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Primary Sclerosing Cholangitis

Resect, Dilate, or Transplant?

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Objective

The current study examines the results of extrahepatic biliary resection, nonoperative endoscopic biliary dilation with or without percutaneous stenting, and liver transplantation in the management of patients with primary sclerosing cholangitis (PSC).

Summary Background Data

Primary sclerosing cholangitis is a progressive inflammatory disease leading to secondary biliary cirrhosis. The most effective management of sclerosing cholangitis before the onset of cirrhosis remains unclear.

Methods

From 1980 to 1994, 146 patients with PSC were managed with either resection of the extrahepatic bile ducts and long-term transhepatic stenting (50 patients), nonoperative endoscopic biliary dilation with or without percutaneous stenting (54 patients), medical therapy (28 patients), and/or liver transplantation (21 patients).

Results

Procedure-related morbidity and mortality rates were similar between surgically resected and nonoperatively managed patients. In noncirrhotic patients, the serum bilirubin level was significantly ($p < 0.05$) reduced from preoperative levels (8.3 ± 1.5 mg/dL) 1 (1.7 ± 0.4 mg/dL) and 3 (2.7 ± 0.9 mg/dL) years after resection, but not after endoscopic or percutaneous management. For noncirrhotic PSC patients, overall 5-year survival (85% *vs.* 59%) and survival until death or transplantation (82% *vs.* 46%) were significantly longer ($p < 0.05$) after resection than after nonoperative dilation with or without stenting. For cirrhotic patients, survival after liver transplantation was longer than after resection or nonoperative dilation with or without stenting. Five patients developed cholangiocarcinoma, including three (6%) of the nonoperatively managed patients but none of the resected patients.

Conclusions

In carefully selected noncirrhotic patients with PSC, resection and long-term stenting remains a good option. Patients with cirrhosis should undergo liver transplantation.

Primary sclerosing cholangitis (PSC) is an idiopathic chronic inflammatory disease resulting in multifocal intra- and extrahepatic biliary strictures, chronic cholestasis, and eventually cirrhosis.[1–4] Once cirrhosis develops, liver transplantation is the only therapeutic option. However, the appropriate management of PSC patients early in the course of their disease remains controversial. Options include medications, endoscopic or percutaneous dilation with or without stenting, various biliary tract surgical procedures, and transplantation.

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Over the past 15 years, several centers have reported good results after extrahepatic biliary resection or bypass with long-term improvement in jaundice and survival in noncirrhotic patients.[5–7] However, results of less extensive biliary operations have been disappointing, and concerns have been raised about the advisability of performing any extrahepatic biliary operation in a patient who may subsequently require liver transplantation.[5,7–10] More recently, several nonoperative methods have been reported to relieve cholangitis and improve liver function.[11–14] Endoscopic balloon dilation with or without stenting and percutaneous transhepatic stenting have the advantage of avoiding an operative procedure before liver transplantation. As a result, these techniques have become popular in managing biliary

obstruction in noncirrhotic PSC patients. However, little information exists on the effect of nonoperative biliary procedures on the natural history and ultimate need for liver transplantation in PSC patients. Similarly, drug therapy with ursodeoxycholic acid or methotrexate has been demonstrated to improve liver function tests, but its effect on survival has yet to be documented.[15,16]

To document the effect of extrahepatic biliary surgery, endoscopic balloon dilation, percutaneous transhepatic stenting, and liver transplantation on the natural history of PSC patients, we reviewed our experience with 146 patients managed at The Johns Hopkins Medical Institutions over a 15-year period. Patients with dominant extrahepatic and hilar strictures have been managed with biliary resection, endoscopic dilation, and/or long-term percutaneous stenting. In addition, patients with end-stage liver disease have undergone liver transplantation. The current study examines the role of each of these procedures in the management of PSC patients.

MATERIALS AND METHODS

Patients

From 1980 through 1994, 146 PSC patients were managed at The Johns Hopkins Hospital. All patients had cholangiographic findings consistent with a diagnosis of PSC, including multifocal stricturing of the intra- or extrahepatic bile ducts, or both.[17] Cholangiographic findings were supported by a clinical history and histologic specimens consistent with PSC. Patients with diffuse biliary strictures secondary to 5-fluorouracil deoxyribonucleoside (FUDR) administration (n = 2) or AIDS were excluded from this analysis. Eight patients had cancer (six cholangiocarcinomas, one gallbladder cancer, and one pancreatic cancer) diagnosed before referral or during initial evaluation at Johns Hopkins. One of these patients was managed with resection of a cholangiocarcinoma, one patient received a liver transplant, and the remainder of the patients were managed with palliative endoscopic or percutaneous stenting. These eight patients were not included in further data analysis.

Patient characteristics are shown in Table 1. The mean age for the remaining 138 patients was 47 years (range 7–89 years). Eighty-nine patients (64%) were male, and 116 (84%) were white. Seventy-seven patients (56%) had inflammatory bowel disease, including 57 with ulcerative colitis, 16 with Crohn's disease, and 4 with nonspecific colitis. Thirty-five patients (25%) had established cirrhosis at the time of referral to Johns Hopkins. Other associated diseases included peptic ulcer disease (12 patients), pancreatitis (11 patients), diabetes (9 patients), and colon cancer (4 patients).

Fifty-eight patients (42%) had had at least one biliary tract operation before referral. Thirty-three patients (24%) had a previous simple cholecystectomy, 25 (18%) underwent prior cholecystectomy, common bile duct exploration, and T-tube drainage, and 16 (12%) had undergone a more complex biliary reconstruction with biliary-enteric anastomosis. Forty-two patients (30%) had had a single previous biliary tract operation, whereas 16 (12%) had undergone two or more prior operations. The treatment groups did not differ significantly in any of these parameters.

Surgical Management

Fifty of the 138 patients (36%) were managed operatively, primarily with resection of the extrahepatic biliary tree and long-term transhepatic stenting. The operative technique used and early results in the initial 31 patients were reported previously.[5] Preoperatively, percutaneous Ring catheters were inserted bilaterally in 19 patients and unilaterally in 19 patients to serve as technical aids at the time of exploration. Twelve patients, all early in the series, were explored without a preoperatively placed transhepatic biliary stent. In 40 patients, the extrahepatic biliary tree and hepatic duct bifurcation were resected as described previously.[5] The intrahepatic biliary tree was then dilated, and 16 Fr. Silastic stents were placed, using the previously placed Ring catheters. Silastic stents were placed unilaterally in 6 patients and bilaterally in 29 patients. Five patients with a hepatic duct trifurcation had three stents placed.

Cholangiojejunostomies were then performed between individual intrahepatic ducts and a Roux-en-Y loop of jejunum. Ten patients with dominant strictures confined to the common bile duct underwent resection of the common bile duct and common hepatic duct excluding the bifurcation and hepaticojejunostomy. One patient thought pre- and intraoperatively to have pancreatic cancer underwent resection of his extrahepatic biliary tree as part of a pancreatoduodenectomy. A single right-sided transhepatic stent was placed across the anastomosis in these 10 patients. Patients managed with extrahepatic biliary resection both with and without resection of the hepatic duct bifurcation were analyzed together as one group. All resected patients were managed postoperatively with long-term transhepatic stents. Seven patients (14%) also received ursodeoxycholic acid during the postoperative period. Most of these patients were managed before 1990 (Fig. 1).

Endoscopic Management

Fifty-four patients were managed nonoperatively with a combination of interventional techniques, including endoscopic biliary dilation with or without percutaneous transhepatic stenting. Patients managed with both endoscopic dilation and percutaneous stenting were grouped according to the method with which they were treated longer or that had the best results. Thirty-nine patients were initially managed endoscopically, and two additional patients were dilated endoscopically after percutaneously placed transhepatic stents had been removed. Endoscopic therapy was

Table 1. PATIENT CHARACTERISTICS*

	Resection (n = 50)	ES/BD (n = 35)	Percutaneous Stenting (n = 19)	Combined Nonoperative (n = 54)	Transplant (n = 21)	All Patients (n = 138)
Age (yr)						
Mean	47	45	55	49	40	47
Range	21–76	22–89	27–79	22–89	22–65	7–89
Age of onset of PSC (yr)	46	44	52	47	38	45
Gender						
Men	34	24	10	34	14	89
Women	16	11	9	20	7	49
Race						
White	40	30	17	47	18	116
Black	9	4	2	6	3	20
Asian	1	1	0	1	0	2
IBD						
UC	13	17	5	22	12	57
CD	7	4	1	5	3	16
Nonspecific	1	3	0	3	1	4
None	29	11	13	24	5	61
Cirrhosis	10	9	2	11	20	35
Prior surgery						
None	25	22	6	28	9	80
CCY	13	7	8	15	6	33
CCY/CBDE	11	7	5	12	5	25
Biliary enteric anastomosis	6	1	7	8	4	16
Prior biliary surgery (no.)						
None	25	22	6	28	9	80
1	20	11	6	17	9	42
2	5	2	6	8	3	15
3	0	0	1	1	0	1

* Data presented for the patients managed with surgical resection, endoscopic balloon dilation and percutaneous transhepatic stenting and for all 138 patients with PSC are at the time of initial presentation to The Johns Hopkins Hospital. Data presented for the transplanted patients are at the time of liver transplantation. Of the 21 patients undergoing liver transplantation, 15 were initially managed with resection, endoscopic dilation and/or percutaneous stenting and are also included in these groups. Twenty-eight patients managed without any invasive attempts at improving biliary drainage are included only in the last column (all patients).
ES/BD = endoscopic sphincterotomy plus balloon dilation; PSC = primary sclerosing cholangitis; IBD = inflammatory bowel disease; UC = ulcerative colitis; CD = Crohn's disease; CCY = cholecystectomy; CBDE = common bile duct exploration.

initially successful in 35 patients. After sphincterotomy, endoscopic biliary catheters were guided into the proximal biliary tree under fluoroscopic guidance. Biliary strictures were dilated sequentially using 4- to 8-mm high-pressure balloons. Postprocedure cholangiograms were obtained to monitor the results of the dilation. Endoscopically placed stents were used in two patients to maintain biliary drainage after dilation. Twenty-nine patients (83%) undergoing endoscopic biliary dilation also received ursodeoxycholic acid. Most of these patients were managed after 1990 (see Fig. 1).

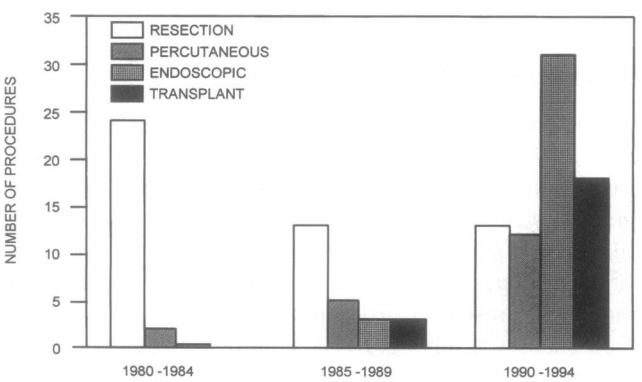

Figure 1. Management by time period.

Percutaneous Management

Nineteen of the 138 patients were managed with percutaneous techniques. This group included one patient in whom initial endoscopic dilation was unsuccessful and three additional patients with persistent jaundice, cholangitis, or both after partial endoscopic dilation of the distal extrahepatic biliary tree. Catheters (8.3 Fr Ring) were

placed unilaterally (10 patients), bilaterally (7 patients), or into three hepatic segments (2 patients). During the initial hospital admission, catheters were usually upsized to 12 or 14 Fr before discharge. Dominant strictures in three patients were balloon-dilated percutaneously through the tube tract. Ten patients (53%) managed with percutaneous stents also received ursodeoxycholic acid. Stent changes were performed over a guidewire every 2 to 3 months, or earlier if patients developed stent occlusion, leakage, or cholangitis. The percutaneous and endoscopic nonoperative treatment groups were analyzed both separately and together as one group.

Liver Transplantation

Twenty-one patients were managed with orthotopic liver transplantation between 1988 and 1994 (see Fig. 1). Six of these patients were treated initially without any prior attempt at biliary drainage. Fifteen patients were transplanted after previous extrahepatic biliary resection (3 patients), endoscopic dilation (10 patients), or percutaneous stenting (2 patients). Biliary reconstruction at transplantation was performed by Roux-en-Y hepaticojejunostomy (19 patients) or choledochocholedochostomy (2 patients). Posttransplant immunosuppression consisted of prednisone, azathioprine, and cyclosporine or FK506.

Medical Management

Twenty-eight patients were managed without any invasive attempts at establishing improved biliary drainage. These patients received corticosteroids (9 patients), ursodeoxycholic acid (10 patients), and/or methotrexate (1 patient) at the discretion of their managing physician. Four of these patients underwent cholecystectomy for symptoms related to gallstones (two open and two laparoscopic). Two patients received liver transplants elsewhere before 1988. Eight of these patients are currently on the waiting list for liver transplantation. Because of the heterogeneity of the patients in this group, they have not been included in the remainder of this analysis. Initial management for all other patients is shown in Figure 1 for three 5-year periods between 1980 and 1994.

Risk Score

A risk score was calculated for each patient at the time of the initial operative or interventional procedure according to a multicenter survival model for PSC.[18] These scores were used to compare disease severity among treatment groups. Patients were stratified into low-, moderate-, and high-risk groups, as described previously.[18] Risk scores were calculated from the patient's age, serum bilirubin level, histologic stage according to the Ludwig criteria, and presence or absence of splenomegaly.[18,19] Histologic stage was determined from hepatic biopsies obtained percutaneously or at the time of operative exploration. In addition, patients with unequivocal evidence of portal hypertension on imaging studies were assigned histologic stage 4. Splenomegaly was diagnosed on physical examination or by computed tomography or magnetic resonance scans.

Forty of the 50 surgical resection patients (80%) were noncirrhotic. Similarly, 43 of the 54 combined nonoperative patients (80%) were noncirrhotic. In comparison, only 1 of the 21 liver transplant patients (5%) did not have established cirrhosis. The surgical resection and combined nonoperative patients were also stratified by risk score. Low-risk patients had scores of 1.02 to 3.56, moderate-risk patients 3.57 to 4.82, and high-risk patients 4.87 to 6.28. The relative percentage of low-, moderate-, and high-risk patients were 44%, 40%, and 16%, respectively, for the surgical resection patients and 45%, 29%, and 26%, respectively, for the combined nonoperative patients. These differences were not statistically significant.

Indications for Treatment

The symptoms, total serum bilirubin level, and risk score at the time treatment was initiated are shown in Table 2. Overall, 94% of the patients were symptomatic at the time treatment was initiated. All the patients undergoing surgical resection or liver transplantation were symptomatic, whereas 94% of the patients treated with endoscopic or percutaneous techniques were symptomatic. The primary indications for treatment in all groups were persistent jaundice and cholangitis. Mean total serum bilirubin levels were highest in the transplant patients (13.0 ± 2.2 mg/dL), intermediate in the surgical resection patients (8.8 ± 1.3 mg/dL), and lowest in the combined nonoperative group (5.8 ± 0.8 mg/dL). Similarly, risk scores were highest in the transplant patients (5.28 ± 0.15) but similar in the surgical (3.75 ± 0.15) and nonoperative (3.80 ± 0.15) patients. Risk scores were slightly, but not significantly, higher in the percutaneously managed patients than in the endoscopically managed patients.

Follow-up and Statistics

Follow-up data were obtained from medical records or personal contact with living patients. Postoperative and postprocedure complications were obtained from review of hospital or interventional radiology records. Follow-up was complete in 97% of patients managed with resection, nonoperative biliary dilation with or without stenting, and transplantation. Overall survival was calculated from the date of the initial procedure until death or last known follow-up. Transplant-free survival was calculated from the date of the initial procedure until liver transplantation or death. Actuarial survival curves were calculated using the Kaplan-Meier method.[20] Survival curves were compared using the log-rank sum test. Comparisons between continuous data were made using Student's t test or analysis of variance;

Table 2. SYMPTOMS, BILIRUBIN, AND RISK SCORE

	Resection (n = 50)	ES/BD (n = 35)	Percutaneous Stenting (n = 19)	Combined Nonoperative (n = 54)	Transplant (n = 21)	All Patients (n = 138)
Symptoms (%)*						
Jaundice	87	67	89	76	86	74
Pain	37	38	47	42	38	39
Pruritus	26	48	32	42	43	31
Cholangitis	37	17	42	27	29	27
None	0	6	5	6	0	6
Bilirubin* (mg/dL)	8.8 ± 1.3	5.6 ± 1.0†	5.7 ± 1.0	5.8 ± 0.8†	13 ± 2.2	7.3 ± 0.8
Risk Score*	3.75 ± 0.15†	3.66 ± 0.24†	4.08 ± 0.39†	3.80 ± 0.20†	5.28 ± 0.15	3.74 ± 0.13

* At the time that treatment was initiated.
† $p < 0.05$ *versus* transplant.
ES/BD = endoscopic sphincterotomy plus balloon dilation.

comparisons between noncontinuous data were made using Fisher's exact test.

RESULTS

Morbidity, Mortality, and Hospital Stay

Three of the 50 patients (6%) managed with resection of the extrahepatic biliary tree died before discharge from the hospital. All three died after a prolonged hospital course with sepsis and liver failure. All three died before 1985, and two of the three had cirrhosis. Operative mortality in patients with and without cirrhosis was 20% and 2.5%, respectively. Postoperative complications developed in 16 patients (32%) (Table 3). Cholangitis was the most frequent complication and occurred in five patients (10%). Four patients, including two who died, developed hemobilia related to the transhepatic stent. In all cases, bleeding was controlled with hepatic artery embolization; however, this procedure may have hastened the development of liver failure in the two patients who died. The overall hospital stay was 24 ± 2 days for the resected patients; however, since 1988 the mean postoperative stay has been only 14 ± 1 days.

Endoscopic biliary dilation was attempted in 41 patients, with no postprocedure mortality. A total of 119 procedures were performed in these 41 patients over a mean follow-up period of 26 months. Thirty-five patients were successfully dilated a mean of 3.2 times, with cholangiographic improvement in some of their biliary strictures. In four patients, the first attempt at endoscopic balloon dilation was unsuccessful, and these patients were not included in the analysis of the endoscopically managed patients. Three of these pa-

Table 3. PROCEDURE-RELATED COMPLICATIONS

Hospital Morbidity	Resection (n = 50)	ERCP/BD (n = 35)	Percutaneous Stenting (n = 19)	Transplant (n = 21)
Cholangitis	5	1	5	0
Sepsis	3	0	2	3
Liver failure	3	0	2	1
Hemobilia	4	0	2	0
Pancreatitis	1	4	0	0
Intraabdominal hemorrhage	0	0	0	4
Wound infection	3	0	0	1
Intraabdominal abscess	1	0	2	0
Bile fistula	1	0	0	1
Ascitic leak	1	0	0	1
Upper gastrointestinal hemorrhage	1	0	0	1
Miscellaneous	2	0	1	7
Total complications	25	5	13	19
Total patients with complications	16 (32%)	5 (14%)	8 (42%)	11 (52%)

ES/BD = endoscopic sphincterotomy plus balloon dilation.

Table 4. OPERATIVE TIME AND ESTIMATED BLOOD LOSS DURING LIVER TRANSPLANT

Group	n	Mean Operative Time (hours/minutes)	EBL (mL)	RBC (units)	Mortality (%)
All patients	21	11:40 ± 0:40	7200 ± 2200	16 ± 4	19
No prior biliary tract operation	9	9:20 ± 0:20	3400 ± 1200	7 ± 2	11
Any prior biliary tract operation	12	13:10 ± 0:50*	9700 ± 3400	21 ± 6	25
Prior cholecystectomy	5	13:00 ± 1:20*	15000 ± 7900	27 ± 13	20
Prior biliary enteric bypass	4	13:40 ± 1:50*	4580 ± 1400	11 ± 3	25

* $p < 0.05$ *versus* no prior biliary tract operation.
EBL = estimated blood loss; RBC = red blood cell.

tients were managed subsequently with percutaneous stenting, and one patient had no further attempts at biliary drainage. Two patients were managed with a single endoscopic dilation after removal of percutaneously placed stents and were not included with the endoscopically managed patients. The overall complication rate was only 14%, and the most common complication was mild pancreatitis, which occurred in four patients (11%) (see Table 3). Intraparenchymal contrast extravasation on completion cholangiography occurred in seven patients (20%). All these patients were managed expectantly with antibiotics, and none developed a biloma or abscess requiring drainage. The overall hospital stay for the initial dilation was 4 ± 0.7 days.

Two hospital deaths occurred in the 19 patients (10.5%) managed with long-term percutaneous stenting. One patient with cirrhosis and cholangitis died of a variceal hemorrhage after several attempts at percutaneous biliary drainage. The second death occurred in a patient with persistent cholangitis after unsuccessful endoscopic dilation. After placement of bilateral percutaneous stents, the patient developed hemobilia requiring hepatic artery embolization. He died several days later of liver failure. The overall complication rate was 42% (see Table 3). A second patient with hemobilia required hepatic artery embolization, and two subphrenic abscesses were managed with percutaneous drainage. In addition, one patient had a percutaneous biliary stent placed through the transverse colon, leading to the formation of an intra-abdominal abscess. This patient was managed with operative drainage of the abscess, right hemicolectomy, and ileostomy. Since 1988, the mean hospital stay after percutaneous stent placement has been 14 ± 3 days.

Four of 21 patients (19%) died after liver transplantation. One patient died of hemorrhage from the gastroduodenal artery on the fourth postoperative day. The others died of sepsis and multiple organ failure. Eleven of the 21 patients (52%) developed postoperative complications after liver transplantation (see Table 3). Four patients, including the one postoperative death, were re-explored for intra-abdominal hemorrhage in the early postoperative period. One patient received a second transplant after primary failure of the initial graft. In addition, acute rejection occurred in 15 patients (71%) after liver transplantation, but it responded to pulse steroids, OKT3, or both in all patients.

Mean operative time and estimated blood loss for liver transplantation are shown in Table 4. Operative time for liver transplant was significantly shorter ($p < 0.05$) in patients who had had no previous biliary tract operations. Biliary resection and biliary enteric anastomosis did not increase estimated blood loss or operative time above values associated with cholecystectomy alone. Operative mortality was not statistically different between patients having prior biliary tract surgery (25%) and those without prior biliary tract surgery (11%).

Long-Term Results

Overall and transplant-free survival rates for the resected, endoscopically dilated, percutaneously stented, and transplanted patients are shown in Tables 5 and 6, respectively. The 1-, 3-, 5-, and 10-year overall survival rates for all 138 PSC patients were 86%, 81%, 71%, and 56%, respectively.

The mean length of follow-up for patients managed with extrahepatic biliary resection was 62 months. Fourteen patients (28%) have died during long-term follow-up after operative resection. Nine of the late deaths after surgery were due to progressive liver failure and complications of portal hypertension. One patient died with uncontrolled sepsis and multiple hepatic abscesses. Two patients died, one early and one late, after liver transplantation. Two patients died of unrelated causes. None of the resected patients have developed cholangiocarcinoma in 3101 months of follow-up. One patient had a colon cancer resected 6 months before undergoing biliary resection and is without evidence of recurrent disease 9 years later. One of the 10 patients managed initially with a choledochojejunostomy for a dominant distal bile duct stricture developed recurrent proximal extrahepatic biliary strictures requiring reoperation, hepaticojejunostomy, and long-term transhepatic stenting. Overall 1-, 3-, 5-, and 10-year survival rates after bile duct resection were 86%, 84%, 76%, and 55%, respectively (see Table 5). Patients without cirrhosis fared better, with 1-, 3-, 5-, and 10-year overall survival rates of 95%, 92%, 85%, and 68%, respectively (Fig. 2).

Seven patients (14%) underwent liver transplantation after resection of the extrahepatic biliary tree. The mean interval between resection and transplant was 63 months

Table 5. OVERALL SURVIVAL BY TREATMENT METHOD ACTUARIAL SURVIVAL IN YEARS (%)

Patients	n	Risk Score	1 Year	3 Year	5 Year
All patients					
Resection	50	3.75 ± 0.15	86	84	76
ES/BD	35	3.66 ± 0.24	91	80	68
Percutaneous stenting	19	4.08 ± 0.39	84	79	60
Combined nonoperative	54	3.80 ± 0.20	86	76	64
Liver transplant	21	5.28 ± 0.15	81	81	–
All patients	138	3.74 ± 0.13	86	81	71
Noncirrhotic patients					
Resection	40	3.36 ± 0.12	95	92	85
ES/BD	26	3.13 ± 0.27	88	72*	58*
Percutaneous stenting	17	3.59 ± 0.28	87	79	63
Combined nonoperative	43	3.27 ± 0.21	87	74†	59†
Liver transplant	1	3.34 ± 0.00	100	–	–
Cirrhotic patients					
Resection	10	5.11 ± 0.17	50	38	38
ES/BD	9	4.73 ± 0.19	100	100	–
Percutaneous stenting	2	6.05 ± 0.17	50	–	–
Combined nonoperative	11	4.95 ± 0.20	92	92	–
Liver transplant	20	5.30 ± 0.15	80	80	–

* $p < 0.01$ versus resection.
† $p < 0.05$ versus resection.
ES/BD = endoscopic sphincterotomy plus balloon dilation.

(range 7–139 months). Three of these transplants were performed at Johns Hopkins, and four were performed elsewhere before 1988. Two of these patients have subsequently died: one died of sepsis in the perioperative period, and the other died 2 years after the transplant of chronic rejection. The transplant-free survival rates at 1-, 3-, 5-, and 10 years after extrahepatic bile duct resection were 86%, 81%, 71%, and 31%, respectively (see Table 6). Noncirrhotic patients

Table 6. TRANSPLANT-FREE SURVIVAL BY TREATMENT METHOD ACTUARIAL SURVIVAL IN YEARS (%)

Patients	n	Risk Score	1 Year	3 Year	5 Year
All patients					
Resection	50	3.75 ± 0.15	86	81	71
ES/BD	35	3.66 ± 0.24	76	55†	36*
Percutaneous stenting	19	4.08 ± 0.39	84	61	49
Combined nonoperative	54	3.80 ± 0.20	78	57†	40*
Liver transplant	21	5.28 ± 0.15	81	81	–
Noncirrhotic patients					
Resection	40	3.36 ± 0.12	95	92	82
ES/BD	26	3.13 ± 0.27	83	56*	42*
Percutaneous stenting	17	3.59 ± 0.28	87	64†	51†
Combined nonoperative	43	3.27 ± 0.21	85	59*	46*
Liver transplant	1	3.34 ± 0.00	100	–	–
Cirrhotic patients					
Resection	10	5.11 ± 0.17	50	38	25
ES/BD	9	4.73 ± 0.19	56	56	–
Percutaneous stenting	2	6.05 ± 0.17	50	–	–
Combined nonoperative	11	4.95 ± 0.20	58	47	–
Liver transplant	20	5.30 ± 0.15	80	80	

* $p < 0.01$ versus resection.
† $p < 0.05$ versus resection.
ES/BD = endoscopic sphincterotomy plus balloon dilation.

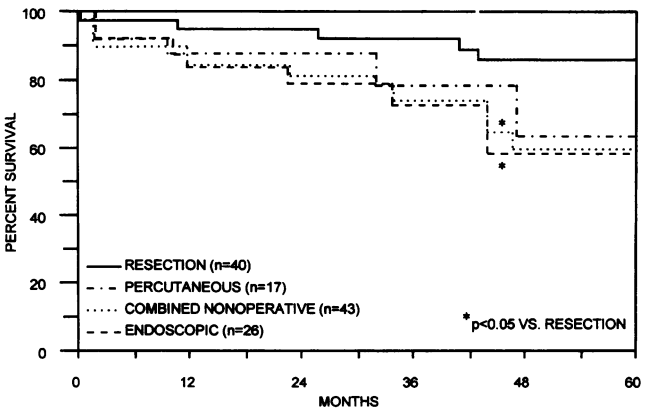

Figure 2. Overall survival for noncirrhotic patients with primary sclerosing cholangitis by treatment method. Overall survival for resected patients was significantly longer than for patients managed with endoscopic dilation ($p < 0.01$) or with both nonoperative techniques ($p < 0.05$).

had transplant-free survival rates of 95%, 92%, 82%, and 53%, respectively, at 1-, 3-, 5-, and 10 years after resection (Fig. 3).

Transhepatic Silastic stents were left in place postoperatively in all patients. Stents were later removed in 6 patients, with subsequent reinsertion in one patient because of jaundice and recurrent cholangitis. Stents remained in place until transplant, death, or last follow-up in the remaining 44 patients. Twenty-three patients continue to be managed with transhepatic stent changes at Johns Hopkins. These patients have undergone 424 stent changes during 945 months of follow-up, or on average once every 2.2 months.

Mean follow-up after endoscopic biliary dilation in 35 patients was 26 months. Seven patients (20%) died during long-term follow-up. Three patients, including one with cirrhosis at initial presentation, died of liver failure. Two patients died of colon cancer. Three patients developed cholangiocarcinoma during 916 patient-months of follow-up. Cholangiocarcinoma was diagnosed at 17, 18, and 25 months after initial endoscopic dilation. Two of these patients died 6 and 10 months after the diagnosis of cholangiocarcinoma; the other is alive 13 months after liver transplantation with no evidence of disease. Overall survival rates 1, 3, and 5 years after endoscopic biliary dilation were 91%, 80%, and 68%, respectively (see Table 5). Noncirrhotic patients had 1-, 3-, and 5-year survival rates of 88%, 72%, and 58%, respectively (see Fig. 2). The 3- and 5-year survival rates were significantly lower ($p < 0.01$) than for surgical resection.

Ten patients (29%) received liver transplants after initial treatment with endoscopic biliary dilation. The mean interval between endoscopic dilation and transplantation was 17 months. All 10 were transplanted at Johns Hopkins and are alive. Transplant-free survival rates 1, 3, and 5 years after endoscopic biliary dilation were 76%, 55%, and 36%, respectively, in all patients and 83%, 56%, and 42%, respectively, in the patients without cirrhosis (see Table 6, Fig. 3). The 3- and 5-year transplant-free survival rates were significantly lower ($p < 0.01$) when the noncirrhotic endoscopically managed patients were compared to those undergoing surgery.

Nineteen patients managed with percutaneous stents were followed for a mean of 26 months. Two late deaths (11%) were due to liver failure. No patient managed with percutaneous stents developed cholangiocarcinoma during 530

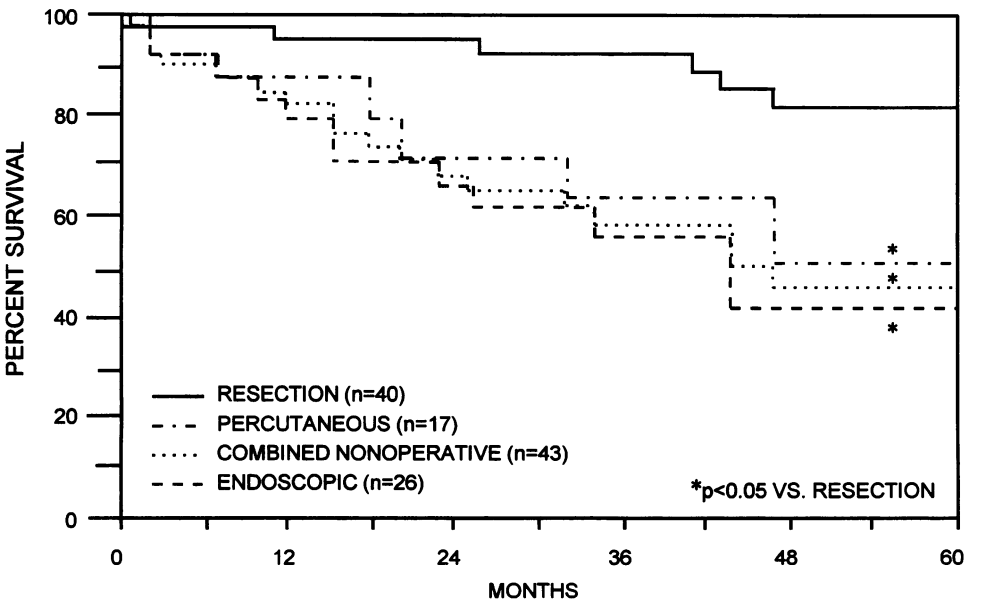

Figure 3. Transplant-free survival for noncirrhotic patients with primary sclerosing cholangitis. Transplant-free survival for resected patients was significantly longer than for patients managed with endoscopic dilation ($p < 0.01$), percutaneous stenting ($p < 0.05$), or both nonoperative techniques ($p < 0.01$).

Table 7. TRANSPLANT-FREE SURVIVAL BY RISK GROUP ACTUARIAL SURVIVAL (%)

Groups	n	1 Year	3 Year	5 Year
Low risk group (1.02 to 3.56)				
Resection	20	100	94	88
Combined nonoperative	17	100	60*	50*
Moderate Risk Group (3.57 to 4.82)				
Resection	18	83	83	75
Combined nonoperative	11	64	55	28*
High risk group (4.87 to 6.28)				
Resection	7	43	28	14
Combined nonoperative	10	45	45	0

* $p < 0.05$ versus resection.

patient-months of follow-up. In addition, no patients managed with percutaneous transhepatic stents have had colon cancer. Stents remained in place until transplantation, death, or last follow-up in 16 patients. Stents were removed in three patients 2, 8, and 19 months after initial placement. Percutaneous stents were changed on average every 1.8 months. Overall survival rates at 1, 3, and 5 years after percutaneous biliary drainage were 84%, 79%, and 60%, respectively, in all patients and 87%, 79%, and 63%, respectively, in patients without cirrhosis (see Table 5, Fig. 2).

Three patients (16%) received liver transplants 19, 21, and 48 months after initial management with percutaneous stents. One of the patients died in the perioperative period, and two are alive 11 and 17 months after transplantation. Transplant-free survival rates at 1, 3, and 5 years were 84%, 61%, and 49%, respectively. Transplant-free survival rates after percutaneous stenting in noncirrhotic patients were 87%, 64%, and 51% at 1, 3, and 5 years, respectively (see Table 6, Fig. 3). The 3- and 5-year transplant-free survival rates were significantly lower ($p < 0.05$) when the percutaneously stented noncirrhotic patients were compared to their surgically managed counterparts.

Overall, 54 patients were managed with a combination of nonoperative endoscopic and percutaneous techniques. Overall and transplant-free survival rates in patients managed with nonoperative biliary drainage are shown in Tables 5 and 6. Both overall and transplant-free survivals after extrahepatic biliary resection were significantly longer in noncirrhotic patients than after nonoperative biliary drainage. Resected and nonoperatively managed patients also were stratified into low-, moderate-, and high-risk groups according to preprocedure Mayo model risk scores (Table 7).[16] Transplant-free survival after resection was significantly longer than after nonoperative management for both low- and moderate-risk patients. No survival difference existed between treatments for high-risk patients, most of whom had cirrhosis.

Long-term survival after liver transplantation is shown in Table 5. Four perioperative and no late deaths occurred after liver transplantation for PSC. Survival rates at 1 and 3 years after liver transplantation were both 81%. One patient developed recurrent sclerosing cholangitis 35 months after his initial transplantation and was retransplanted.

Serum bilirubin levels both before and after extrahepatic biliary resection and combined nonoperative management in noncirrhotic patients are shown in Figure 4. Biliary resection significantly reduced serum bilirubin levels at 1, 2,

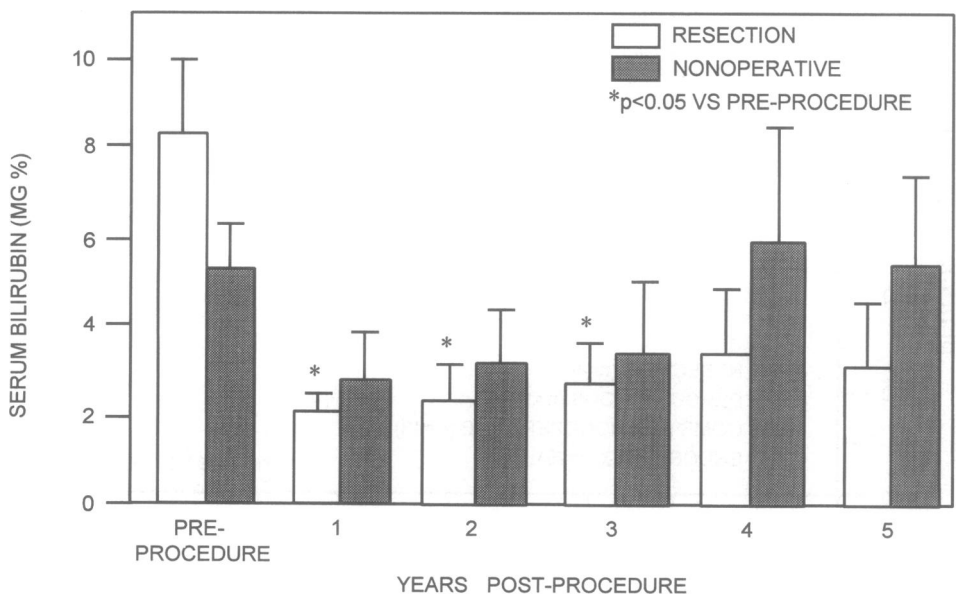

Figure 4. Serum bilirubin levels after resection and nonoperative biliary drainage. Serum bilirubin levels were significantly ($p < 0.05$) lower 1, 2, and 3 years after resection compared to preoperative levels.

and 3 years after resection when compared to preoperative levels. Nonoperative biliary dilation or stenting reduced serum bilirubin levels, but this difference did not achieve statistical significance. At 1 year, none of the cirrhotic patients managed nonoperatively with endoscopic dilation or percutaneous stenting with an initial bilirubin level of 5.0 mg/dL or greater had a decrease from the initial level.

Since 1988, the initial hospital stay has been 14 ± 1 days for surgical resection compared to 4 ± 0.7 days for endoscopic dilation, 14 ± 3 days for percutaneous stenting, and 20 ± 2 days for transplantation. The hospital stay after endoscopic dilation was significantly ($p < 0.001$) shorter than the hospital stay after resection, percutaneous stenting, or transplantation. Mean annual inpatient hospital stays were also calculated for each patient group from the time of their initial biliary drainage procedure until last follow-up, transplant, or death. Patients managed with resection of the extrahepatic biliary tree, endoscopic biliary drainage, or percutaneous stenting spent a mean of 3.7, 7.1, or 3.3 days per year in the hospital, respectively. These differences were not statistically significant.

DISCUSSION

Primary sclerosing cholangitis is a progressive disease that eventually leads to cirrhosis, portal hypertension, and liver failure.[3,4] Short-term improvement in symptoms and the serum bilirubin level have been reported with ursodeoxycholic acid, methotrexate, endoscopic dilation, and percutaneous dilation and stenting.[11–14,15,16] Longer follow-up is available for operatively managed patients; however, results vary considerably among reported series.[5–10] Despite the variety of therapeutic options, only the use of liver transplantation in patients with advanced disease has been shown convincingly to alter the natural history.[9,21]

Although PSC involves both intrahepatic and extrahepatic bile ducts in most patients, the hepatic duct bifurcation is often the most severely involved region.[17,22] Recognizing this distribution, the surgical approach used in the current series involves resection of the entire extrahepatic biliary tree, including the hepatic duct bifurcation, and dilation of the intrahepatic biliary tree.[5] Long-term transhepatic stents are used to prevent restricturing of the intrahepatic bile ducts. This approach has produced a lasting decrease in the serum bilirubin level and good overall and transplant-free survival in patients without cirrhosis.[5]

Myburgh[7] reported results with the Hepp-Couinaud hepaticojejunostomy in PSC patients. Actuarial survival in the 16 patients without cirrhosis managed with this approach was 100% with a median follow-up of 6.5 years. This approach leaves *in situ* the extrahepatic biliary tree, with its malignant potential, but clearly improves the natural history of this disease in patients with dominant hilar and extrahepatic strictures. The variability of results reported with surgical therapy of PSC may be due to the extent of biliary resection: resection of the distal extrahepatic biliary tree without including a dominant hilar stricture will lead to predictably poor results.

More recently, endoscopic and percutaneous methods for biliary dilation have evolved, providing a group of nonoperatively managed patients. Although follow-up was shorter in the nonoperatively managed patients in this report, pretreatment risk scores were similar between the operatively and nonoperatively managed patients (see Table 2). Several centers have reported series of patients with major ductal strictures associated with PSC managed with endoscopic biliary dilation.[12–14] Most patients had improvement in their predilation symptoms, and the mean serum bilirubin level was decreased in all three series after short follow-up. Johnson et al.[12] reported a persistent decrease in the serum bilirubin level 2 years after the initial dilation; this was not observed in our series. However, none of these series have examined the long-term effect of nonoperative biliary dilation on survival or the eventual need for liver transplantation.

Transplant-free survival was significantly longer after surgical resection than after either endoscopic biliary dilation or long-term percutaneous stenting. Fewer initially noncirrhotic patients (18%) had died or needed a liver transplant 5 years after biliary resection than in the 5 years after nonoperative biliary dilation (54%). Overall survival after resection was also significantly longer than after nonoperative biliary drainage. This difference was due in part to the higher incidence of cholangiocarcinoma after nonoperative therapy.

Liver transplantation is clearly the best treatment option once cirrhosis has developed. Results of nontransplant surgical treatment in cirrhotic patients were poor in our study, with a high operative mortality (20%) and a poor long-term survival rate (38% transplant-free survival at 3 years). Similar results of nontransplant surgical therapy have been reported by others in cirrhotic patients.[7–10] Currently, the only indication for nontransplant operative management in the cirrhotic PSC patient is the suspicion of a cholangiocarcinoma. Results of endoscopic balloon dilation and percutaneous stenting were similar to those of resection for cirrhotic patients; neither procedure delayed the need for liver transplantation. In addition, patients with a serum bilirubin level >5.0 mg/dL and cirrhosis had no long-term decrease in their serum bilirubin level after either endoscopic dilation or percutaneous stenting. Biliary dilation is of little benefit in cirrhotic patients, except possibly in the patient with episodes of cholangitis. In patients with cholangitis and cirrhosis, endoscopic balloon dilation is safer and has a lower procedure-related mortality than percutaneous stenting.

The impact of each biliary drainage procedure on the future results of liver transplantation is an important consideration in selecting therapy for PSC patients. Several authors have expressed concern about the effect of prior biliary surgery on the morbidity and mortality of a future liver transplant.[9,10,23,24] In the largest reported series of liver

transplantation for PSC, a trend toward decreased survival was noted in patients who had had prior biliary tract or prior portal hypertensive surgery.[21] However, this trend did not reach statistical significance, and the effect of biliary tract surgery alone on survival was not reported.

Farges et al.[9] reported an increase in operative mortality and morbidity and an increase in operative time and blood loss in patients who had had any prior abdominal operation before liver transplantation for PSC. In comparison, Narumi et al.[25] noted an increase in operative time and blood loss without an increase in morbidity or mortality. In our series, only operative time was significantly increased in patients who had had any prior biliary operation, including cholecystectomy. A trend toward increased blood loss and mortality was observed in the patients who had had prior surgery; however, this increase was similar for simple cholecystectomy, cholecystectomy plus T-tube drainage, or biliary-enteric anastomosis. Thus, this increase in operative risk for liver transplantation is often present at the time of referral to a tertiary center. Approximately 50% of the resected, nonoperatively managed, and transplanted patients had already had a biliary operation before referral to The Johns Hopkins Hospital for management of their PSC.

With recent improvements in survival after liver transplantation for PSC, some authors have advocated performing a liver transplant earlier in the course of the disease.[9] Several studies have demonstrated a significant improvement in long-term survival after transplantation when compared to the predicted survival in high-risk cirrhotic PSC patients who are not transplanted.[9,21] However, caution should be exercised in extrapolating these results to noncirrhotic patients, who have a more favorable prognosis and longer predicted survival. The operative mortality for liver transplants continues to be relatively high when compared to the mortality for both operative (2.5%) and nonoperative (2.3%) biliary drainage procedures in noncirrhotic patients.

Long-term graft survival after liver transplantation for PSC is substantially shorter than patient survival. Sixteen percent of patients receiving a liver transplant for PSC in a recent series were retransplanted within 25 months of the initial transplant because of chronic rejection.[9] Intrahepatic and nonanastomotic extrahepatic biliary strictures typical of PSC also have been reported after liver transplantation.[26] In addition, Harrison et al.[27] reported histologic evidence of recurrent sclerosing cholangitis in 27% of liver allografts biopsied 18 to 62 months after transplantation. In our series, 1 of the 17 long-term survivors after transplantation developed cholangiographic evidence of recurrent sclerosing cholangitis 20 months after transplant and was retransplanted 43 months after his initial transplant. The long-term incidence of recurrent sclerosing cholangitis on liver allograft survival remains to be determined.

Cholangiocarcinoma develops in approximately 10% to 15% of PSC patients followed for 5 years[27,28] and up to 30% of patients followed for >10 years.[9] Early detection is rare, and the long-term survival of patients with cholangiocarcinoma is predictably dismal. Even the presence of an incidental cholangiocarcinoma found at liver transplantation adversely affects survival.[21,29] None of the current diagnostic techniques, such as cholangiographic appearance, biopsy, or biliary cytology, are accurate in diagnosing cholangiocarcinoma. Serum tumor markers are rarely elevated in patients with resectable disease.[29,30] Whether measurement of bile carcinoembryonic antigen, as suggested by Nakeeb et al.,[31] will enhance early diagnosis and improve survival remains to be seen. Similarly, whether the added mortality of early transplantation is less than the potential risk from cholangiocarcinoma has yet to be determined.

None of our 50 surgically resected patients developed cholangiocarcinoma during a mean follow-up of 62 months. Natural history data suggest that seven or eight of these patients should have developed a bile duct malignancy.[9] The entire extrahepatic biliary tree, including the hepatic duct bifurcation, was resected in 80% of these patients. Cholangiocarcinoma has been reported in several PSC patients after endoscopic dilation.[12–14] In our series, three patients were diagnosed with cholangiocarcinoma within 25 months of the initial endoscopic dilation, underscoring the difficulty of diagnosing the disease in these patients. Two of the three patients died of their tumor. As in other series, patients were either diagnosed with incidental cholangiocarcinoma at the time of liver transplantation or with metastatic disease. Most cancers (72%) found incidentally at transplantation were at the hepatic duct bifurcation; only 11% were intrahepatic.[32] This distribution supports the potential role of bifurcation resection in lowering the risk of cholangiocarcinoma in PSC patients. The lower incidence of cholangiocarcinoma in the surgically resected patients was responsible, in part, for the greater overall survival in the noncirrhotic patients managed with this technique.

In our series, 94% of the patients, including all the patients who underwent resection and liver transplantation, had one or more signs and symptoms of PSC. Only 3 of the 54 patients (6%) managed nonoperatively were asymptomatic at the time of their initial endoscopic dilation or percutaneous stenting. Wiesner et al.[3] previously demonstrated that symptomatic PSC patients have a worse prognosis than patients without symptoms. The low percentage of patients with asymptomatic PSC in this series reflects the authors' bias for the indications for treatment. This fact may also be responsible for the lower-than-predicted survival in the nonoperatively managed patients.

Resection of the hepatic duct bifurcation with long-term transhepatic stenting continues to be a good option for noncirrhotic PSC patients who have dominant extrahepatic and hilar strictures. The need for liver transplantation may be significantly delayed in this group of patients. Nonoperative biliary dilation provides symptomatic and biochemical improvement in noncirrhotic patients; however, this option provides a shorter overall and transplant-free survival than resection and may be associated with a higher incidence of cholangiocarcinoma. Liver transplantation is the therapy of choice for PSC patients once cirrhosis develops.

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