was performed through the umbilicus. A working chamber was produced by elevation of the mechanical retractor (Laparotensor) (Fig. 1). A valveless 10 mm port was inserted, and one 10 mm and two 5 mm valveless ports were inserted under direct vision. After the working chamber was created, cholecystectomy was performed using identical technique and instruments, a curved dissector and monopolar electrocautery. Cholangiography was not routinely performed. Once the cystic duct and artery were clipped and divided, the gallbladder was detached from the liver bed and placed over the liver. The gallbladder was removed through the umbilical incision via a 20 mm port in the CLC group and through the 15 mm incision in the GLC group. Immediately after the operation, the surgeon rated the procedure on a scale of 1 to 5 (impossible = 1, easy = 5) according to the following parameters: overall exposure of the operative field, dissection of the triangle of Calot, application of clips, dissection of the gallbladder from the liver bed, and removal of the gallbladder. Furthermore, perioperative complications such as bleeding and perforation of the gallbladder were recorded. Gentamycin (240 mg) was given to all patients 1 hour before the procedure.

Anesthesia

Patients were not premedicated to avoid interference with pulmonary or circulatory functions. Local anesthesia (bupivacaine 0.5%) was injected before the insertion of the ports and subdiaphragmatically after the gallbladder had been removed. Before the induction of anesthesia, 10 ml/kg sodium chloride was infused. Anesthesia was induced with 2.5 mg midazolam and a bolus of 2.5 mg/kg propofol intravenously. The patient was given a 5 μg/kg dose of fentanyl during the first hour of anesthesia and 2.5 μg/kg intravenously for the remaining time. Endotracheal intubation was facilitated by 0.1 mg/kg cisatracurium. Muscle relaxation was maintained by cisatracurium. During the operation, muscle relaxation was estimated by nerve stimulation, and doses of cisatracurium were administered when needed. Patients were ventilated by means of a Servo 900 C respirator (Siemens) with a tidal volume of 7 ml/kg and a frequency of 12 respirations/min and $F_IO_2 = 0.30$. Pulmonary peak pressure and pause pressure were measured to give an estimate of static compliance. An antiemetic dose of ondansetron (4 mg intravenously) and ketoprofen (100 mg) was given 30 minutes prior to the expected time of ex-

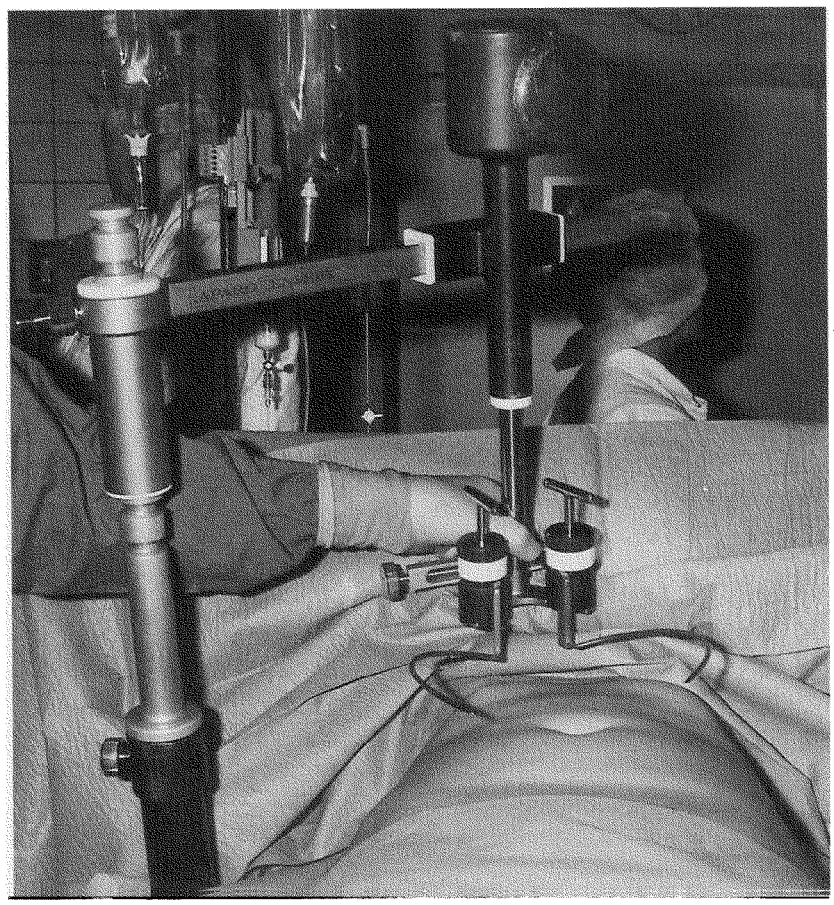

Fig. 1. The Laparotensor, which is used for gasless laparoscopic cholecystectomy.

tubation. Patients were given 2.5 mg/0.4 mg Neostigmine/glycopyrron at the end of anesthesia to prevent postanesthetic relaxation. Finally, the patients were extubated. Postoperatively, ketoprofen (100 mg twice a day) and Paracetamol (1 g four times a day) were given as a standard dose. Morphine injections were given when requested by the patient and recorded in the patient's chart.

Postoperative Course

Without knowing which procedure had been selected, patients were asked to rate their pain using a visual analogue scale ranging from 0 to 10. Patients recorded pain at rest and during mobilization, and specifically at the incision sites, the shoulders, and the abdominal wall. Recording was done 4 hours after surgery (phase 1), 8 hours after surgery (phase 2), in the morning (phase 3), and in the afternoon (phase 4) of the first postoperative day. During hospitalization, the use of pain medicine was recorded daily. At discharge, a questionnaire was given to the patients and they were asked to score daily for 14 days their pain (1 = no pain, 2 = moderate pain, 3 = severe pain) and activity (1 = as before operation, 2 = reduced, 3 = bedridden); they were also asked to note daily the following: nausea, dizziness, fatigue, pneumonia, wound complications, and fever. In addition, patients were asked to rate their satisfaction with the overall results of the operation (1 = very satisfied, 2 = satisfied, 3 = same symptoms as preoperatively).

Statistial Analysis

The nonparametric Mann-Whitney test was used to compare the two groups. Fisher's exact test was applied in cases where the frequency was less than five. Friedman's analysis was used to detect changes over time within each group. Data are expressed as median and range. P values <0.05 were considered significant.

RESULTS

The two groups were comparable in terms of age, sex, body mass index, and previous abdominal operations (Table I).

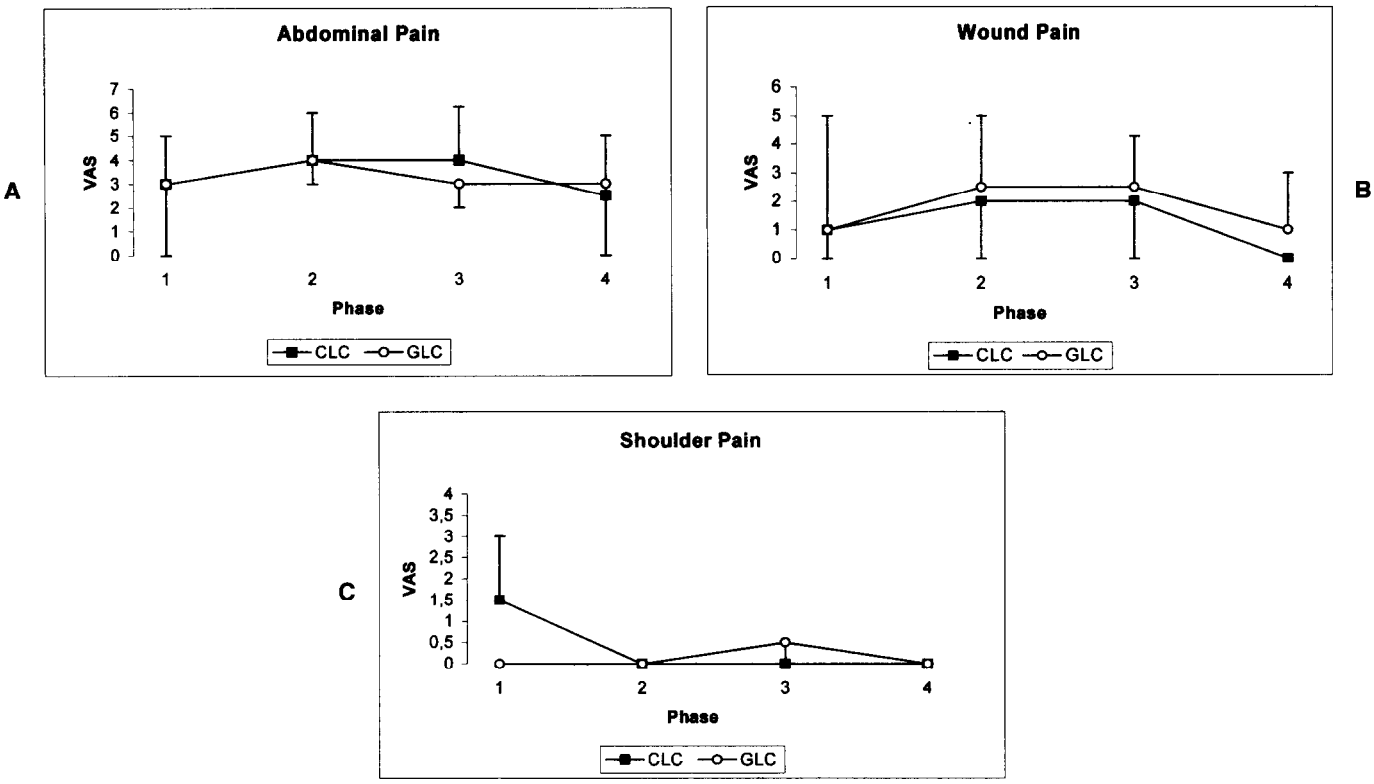

Fig. 2. Pain scores measured by a visual analogue scale *(VAS)* in the abdomen **(A)**, wound **(B)**, and shoulder **(C)**. Each point represents median values; ⊤ represents upper quartiles; ⊥ represents lower quartiles. Phase 1 = day 0, four hours postoperatively; phase 2 = day 0, evening; phase 3 = postoperative day 1, morning; phase 4 = postoperative day 1, afternoon. CLC = conventional laparoscopic cholecystectomy; GLC = gasless laparoscopic cholecystectomy.

Table I. Patient data

	Conventional laparoscopic cholecystectomy (n = 26)	Gasless laparoscopic cholecystectomy (n = 24)
Age (yr)	52 (range 29-75)	49.5 (range 29-71)
Sex (male/female)	8/18	7/17
Body mass index ($kg \cdot m^{-2}$)	26 (range 20-30)	27 (range 23-30)

Values are median and with range in parentheses.

Intraoperative Course

The duration of surgery was 78 minutes (range 45 to 170) in the CLC group and 102 minutes (range 40 to 210) in the GLC group ($P = 0.086$). Overall exposure of the operative field was significantly poor in the gasless group compared to the conventional group ($P = 0.006$). However, no significant differences were noted when dissecting the triangle of Calot, placing clips, and dissecting the gallbladder from the hepatic bed. Removal of the gallbladder from the abdominal cavity was easiest in the gasless group ($P = 0.017$). Four patients in the gasless group were converted as follows: one patient was converted to CLC, three patients were converted to open cholecystectomy because of a poor overview due to empyema of the gallbladder, and the fourth patient was converted because of a poor overview due to the absence of counterpressure on the intestine. One patient in the CLC group was converted to open surgery because of chronic cholecystitis and Mirizzie's syndrome. No statistical difference was found in conversion rates ($P = 0.182$). No major intraoperative complications occurred in either group.

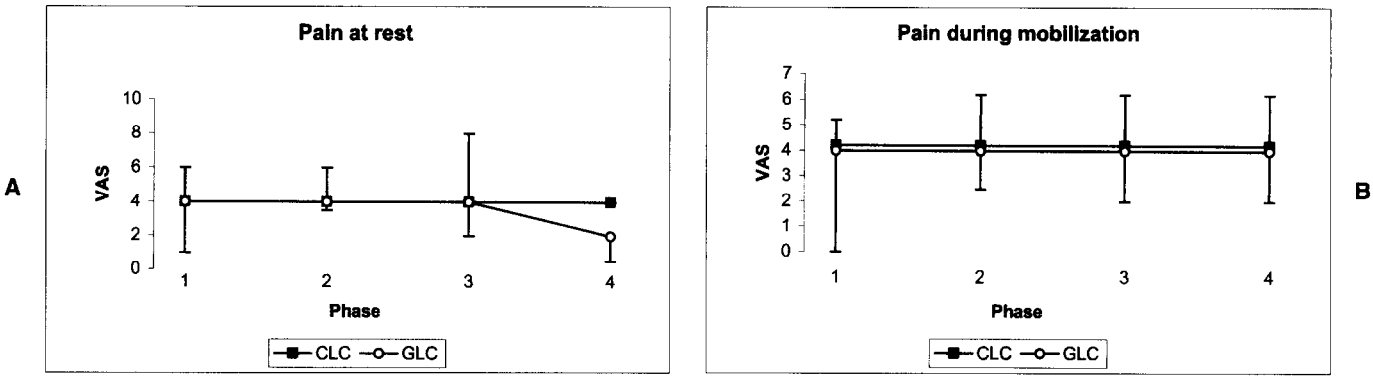

Fig. 3. Pain scores measured by a visual analogue scale *(VAS)* at rest **(A)** and during mobilization **(B).** Each point represents median values; ⊤ represents upper quartiles; ⊥ represents lower quartiles. Phase 1 = day 0, four hours postoperatively; phase 2 = day 0, evening; phase 3 = postoperative day 1, morning; phase 4 = postoperative day 1, afternoon. CLC = conventional laparoscopic cholecystectomy; GLC = gasless laparoscopic cholecystectomy.

Postoperative Course During Hospital Stay

The median postoperative hospital stay was 1 day (range 1 to 31 days) in the CLC group and 1 day (range 1 to 3 days) in the GLC group. Postoperative wound pain, abdominal pain, and shoulder pain were similar in the CLC and GLC groups (Fig. 2). No significant differences in pain scores were found at rest or during mobilization within or between the groups during the hospital stay (Fig. 3), or in morphine consumption on day 0 ($P = 0.377$) and day 1 ($P = 0.447$).

After Discharge

The period to complete relief of pain was similar in the two groups: 8 days (range 1 to 15) in the CLC group vs. 5 days (range 1 to 15) in the GLC group ($P = 0.234$). However, the time to return to normal activity was significantly shorter in the gasless group (6 days [range 1 to 15]) compared to the conventional group (8 days [range 2 to 15]) ($P = 0.031$). No difference was found between the two groups with regard to fatigue, dizziness and nausea, and overall satisfaction with the outcome of the operation. Three patients were readmitted, all of them from the CLC group. One patient in the CLC group developed bile leakage due to an aberrant duct and was treated with endoscopic stenting. The patient was discharged after 31 days. Two patients were readmitted with fever and abdominal pain, but they were discharged after 1 and 3 days, respectively. No significant difference was found between the two groups concerning the overall results of the operation ($P = 0.965$).

DISCUSSION

This study demonstrates a significantly shorter convalescence after laparoscopic cholecystectomy by the gasless technique than with conventional CO_2 pneumoperitoneum. The exposure of the operative field was less than optimal using the gasless technique. However, the operative time was not significantly extended, and there were not any more intraoperative or postoperative complications in the gasless group.

Few studies have investigated and compared the laparoscopic techniques performed with pneumoperitoneum or mechanical traction within the fields of gynecology[6-8] and general surgery.[9-11] Duration of surgery, intraoperative complications, and conversion rates are the typical objective parameters.[6-11] In general, the duration of surgery is found to be longer when the gasless technique is used. We also found that the operative time for the GLC group tended to be longer than that for the CLC group and that the conversion rate also tended to be higher, although the difference was not significant. The lack of statistical significance, however, may be due to a type II error.

In this study we used a quantitative system to assess exposure of the operative field and the different steps involved in the operation. Applying this scoring system, the gasless technique provided inferior exposure. We noticed that with the gasless technique, the transverse colon in some cases hindered exposure of the operative field more frequently than during conventional laparoscopic cholecystectomy, probably because of the absence of counterpressure on the bowel. However, when the exposure was good, no difference was found concerning the individual steps involved in

the procedure, apart from removal of the gallbladder from the abdominal cavity, which was easier in the gasless group because of the minilaparotomy incision. In patients of normal weight, we had no problems creating a dome-like working cavity using the Laparotensor device. However, when performing laparoscopic cholecystectomy, it is important to insert the subcutaneous needles over the costal margin in order to lift up the gallbladder, especially in obese patients. In two randomized studies comparing the gasless and conventional laparoscopic procedures on the basis of intraoperative visualization and procedural difficulty during pelvic surgery, increased technical difficulty and poorer visualization were found with the use of an intra-abdominal fan retractor (Laparolift).[7,8]

Our concern that traction on the abdominal wall by the subcutaneous needles in the gasless group would result in more discomfort or pain was not confirmed. During the hospital stay, no differences in somatic or visceral pain were found between the conventional and gasless groups. Our results are in agreement with those of the randomized study by Koivusalo et al.,[11] who found that postoperative nausea, vomiting, and pain in the right shoulder occurred less often after gasless cholecystectomy (Laparolift). However, greater technical difficulties and postoperative pain were reported with the gasless technique using the Laparolift fan retractor for gynecologic laparoscopy.[7,8] Furthermore, increased pain during mobilization and coughing was registered in the gasless group when comparing gasless and CO_2 laparoscopic colon resections.[12] These conflicting results may reflect procedural differences rather than pathophysiologic differences between gasless and conventional laparoscopy.

The postoperative period was monitored daily by the patients who recorded their pain and daily activities for 14 days. Patients in the GLC group returned to their normal activities sooner than those in the CLC group, supposedly because they had less postoperative pain. Concerning fatigue, dizziness, nausea, and wound problems, no differences were found. From the patients' point of view, there were no differences in terms of overall satisfaction with the results of the operation.

Further research is required to explore the potential of other mechanical methods or the combination of low-pressure pneumoperitoneum and traction. More comparative studies of the conventional and gasless method are also needed in the effort to investigate the cardiovascular, respiratory, neuroendocrine, and renal effects of laparoscopic surgery.

REFERENCES

1. Schulze S, Thorup J. Pulmonary function, pain, and fatigue after laparoscopic cholecystectomy. Eur J Surg 1993;159:361-364.
2. Struthers AD, Cuschieri A. Cardiovascular consequences of laparoscopic surgery. Lancet 1998;352:568-570.
3. Cunningham AJ, Turner J, Rosenbaum S, Rafferty T. Transoesophageal echocardiographic assessment of haemodynamic function during laparoscopic cholecystectomy. Br J Anaesth 1993;70:621-625.
4. Harris SN, Ballantyne GH, Luther MA, Perrino AC. Alterations of cardiovascular performance during laparoscopic colectomy: A combined hemodynamic and echocardiographic analysis. Anesth Analg 1996;83:482-487.
5. Martin IG, McMahon MJ. Gasless laparoscopy. J R Coll Surg Edinb 1996;41:72-74.
6. Cravello L, D'Ercole C, Roger V, Samson D, Blanc B. Laparoscopic surgery in gynecology: Randomized prospective study comparing pneumoperitoneum and abdominal wall suspension. Eur J Obstet Gynecol Reprod Biol 1999;83:9-14.
7. Johnson PL, Sibert KS. Laparoscopy. Gasless vs. CO_2 pneumoperitoneum. J Reprod Med 1997;42:255-259.
8. Goldberg JM, Maurer WG. A randomized comparison of gasless laparoscopy and CO_2 pneumoperitoneum. Obstet Gynecol 1997;90:416-420.
9. Kitano S, Iso Y, Tomikawa M, Moriyama M, Sugimachi K. A prospective randomized trial comparing pneumoperitoneum and U-shaped retractor elevation for laparoscopic cholecystectomy. Surg Endosc 1993;7:311-314.
10. Meijer DW, Rademaker BP, Schlooz S, Bemelman WA, de Wit LT, Bannenberg JJ, Stijnen T, Gouma DF. Laparoscopic cholecystectomy using abdominal wall retraction. Hemodynamics and gas exchange, a comparison with conventional pneumoperitoneum. Surg Endosc 1997;11:645-649.
11. Koivusalo AM, Kellokumpu I, Lindgren L. Gasless laparoscopic cholecystectomy: Comparison of postoperative recovery with conventional technique. Br J Anaesth 1996;77:576-580.
12. Schulze S, Lyng KM, Bugge K, Perner A, Bendtsen A, Thorup J, Nielsen HJ, Rasmussen J. Cardiovascular and respiratory changes and convalescence in laparoscopic colonic surgery: Comparison between carbon dioxide pneumoperitoneum and gasless laparoscopy. Arch Surg 1999;134:112-118.

Statement on Submission and Publication of Manuscripts

The Surgical Journal Editors Group

Increasing problems of duplicate and fraudulent submissions and publications have prompted the undersigned editors of surgical journals to support these overall principles of publication.

Duplicate Submission and Publication:

In general, if a manuscript has been peer-reviewed and published, any subsequent publication is duplication.

Exceptions to this general rule may be:

(a) Prior publication in meeting program abstract booklets or expanded abstracts such as those published by the *Surgical Forum* of the American College of Surgeons or *Transplantation Proceedings*. However, these must be referenced in the final manuscript.

(b) A manuscript that extends an original database (a good rule might be expansion by 50% or more) or analyzes the original database in a different way in order to prove or disprove a different hypothesis. Previous manuscripts reporting the original database must, however, be referenced.

(c) Manuscripts that have been published originally in non–English language journals, provided that the prior publication is clearly indicated on the English language submission and referenced in the manuscript. In some circumstances, permission to publish may need to be obtained from the non–English language journal.

For example, any submission duplicating material previously published in full in "Proceedings" or book chapters is considered duplicate unless the exceptions in (a) above apply. Similarly, manuscripts dealing with subgroups of data (i.e., patients) that have previously been analyzed, discussed, and published as a larger group are considered duplicate unless (b) above applies.

The Internet raises special concerns. If data have previously appeared on the Internet, submission of that data for publication is considered duplication. If Internet publication *follows* journal publication, the journal publication should be clearly referenced. Some journals may provide early Internet publication of accepted peer-reviewed papers that are subsequently published in that journal. This does not constitute duplication if both manuscripts are identical *and* covered by the same single copyright.

Fraudulent Publication:

The following activities are examples of fraudulent publication practices:

(a) Willful and knowing submissions of false data for publication

(b) Submission of data from sources not the author's (or authors') own

(c) Falsely certifying that the submitted work is original and has not been submitted to, or accepted by, another journal

(d) Sponsoring or vouching for a manuscript containing data over which the sponsor has no control or knowledge

(e) Allowing one's name to appear as an author without having contributed significantly to the study

(f) Adding an author's name to a manuscript to which he/she has not contributed, or reviewed or agreed to in its current form

(g) Flagrant omission of reference to work of other investigators that established their priority

(h) Falsification of any item on the copyright form

(i) Failure to disclose potential conflict of interest with a sponsoring agency

Although not intended as an all-inclusive document, these examples and guidelines should alert authors to potential problems that should be avoided when they are considering submission of a manuscript to a peer-reviewed journal.

Members of the Surgical Journal Editors Group include the following:

American Journal of Surgery	Hiram C. Polk, Jr., M.D.
American Surgeon	Talmadge A. Bowden, Jr., M.D.
Annals of Surgery	Layton F. Rikkers, M.D.
Annals of Surgical Oncology	Charles M. Balch, M.D.
Current Surgery	Walter J. Pories, M.D.
Digestive Surgery	Eduard H. Farthmann, M.D. Markus W. Büchler, M.D.
Diseases of the Colon and Rectum	Victor Fazio, M.D.
Journal of the American College of Surgeons	Seymour Schwartz, M.D.
Journal of Gastrointestinal Surgery	John L. Cameron, M.D. Keith A. Kelly, M.D.
Journal of Japan Medical Association	Yasuo Idezuki, M.D.
Journal of Japan Society for Endoscopic Surgery	Yasuo Idezuki, M.D.
Journal of Japan Surgical Association	Yasuo Idezuki, M.D.
Journal of Pediatric Surgery	Jay Grosfeld, M.D.
Journal of Surgical Research	Wiley W. Souba, M.D. David W. McFadden, M.D.
Journal of Thoracic and Cardiovascular Surgery	Andrew S. Wechsler, M.D.
Journal of Vascular Surgery	Robert B. Rutherford, M.D. K. Wayne Johnston, M.D.
Journal of Parenteral and Enteral Nutrition	Danny O. Jacobs, M.D.
Journal of Trauma	Basil A. Pruitt, Jr., M.D.
Surgery	Andrew L. Warshaw, M.D. Michael Sarr, M.D.
Surgical Endoscopy	Bruce V. MacFadyen, Jr., M.D. Sir Alfred Cuschieri, M.D.
Surgical Laparoscopy, Endoscopy and Percutaneous Techniques	Carol E.H. Scott-Conner, M.D., Ph.D. Maurice Arregui, M.D.
World Journal of Surgery	Ronald K. Tompkins, M.D.
Zentralblatt für Chirurgie	Albrecht Encke, M.D.

Duplicate Publication in Surgical Journals

Keith A. Kelly, M.D., John L. Cameron, M.D., Co-Editors

Matters of duplicate and fraudulent publication are of great concern to editors of surgical journals and to the surgical community at large. The Surgical Journal Editors Group, a group of editors of major surgical journals in the United States and abroad, has prepared a set of principles regarding these matters. These principles are published in this issue of the JOURNAL OF GASTROINTESTINAL SURGERY. We strongly subscribe to them.

We recognize that identifying and preventing violations of these principles is not always easy, and that editors sometimes need to use their best judgment in making decisions regarding them. When doing so, however, editors should feel free to ask for counsel and advice from their editorial boards, from the society sponsoring their journal, and from others.

Fortunately, violation of these principles is not common. Most authors are aware of them and abide by them. They take seriously the signing of the copyright assignment form that journals require when a manuscript is submitted or accepted for publication. These forms usually state, as does ours, that none of the material being submitted has been published previously, is included in another manuscript, or is currently under consideration for publication elsewhere or accepted for publication elsewhere. Nonetheless, violations do occur, and when they are discovered in material submitted for publication to the JOURNAL OF GASTROINTESTINAL SURGERY, they will not be tolerated.

We welcome comments from our readers and from members of The Society for Surgery of the Alimentary Tract regarding the principles of the Surgical Journal Editors Group. Critique of, addition to, or suggested changes in the principles would be welcome. We suggest, for example, that the statement "if a manuscript has been peer-reviewed and published, any subsequent publication is duplication" should be changed to "If a manuscript has been peer-reviewed and published, any subsequent publication of the manuscript ***or any part of it*** is duplication."

We look forward to hearing from you.