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Orthotopic Liver Transplantation for Primary Sclerosing Cholangitis

A 12-Year Single Center Experience

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Objective
The purpose of this study was to analyze a single center's 12-year experience with 127 orthotopic liver transplantations (OLT) for primary sclerosing cholangitis (PSC).

Summary Background Data
Primary sclerosing cholangitis is a chronic cholestatic liver disease of unknown origin that occurs most commonly in young men and is associated frequently (70%–80%) with inflammatory bowel disease (IBD). Patients with PSC also are at risk for the development of cholangiocarcinoma (CCA) and those with IBD for colon carcinoma. Although the course of PSC is variable, it frequently is progressive, leading to cirrhosis and requirement for OLT.

Methods
The medical records of 127 consecutive patients undergoing OLT for PSC from July 1, 1984, to May 30, 1996, were reviewed. Actuarial patient and graft survival was determined at 1, 2, and 5 years. The incidence and outcome of patients with CCA, recurrent sclerosing cholangitis, and post-transplant colon carcinoma was determined. Results were analyzed by way of stepwise Cox regression to determine the statistical strength of independent associations between pretransplant covariates and patient survival. The median follow-up period was 3.01 years. Incidental cholangiocarcinoma (ICCA) was defined as a tumor <1 cm in size that was discovered at the time of pathologic sectioning of the explanted liver.

Results
Ninety-two patients (72%) had associated IBD. Seventy-nine (62%) had undergone previous biliary tract surgery. One hundred seven patients (84%) received a single graft, whereas 20 patients (16%) required 22 retransplants. Patients received either cyclosporine- ($n = 76$) or tacrolimus- ($n = 51$) based immunosuppression. The 1-, 2-, and 5-year actuarial patient survivals were 90%, 86%, and 85%, respectively, whereas graft survival was 82%, 77%, and 72%, respectively. The presence of previous biliary surgery had no effect on patient survival. Ten patients (8%) had ICCA and their survival was not significantly different from patients without ICCA (100%, 83%, and 83% at 1, 2, and 5 years, respectively). Four patients were known to have CCA at the time of OLT, all recurred within 6 months, and had a significantly worse outcome ($p < 0.0001$). Recurrent sclerosing cholangitis developed in 11 patients (8.6%). The patient and graft survival in this group was not different from those in whom recurrence did not develop (patient: 100%, 90%, and 90%;

graft: 80%, 70%, and 52%). Thirty patients (23%) underwent colectomy after liver transplantation for dysplasia–carcinoma or symptomatic colitis. Of the nine covariates entered into the Cox multivariate regression analysis, only common bile duct frozen section biopsy specimen showing CCA was predictive of a survival disadvantage.

Conclusions

Liver transplantation provides excellent patient and graft survival rates for patients affected with PSC independent of pretransplant biliary tract surgery. Incidental cholangiocarcinoma does not affect patient survival significantly. However, known CCA or common duct frozen section biopsy specimen or both showing CCA are associated with poor recipient survival, and OLT should be proscribed in these cases. Recurrent PSC occurs in approximately 9% of cases but does not affect patient survival. Post-transplant colectomy does not affect patient survival adversely.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by fibrosing inflammation of the intrahepatic and extrahepatic bile ducts that results in multiple fibrotic strictures and typically occurs in men younger than 50 years of age.[1–5] Although PSC frequently (>70% of affected patients) is associated with chronic ulcerative colitis (UC), its cause remains unclear.[6,7] Proposed mechanisms have included immunologic, bile, and biliary mucosal abnormalities and infectious agents.[8] The onset of PSC usually is insidious and is typified by a persistent elevation in serum alkaline phosphatase levels, usually of 6 months' or more duration. The clinical course of PSC is variable but usually progressive, with patients having a median survival of 10 to 15 years from the time of diagnosis.[9] Death usually results from complications of portal hypertension but can be caused by recurrent bacterial cholangitis associated with overwhelming sepsis or the presence of hepatobiliary malignancy, most commonly intrahepatic cholangiocarcinoma (CCA), gallbladder carcinoma, or extrahepatic bile duct carcinoma.[10–13] In addition, patients with PSC, if they have longstanding UC, are at risk for the development of colon carcinoma.

A variety of anti-inflammatory and immunosuppressive treatments have been used in patients with PSC, but none have proved to be effective. Multiple reports from several transplant centers[14–17] have shown high actuarial patient and allograft survivals after liver transplantation for PSC. These data are most impressive when compared with those of estimated survival calculated by specific risk scores based on the natural history of PSC.[18] These reports also have documented a 10% to 36% incidence of biliary carcinomas at the time of liver transplantation and an approximately 6% incidence of post-transplant colon carcinoma after orthotopic liver transplantation (OLT).[19] These observations are of interest because they both could have detrimental effects on patient survival.

In this study, we have reviewed our 12-year experience with OLT in patients with end-stage PSC. Specific emphasis has been placed on determining long-term patient and graft survival, as well as the incidence and outcome of patients affected with CCA, and recurrent PSC. The impact of post-transplant colectomy and previous biliary tract surgery on patient survival also was evaluated. We also attempted to identify pretransplant covariates that affect patient survival adversely and to outline post-transplant complications.

MATERIALS AND METHODS

Patient Population

Between July 1, 1984, and May 30, 1996, 127 patients with PSC underwent OLT at the UCLA Center for Health Sciences. The following criteria were used to establish the diagnosis of end-stage liver disease secondary to PSC: 1) clinical signs and symptoms of jaundice, pruritus, cholangitis, and complications of portal hypertension; 2) endoscopic retrograde cholangiopancreatography or transhepatic cholangiography that showed the typical findings of multiple strictures and dilatations of the intrahepatic and extrahepatic biliary ducts; and 3) preoperative liver biopsy specimen showing histologic findings of periportal fibrosis and advanced cirrhosis. These findings were confirmed by microscopic examination of the explanted liver after OLT. All operations were performed by the same surgical team under the direction of the senior author (RWB). Data for this study were obtained by reviewing the inpatient and outpatient hospital medical records of the respective patients. The median follow-up period was 3.01 years.

Organ Procurement, Preservation, and Operative Procedures

Before 1989 donor livers were stored in Euro–Collins solution at 4 C; since that time, all donor livers have been

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stored at 4 C in University of Wisconsin solution.[20] The fundamental principles of the recipient hepatectomy and liver implantation have been described previously.[21,22] The only modification was routine frozen section biopsy specimen of the common bile duct and reconstruction of the biliary system with a Roux-en-Y choledochojejunostomy if inflammation was noted. If atypia was present on the frozen section biopsy specimen, the entire common bile duct was resected to the level of the pancreas.

Definition of Incidental Cholangiocarcinoma

The diagnosis of incidental CCA (ICCA) was established according to the following criteria: 1) no pretransplant evidence of CCA clinically or radiographically; 2) the results of hilar lymph nodes negative for CCA on microscopic examination; 3) no evidence of intrahepatic or extrahepatic CCA at exploratory laparotomy; 4) a negative biopsy specimen of the common bile duct at the time of exploratory laparotomy; 5) a single intrahepatic tumor, <1 cm in greatest dimension, found at the time of pathologic examination of the explanted liver.

Immunosuppression

Before July 1994, immunosuppression consisted of cyclosporine (Sandimmune; Sandoz, East Hanover, NJ) administered intravenously or orally to maintain a trough level between 250 and 300 ng/mL as measured by whole blood radioimmunoassay. Methylprednisolone was begun at 1 g/day and rapidly tapered over 7 days to 20 mg/day. Maintenance oral prednisone was later substituted at the same respective dose. Intravenous azathioprine (2 mg/kg per day) was started on the first post-transplant day, was converted subsequently to oral administration, and decreased to 1 mg/kg per day on post-transplant day 7. Leukocyte counts <4000/mL, systemic sepsis, or pancreatitis was a contraindication to starting azathioprine or continuing its use.

Since July 1994, patients have been randomized to receive the above outlined triple drug immunosuppressive regimen or a tacrolimus-based dual-drug regimen. Tacrolimus (FK506; Prograf, Fujisawa USA, Deerfield, IL) was given orally every 12 hours to maintain a whole blood trough level of 5 to 10 ng/mL. Methylprednisolone was tapered from 1 g/day over 7 days to 20 mg/day and was followed by oral prednisone at 20 mg/day.

Diagnosis of Recurrent Sclerosing Cholangitis

The diagnosis of recurrent sclerosing cholangitis was made in patients meeting the following criteria at least 6 months after liver transplantation: 1) clinical signs and symptoms of jaundice, pruritus, or cholangitis; 2) cholangiographic findings showing nonanastomotic strictures with intrahepatic or extrahepatic bile duct dilatation or both; 3) a combination of histologic findings consistent with sclerosing cholangitis, including multifocal strictures associated with irregularities and tortuosities of the extrahepatic and intrahepatic bile ducts, periductal inflammation and fibrosis, and features of large bile duct obstruction as outlined by Sebagh et al.[23]; and 4) patency of the hepatic artery by Doppler ultrasound or hepatic angiography.

Assessment of Colonic Disease

All patients who had been evaluated for OLT underwent a preoperative assessment of their colonic disease. History of active UC, abdominal pain, diarrhea, or bloody diarrhea at any time before the evaluation mandated preoperative colonoscopy and biopsy to rule out malignancy. Exceptions were patients who underwent proctocolectomy and did not report any symptoms of bowel disease after the operation. Patients undergoing OLT suffering from UC were observed for the development of colonic disease. Surveillance colonoscopy and colon biopsies were performed at 6-month intervals and when indicated. Patients found to have colonic dysplasia or colon carcinoma develop were referred immediately for colectomy. In addition, patients suffering from recalcitrant UC also were referred for colectomy.

Statistical Evaluation

The Kaplan–Meier product-limit estimate was used for univariate calculations of time-dependent events with statistical comparisons between groups done by way of the log–rank test. Stepwise Cox regression analysis was performed to test the statistical strength of independent associations between selected covariates and patient survival. Statistical calculations were performed using the SPSS (SPSS, Chicago, IL) advanced statistics module.

RESULTS

Pretransplant Patient Demographics

Table 1 depicts the pretransplant demographics of the 127 patients undergoing OLT for PSC. The median age at the time of transplantation in these patients was 47 years with a range from 7 years to 70 years. Eighty-seven patients (69%) were men, whereas the remaining 40 (31%) were women. Ninety-two patients (72%) had associated inflammatory bowel disease (IBD). Seventy-nine patients (62%) had undergone previous biliary tract surgery. At the time of transplantation, 18 patients (14%) were confined to the intensive care unit (United Network of Organ Sharing status 1) and 10

Table 1. PRETRANSPLANT DEMOGRAPHICS OF PATIENTS UNDERGOING ORTHOTOPIC LIVER TRANSPLANTATION FOR PRIMARY SCLEROSING CHOLANGITIS

Characteristic	Value
Period	7/1/84–5/30/96
Patients	127
Median age (range) (yr)	47 (7–70)
Sex (M/F)	87/40
Inflammatory bowel disease	92 (72%)
Previous biliary surgery	79 (62%)
UNOS status	
1	18 (14%)
2	10 (8%)
3	99 (78%)

UNOS = United Network of Organ Sharing.

patients (8%) were hospitalized (United Network of Organ Sharing status 2), whereas 99 patients (78%) were awaiting liver transplantation at home (United Network of Organ Sharing status 3).

Patient and Allograft Survival

Of the 127 patients transplanted, 108 (85%) currently are alive. Overall 1-, 2-, and 5-year actuarial patient survivals were 90%, 86%, and 85%, respectively, whereas the 1-, 2-, and 5-year actuarial graft survivals were 82%, 77%, and 72%, respectively (Fig. 1). The type of liver allograft used in these patients included 147 whole and 2 split organs. In this population, 107 patients (84%) received a single graft, whereas 20 patients (16%) required 22 retransplants. Eighteen patients were retransplanted once, and 2 patents were retransplanted twice. The indications for retransplantation were chronic rejection (n = 6), primary nonfunction (n = 5), recurrent sclerosing cholangitis (n = 4), hepatic artery thrombosis (n = 3), de novo hepatitis C (n = 2), and late graft dysfunction of undetermined cause (n = 2).

Incidence and Outcome of Patients with Cholangiocarcinoma

The actuarial patient survival for patients undergoing OLT for PSC with concomitant CCA is shown in Figure 2. One hundred thirteen patients (89%) were transplanted without any evidence of CCA and had a 1-, 2-, and 5-year actuarial survival of 90%, 88%, and 87%, respectively. Four patients (3%) were known to have CCA at the time of liver transplantation. All tumors recurred within 6 months, and these patients had a significantly worse 1-, 2-, and 5-year actuarial survival (33%, 33%, and 0%) ($p < 0.0001$) when compared to patients without known CCA. Ten patients (8%) were found to have ICCA as defined above. This group of patients had a 1-, 2-, and 5-year actuarial survival of 100%, 83%, and 83%, respectively, which is not significantly ($p = 0.24$) different from the 1-, 2-, and 5-year actuarial survival of the 113 patients undergoing OLT without CCA. These data show that while OLT in a patient with a known CCA can be expected to have a poor outcome, the incidental histopathologic identification of a small intrahepatic CCA does not portend the same prognosis.

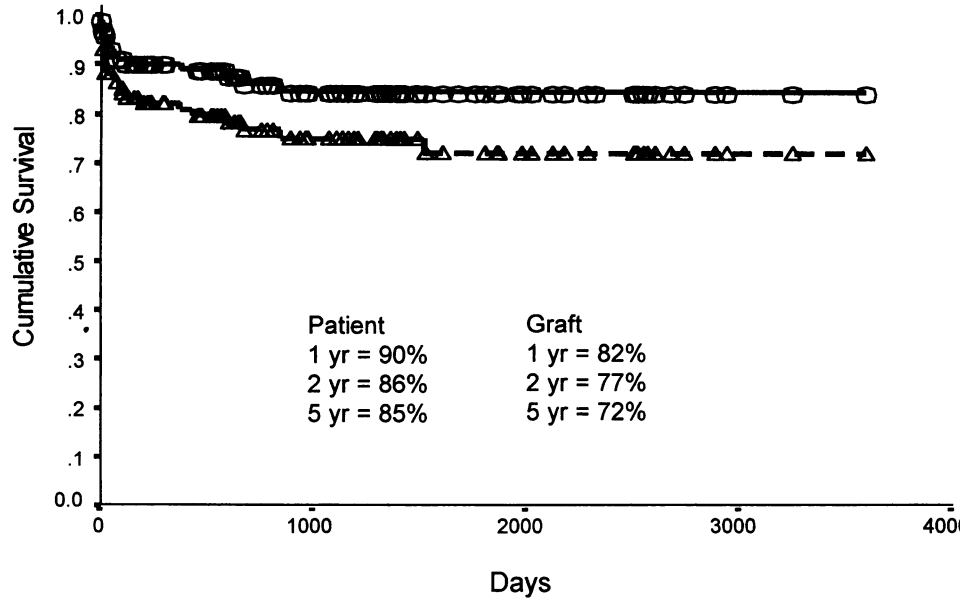

Figure 1. Kaplan–Meier survival curves showing 1-, 2-, and 5-year actuarial patient (○) and liver allograft survival (△).

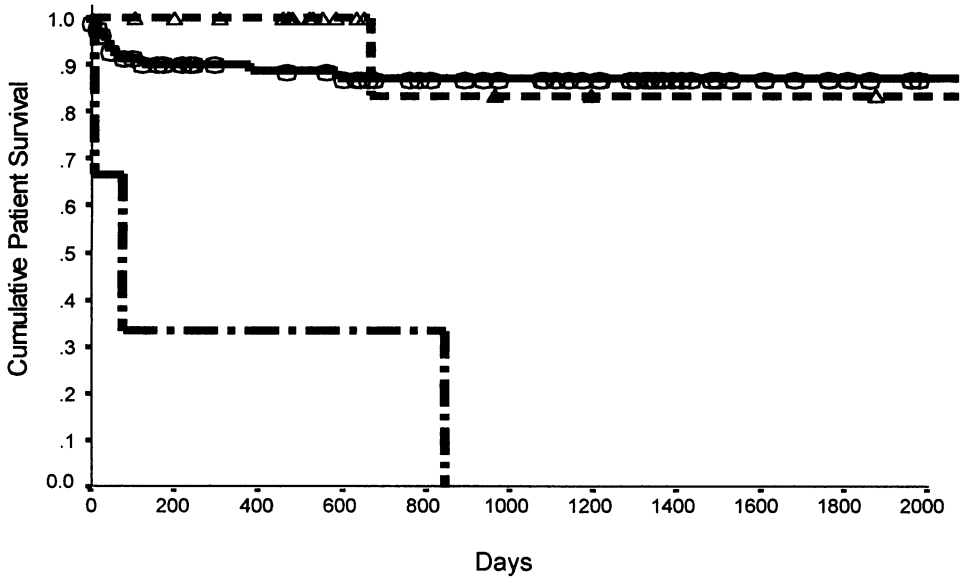

Figure 2. Kaplan–Meier 1-, 2-, and 5-year actuarial patient survival curves for recipient groups based on the presence of cholangiocarcinoma. Patients with a known cholangiocarcinoma (N = 4, –·) have a significantly ($p < 0.0001$) worse 1-, 2-, and 5-year patient survival than those patients undergoing orthotopic liver transplantation for primary sclerosing cholangitis without any evidence of cholangiocarcinoma (N = 113, O) or those patients with an incidental finding of cholangiocarcinoma (N = 10, △).

Recurrent Sclerosing Cholangitis, Incidence, and Outcome

The 1-, 2-, and 5-year actuarial patient and graft survival rates are shown in Figures 3A and 3B. One hundred sixteen patients (91.4%) underwent OLT for PSC without the development of recurrent disease. The 1-, 2-, and 5-year actuarial patient survival rates in this group were 89%, 85%, and 84%, respectively, whereas the graft survival rates were 82%, 79%, and 77%, respectively, at the same timepoints. Recurrent sclerosing cholangitis developed in 11 patients (8.6%), according to the above outlined criteria, and these patients had a 1-, 2-, and 5-year actuarial patient survival of 90%, 90%, and 90%, respectively, with the graft survival being 80%, 70%, and 53% at the same timepoints. These data show that the recurrence of sclerosing cholangitis after liver transplantation is unusual and that the development of this process did not result in a lower patient or graft survival.

Incidence and Outcome of Post-Transplant Colon Carcinoma

It is known that PSC is associated with IBD, usually UC, and that the longer the duration of the disease, the higher the incidence of the development of colon carcinoma. A previous report with a mean follow-up of 45 months[19] showed a 6% incidence of post-transplant colon carcinoma. We sought to determine the incidence of post-transplant colon carcinoma in our series and to determine its impact on patient survival. Thirty (23%) of our patients transplanted for PSC have undergone colectomy: 27 patients for biopsy-proved dysplasia or carcinoma (dyspla-

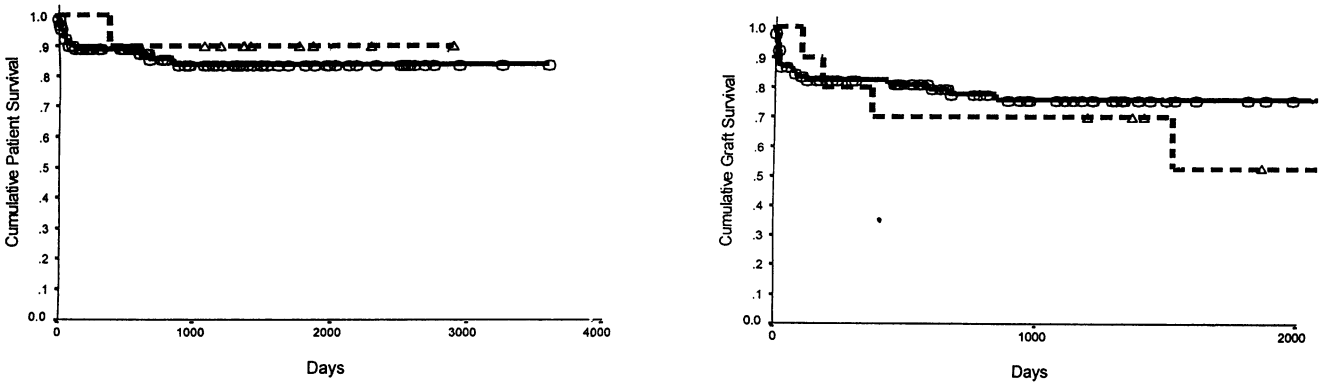

Figure 3. Kaplan–Meier actuarial 1-, 2-, and 5-year patient (A) and allograft (B) survival curves for patients undergoing orthotopic liver transplantation for primary sclerosing cholangitis. There is no significant difference in either patient or graft survival when those patients with recurrent sclerosing cholangitis (N = 11, △) are compared to those without recurrent sclerosing cholangitis (N = 116, O).

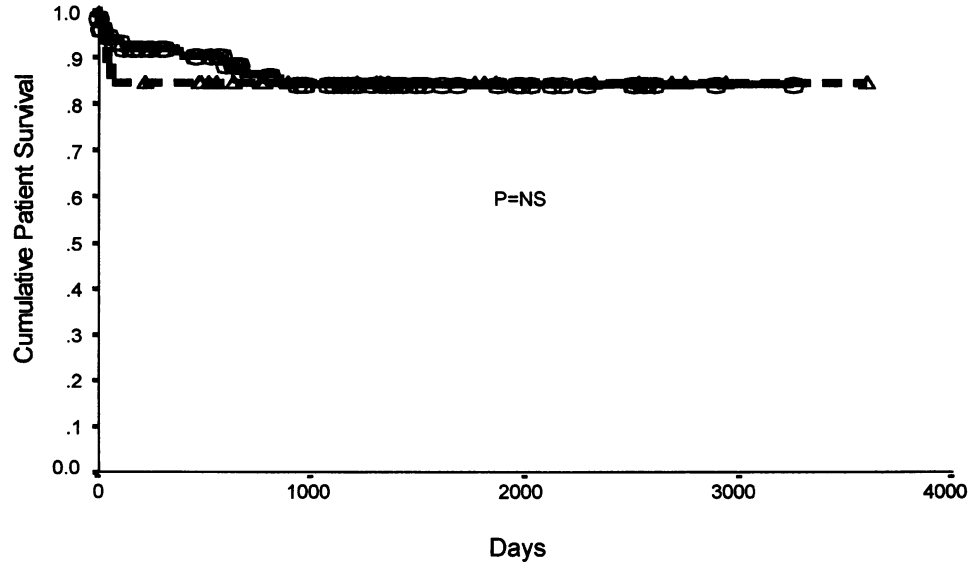

Figure 4. Kaplan–Meier survival curves showing the 1-, 2-, and 5-year actuarial patient survival for patients requiring post-transplant colectomy (N = 30, O) and for patients not requiring post-transplant colectomy (N = 97, Δ).

sia [n = 15], carcinoma *in situ* [n = 6], Duke's A [n = 4], Duke's C [n = 2]) and 3 for persistent UC. The 1-, 2-, and 5-year actuarial patient survivals of these 30 patients and the remaining 97 are shown in Figure 4. There was no significant difference (p = 0.59) in actuarial patient survivals at 1, 2, and 5 years of the 30 patients undergoing colectomy (88%, 84%, and 84%) when compared to the 97 patients without post-transplant colectomy (92%, 88%, and 84%). These data show that colon carcinoma does not develop in this patient population more frequently than would be expected for a similar population of patients with UC. Additionally, close colonoscopic follow-up in the post-transplant period is mandatory because, as shown in the above data, patient survival can continue to be excellent when the colon is removed at the earliest sign of dysplasia or carcinoma.

Effect of Pretransplant Biliary Tract Surgery on Patient Survival

Previous studies[24–26] have stated that previous biliary tract surgery had an adverse effect on the outcome of liver transplantation in patients with PSC. Therefore, we determined the incidence of previous biliary tract surgery and its effect on patient survival in our series. Seventy-nine patients (62%) had undergone previous biliary tract surgery: 38 patients with choledochojejunostomy, 20 patients with cholecystectomy and common bile duct exploration, 14 patients with cholecystectomy alone, and 7 other biliary tract procedures. Figure 5 shows the 1-, 2-, and 5-year actuarial survivals of patients with and without pretransplant biliary tract surgery. The 1-, 2-, and 5-year actuarial patient survivals were 86%, 80%, and 79%, respectively for patients without previous biliary tract surgery. These data are not different significantly (p = 0.19) from the 1-, 2-, and 5-year actuarial patient survivals of patients who had had prior biliary tract surgery (93%, 88%, and 81%). These data indicate that we have found that previous biliary tract surgery does not affect patient survival adversely.

Multivariate Analysis

To determine pretransplant variables that affect patient survival specifically, Cox multivariate regression analysis was performed. The covariates entered included pretransplant age, pretransplant biliary tract surgery, duration of IBD, duration of PSC, pretransplant total bilirubin, pretransplant alkaline phosphatase, common bile duct frozen section, explant pathology (excluding cases of known CCA), and recurrence of PSC. This analysis found common bile duct frozen section to be significantly associated with patient survival (Table 2). Interestingly, however, pretransplant biliary tract manipulation, recurrence of sclerosing cholangitis, pretransplant age, total bilirubin, and alkaline phosphatase as well as duration of IBD and PSC had no effect on patient survival.

Complications After Orthotopic Liver Transplantation for Primary Sclerosing Cholangitis

Table 3 outlines the most common complications found in our experience. Over a 12-year period, biliary complications occurred in 8%, hepatic artery thrombosis in 3%, and portal vein thrombosis in 1.6% of patients.

Table 3 also outlines the medical complications encountered and shows that these patients have averaged 2.22 biopsy-proved rejection episodes per case. The incidence of post-transplant lymphoproliferative disease was 1%. In addition, the incidence of culture-proved bacterial, viral, and fungal infections per case was 1.10, 0.27, and 0.04, respectively.

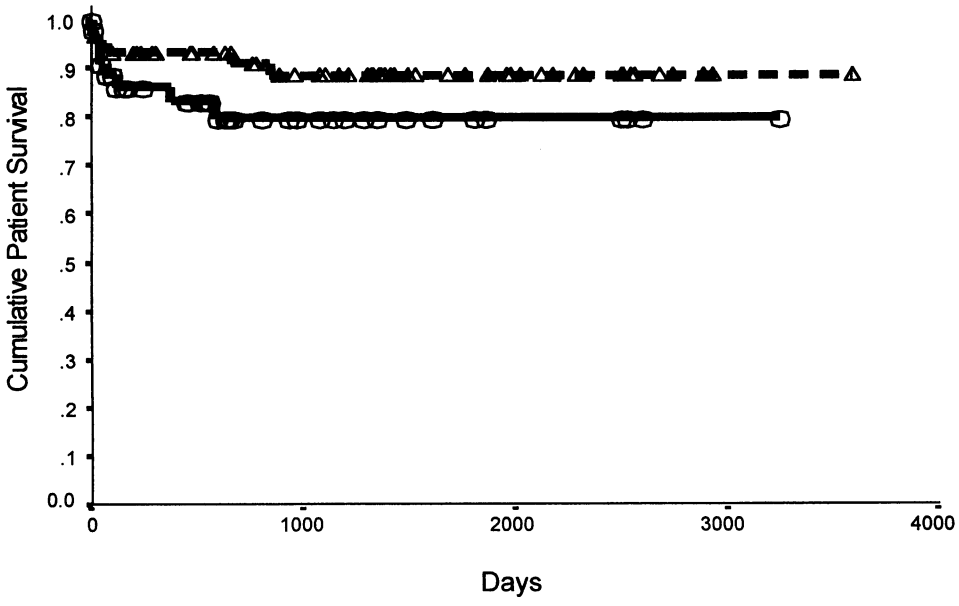

Figure 5. Kaplan–Meier 1-, 2-, and 5-year actuarial patient survival curves for patients without pretransplant biliary tract surgery (N = 48, O) and for those patients with pretransplant biliary tract surgery (N = 79, △).

DISCUSSION

Primary sclerosing cholangitis is a disease of unknown origin that is characterized by fibrosing inflammation of both the intrahepatic and extrahepatic biliary tree. The clinical course of PSC is highly variable but usually is progressive, with patients having a median survival of 10 to 15 years after diagnosis.[9] Multiple medical regimens, including steroids, cholestyramine, azathioprine, and D-penicillamine,[3] have been used to treat PSC. However, none have shown consistent success. Wiesner and LaRusso[1] have reported the largest group of patients with PSC treated without transplantation at a single institute. On analyzing the results of medical treatment, it is shown that of the original 39 patients treated, 25 (64%) were either dead or suffered from end-stage liver disease.

Nontransplant surgical attempts at treating PSC have included biliary tract drainage by T-tube or silastic transhepatic stent[10] and generally have not enjoyed long-term success. Cameron et al.[10] reported their early experience with operative placement of silastic transhepatic stents in a group of 11 patients. At follow-up, the majority of patients had either died or come to transplantation. A subsequent report[27] summarized the results of 31 patients treated by this technique of 100 patients with PSC referred to their center over an 8-year period. Five of their patients had cirrhosis, 2 (40%) died after surgery, 2 other patients with cirrhosis died of liver failure within 18 months of

Table 2. RESULTS OF STEPWISE COX MULTIVARIATE REGRESSION ANALYSIS REGARDING PATIENT SURVIVAL IN ORTHOTOPIC LIVER TRANSPLANTATION FOR PRIMARY SCLEROSING CHOLANGITIS

Covariate	Regression Coefficient	p Value
Age	0.1036	0.0719
Previous biliary survey	0.010	0.6138
Duration of IBD	0.0000	0.6874
Duration of PSC	0.0000	0.3843
Total bilirubin*	0.0000	0.573
Alkaline phosphatase*	0.0000	0.9657
CBD frozen section	**0.3406**	**0.0002**
Explant pathology†	0.0000	0.2653
Recurrent PSC	0.0000	0.7408

IBD = Inflammatory Bowel Disease; PSC = primary sclerosing cholangitis; CBD = common bile duct.
* Pretransplant values.
† Excluding cases of known cholangiocarcinoma.

Table 3. COMPLICATIONS FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION FOR PRIMARY SCLEROSING CHOLANGITIS

Complication	%
Biliary leak/stricture	8
Hepatic artery thrombosis	3
Portal vein thrombosis	1.6
Lymphoproliferative disease	1
Average incidence per case	
Resection (biopsy-proven)	2.22
Bacterial infection*	1.10
Viral infection	0.27
Fungal infection	0.04

* Culture proven.

surgery, and the only survivor was awaiting transplantation at the time of reporting the data. The authors concluded from these data that patients with cirrhosis should not receive this mode of therapy. A similar approach was taken by Pitt et al.[28] in which 22 patients with a dominant stricture underwent either a biliary-enteric anastomosis (n = 17) or T-tube decompression (n = 5). Again, most of the postoperative mortality was seen among the patients with cirrhosis (three of four deaths). As the results of liver transplantation continue to improve, the only option for long-term survival in patients with cirrhosis secondary to PSC is liver transplantation.

Sclerosing cholangitis accounts for nearly 10% of all liver transplants in North America,[29] surpassed only by postnecrotic cirrhosis and primary biliary cirrhosis. Increasingly, liver transplantation is being recognized as a definitive treatment for PSC once disease advancement with cirrhosis and portal hypertension is recognized. Although patients with strictures who have not progressed to portal hypertension or cirrhosis may benefit from conservative therapy, both biliary dilatation and surgical intervention become hazardous and unsuccessful once parenchymal liver disease has occurred. The risk of hemorrhage and infection results in high morbidity and mortality. Other studies also support the viewpoint that biliary tract procedures should be limited to the 25% of patients with extrahepatic disease, whereas patients with diffuse disease and those with impaired liver function should be considered for liver transplantation.[30]

The improvements in surgical technique, the control of coagulopathy, and the use of venous bypass have led to improved patient survival after liver transplantation for PSC. The most recent data from the Pittsburgh–United Network of Organ Sharing Liver Transplant Registry report a 1-year cumulative survival rate of 84%, which compares favorably with the 82% 1-year survival for primary biliary cirrhosis.[31] The current report consists of 127 patients transplanted for PSC and shows a 1-, 2-, and 5-year actuarial patient survival of 90%, 86%, and 85%, respectively (Fig. 1). This report, which is the largest in the literature, shows an excellent long-term survival for these chronically ill patients and compares favorably with smaller reports reviewing patient survival after liver transplantation for sclerosing cholangitis.[15,32]

When liver transplantation was in its infancy, morbidity and mortality increased when liver replacement was undertaken after previous major biliary surgery, and a number of transplant centers have shown an adverse effect of previous biliary surgery on the outcome of liver transplantation in patients with PSC.[16,26] Recent reports still associate liver transplantation after biliary tract surgery with a longer hospital stay and an increased rate of morbidity and mortality.[32] In the current report, previous biliary tract surgery did not affect long-term patient survival adversely (Fig. 5). Both groups had excellent survival rates, thereby leading us to conclude that in the small group of patients with no cirrhosis with a dominant extrahepatic stricture, biliary-enteric anastomosis should be performed; however, once cirrhosis and portal hypertension are apparent, no further surgical therapy should be attempted and the patient should be referred for liver transplantation.

Occult CCAs continue to present problems. A recent review from the University of Pittsburgh Medical Center analyzing the patients undergoing liver transplantation for PSC found the incidence of CCA to be 10.6%. The presence of tumor was unrecognized in half of the cases before liver transplantation. A review of their series showed no specific discriminate factors to indicate the presence of malignancy. The fact that tumor was present at the resection margin in a third of cases, with results from hilar lymph nodes positive in 16.7% of cases, had an important impact on outcome. In patients with PSC without CCA, the authors reported 1- and 5-year patient survival rates of 85% and 76%, respectively. When cases of CCA were included, survival fell to 27% at 5 years.[33] A recent report by Nashan et al.[34] also attempted to identify factors associated with CCA in the patient with sclerosing cholangitis, but no definitive characteristics could be identified. This study also showed a decreased survival rate in the patients with T2 or larger CCAs. In the current report, we also sought to determine the incidence of CCA in our series and its effect on patient survival. As illustrated in Figure 2, 14 (11%) of the 127 patients transplanted for sclerosing cholangitis were found to have CCA. We subsequently divided those patients into two groups: the first consisting of patients known either pretransplant or at the time of exploratory laparotomy and common bile duct frozen section biopsy to have CCA, and the second consisting of patients in whom a small incidental intrahepatic (<1 cm) CCA was identified at the time of pathologic explant examination. All patients who had known CCA had recurrence of the carcinoma and no patient has survived long term. In contrast, the patients who had an ICCA have had 1-, 2-, and 5-year patient survivals similar to those patients without any evidence of CCA. These data show that liver transplantation in patients with PSC with known CCA can be expected to have a poor outcome and should be proscribed; however, the histopathologic identification of an intrahepatic ICCA does not always protend the same prognosis.

Until recently, the diagnosis of recurrent sclerosing cholangitis has been elusive. Biliary strictures may be secondary to low-grade bacterial cholangitis related to the Roux-en-Y bile duct anastomosis, which is performed routinely in patients with PSC. Additionally, ischemia related to chronic rejection, preservation injury, blood group mismatch, hepatic artery thrombosis, and viral infections also is known to contribute to biliary strictures. However, recent studies suggest that there is a low inci-

dence of classical fibro-obliterative lesions seen in the liver biopsy specimens of patients transplanted for PSC. Such histologic appearances have been reported in a patient with an elevated alkaline phosphatase level and active colitis requiring proctocolectomy after liver transplantation.[35] In a study of 22 patients transplanted for PSC, 51 allograft specimens were examined by a single pathologist and compared with samples from a control group of OLT recipients without PSC who had undergone liver transplantation with Roux-en-Y hepaticojejunostomies. The classical fibro-obliterative lesions and periductal fibrosis were seen almost exclusively in the patients having undergone liver transplantation for sclerosing cholangitis.[36] A large study reported recently from the University of Pittsburgh evaluated biliary strictures in 643 patients who underwent liver transplantation and Roux-en-Y choledochojejunostomy.[37] The investigators reported that intrahepatic and nonanastomotic extrahepatic biliary strictures occur significantly more often in patients who undergo liver transplantation for PSC. They concluded that the nonanastomotic biliary strictures were caused by recurrent PSC because no other cause could be identified. These characteristic lesions were found in 11 (8.6%) of our patients post-transplant, as illustrated in Figures 3A and 3B. Their presence to date has not had a significant effect on patient or allograft survival. However, at this time, our median follow-up is 3.01 years, and recognizing that sclerosing cholangitis is a progressive disease may lead us to postulate that, in the future, if the inflammatory process progresses, there will be an effect on both allograft and patient survival.

Primary sclerosing cholangitis is associated with IBD, mainly UC, in approximately 70% of cases.[3] Risk factors for the development of colorectal carcinoma in patients with UC include prolonged duration or early onset of UC and extensive involvement along with dysplasia of the colonic mucosa.[38] It also has been well documented that immunosuppression after transplantation leads to the development of certain forms of cancer.[39] The incidence of colorectal cancer after 15 to 25 years of UC has been reported to be from 1.5% to 35%. In the current report, 30 patients (23%) have undergone colectomy since the time of their liver transplant. All patients are followed with semiannual colonoscopy, and 27 patients have been found to have dysplasia or overt colorectal carcinoma develop. The remaining three patients had recalcitrant UC that was difficult to manage medically. As shown in Figure 5, the patient survival was not affected significantly by the development of dysplasia or colorectal carcinoma. We, therefore, think that all patients should undergo colonoscopy at least every 6 months and that colectomy should be performed as soon as dysplasia is found.

Our experience reported herein shows that excellent long-term survival can be achieved with liver transplantation for PSC. We have shown that patient outcome is independent of previous biliary tract surgery and multiple other pretransplant covariates. We also have shown that the known presence of CCA is associated uniformly with a poor outcome and the incidental finding of intrahepatic CCA can, in certain patients, still allow a favorable outcome. Recurrent sclerosing cholangitis is a relatively unusual finding after liver transplantation for PSC and, to date, has not affected patient survival. Colon carcinoma does develop after liver transplantation in patients with associated UC; however, its incidence is not higher than that expected for a nontransplant population of patients with UC, and the prognosis can be favorable if surveillance is frequent and colectomy is performed at the first inclination of colonic dysplasia or carcinoma.

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Discussion

DR. JOHN C. MCDONALD (Shreveport, Louisiana): Mr. Chairman, Members, and Guests. This paper describes the UCLA experience with 124 liver transplants performed in patients with primary sclerosing cholangitis (PSC). It is one of the largest, if not the largest, such series yet presented. The paper is well written; the data are carefully analyzed, and they speak for themselves.

There are a few issues of biologic interest to me that I would like to give them an opportunity to speculate on or amplify. There were six allograft failures attributed to chronic rejection, a condition of some interest. Would you comment upon the criteria for this diagnosis as well as the length of survival of these grafts? Was this early or late disease, and do you think it was different in this group of patients than in your patients in general?

Second, there are 11 patients that developed recurrent disease. Because there has not yet been a loss of graft with this recurrent disease, how secure are you in this diagnosis? You have pointed out that all such patients have intact hepatic arteries. Can you relate the prognosis of the recurrent disease to that of the original disease? That is, does immunosuppression seem to modify the course of sclerosing cholangitis?

Finally, there were 30 patients who required posttransplant colectomy because of chronic ulcerative colitis. Twenty-seven were related to dysplasia or carcinoma. Apparently, no patient required colectomy pretransplant. Does this imply a conservative preoperative approach to chronic colonic disease, or is it associated with an accelerated postoperative disease? Do you believe that immunosuppression accelerated the neoplasia? I do not think that multi-institutional studies in Europe following kidney transplants for many years have shown an increased incidence in colonic neoplasia.

This is an important paper, and I thank you for the opportunity of making these remarks.

DR. GORAN KLINTMALM (Dallas, Texas): Dr. Cameron, Dr. Copeland, Members, and Guests. We have just had the pleasure to listen to the latest contribution to our knowledge and understanding of the perplexing disease primary sclerosing cholangitis. It is these kinds of studies from large transplant centers that continuously expand our horizon, resulting in safer and more successful treatment for our patients.

Only ten years ago, primary sclerosing cholangitis was the third most common indication for adult liver transplantation. In today's reality, hepatitis C and the Laennec's cirrhosis are the problems that transplant surgeons face.

The presented experience with PSC is by far the largest of its kind. There are many important lessons shared by the authors. The first, simple but major, is that in the hands of an experienced transplant surgeon in a high-volume setting, previous right upper quadrant surgery has absolutely no impact on the outcome of the procedure itself.

Another lesson is that colon carcinoma is not seen more often in these patients than in the normal transplant patients with