Long-Term, Tumor-Free Survival After Radiotherapy Combining Hepatectomy-Whipple En Bloc and Orthotopic Liver Transplantation for Early-Stage Hilar Cholangiocarcinoma

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This retrospective study reviews our experience in surveillance and early detection of cholangiocarcinoma (CC) and in using en bloc total hepatectomy–pancreaticoduodenectomy–orthotopic liver transplantation (OLT-Whipple) to achieve complete eradication of early-stage CC complicating primary sclerosing cholangitis (PSC). Asymptomatic PSC patients underwent surveillance using endoscopic ultrasound and endoscopic retrograde cholangiopancreatography (ERCP) with multilevel brushings for cytological evaluation. Patients diagnosed with CC were treated with combined extra-beam radiotherapy, lesion-focused brachytherapy, and OLT-Whipple. Between 1988 and 2001, 42 of 119 PSC patients were followed according to the surveillance protocol. CC was detected in 8 patients, 6 of whom underwent OLT-Whipple. Of those 6 patients, 4 had stage I CC, and 2 had stage II CC. All 6 OLT-Whipple patients received combined external-beam and brachytherapy radiotherapy. The median time from diagnosis to OLT-Whipple was 144 days. One patient died 55 months post-transplant of an unrelated cause, without tumor recurrence. The other 5 are well without recurrence at 5.7, 7.0, 8.7, 8.8, and 10.1 years. In conclusion, for patients with PSC, ERCP surveillance cytology and intralumenal endoscopic ultrasound examination allow for early detection of CC. Broad and lesion-focused radiotherapy combined with OLT-Whipple to remove the biliary epithelium en bloc offers promising long-term, tumor-free survival. All patients tolerated this extensive surgery well with good quality of life following surgery and recovery. These findings support consideration of the complete excision of an intact biliary tree via OLT-Whipple in patients with early-stage hilar CC complicating PSC. Liver Transpl 14:279-286, 2008. © 2008 AASLD.

Hilar cholangiocarcinoma (CC) is a deadly malignant tumor that arises from the bile duct epithelium. CC is often diagnosed at an untreated advanced stage. National tumor registry data show that approximately two-thirds of patients with CC have, at minimum, regional lymph node or adjacent organ involvement at presentation. Such advanced disease is uniformly fatal. Although surgical strategies afford patients the best chance for short-term survival, with resection, 5-year survival is less than 50%, despite a notably high rate (nearly 90%) of complete excision. Orthotopic liver transplantation (OLT) for otherwise unresectable CC has also been associated with limited success, with 5-year survival reported to range from 0% to 55% (transplant registry data: 23%).4,12-20 Because of this poor survival after OLT, CC has become recognized as a contraindication to OLT (except in experimental protocols). However, a recent report describing chemoradiation followed by OLT for early-stage CC located above the cystic duct demonstrated encouraging 5-year...
survival rates (82%) but still was hampered by a 13% tumor recurrence rate.21 Thus, early diagnosis and treatment of CC complicating primary sclerosing cholangitis (PSC) remain a complex challenge.

There are several factors associated with the development of CC. PSC is widely regarded as a risk factor for CC.22 The reported incidence of CC in PSC is approximately 7% (range: 6%-36%), and the rate of developing CC is 0.6% per year.23,24 In actuality, the rate of CC in PSC patients is probably greater as histological examination of the livers in PSC patients who died or underwent OLT revealed a 30% rate of CC.22 Detection of CC in PSC remains a key challenge despite recent advances. To detect early-stage CC complicating PSC, surveillance with both tumor markers and endoscopic retrograde cholangiopancreatography (ERCP) with cytological brushings has been applied.21,25-28 Making things more difficult, CC in PSC may actually be a diffuse disease, arising from multifocal areas of dysplasia.29,30 Indeed, if it is diffusely located in multiple areas of the biliary tree, a cure can be obtained only if all tissue at risk for CC in patients with PSC can be removed.

Using our screening protocol, we identified 8 patients with early-stage CC accompanied by atypia or dysplasia in PSC. Hypothesizing that a cure could be obtained only if the entire biliary tree was treated, we offered 6 of those patients combined radiation therapy and OLT-Whipple. Herein we report our initial experience using surveillance cytology complemented by endoscopic ultrasound–based intralumenal staging of CC and treatment with radiotherapy and OLT-Whipple. The encouraging results that we observed suggest that long-term, tumor-free survival in patients with early-stage CC complicating PSC can be achieved.

PATIENTS AND METHODS

Screening Protocol

In March 2007, using our longitudinal database, we retrospectively reviewed clinical data for all PSC patients referred for ERCP from 1988 until 2001. Patients were referred for ERCP on the basis of mild liver chemistry abnormalities, including elevated carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA), and underwent brushing cytology to screen for CC.26,27,28 This cytological screening protocol is shown in Fig. 1. Upon referral to our center, all patients underwent an ERCP with brushings of the right and left hepatic ducts, the hepatic duct, and the common bile duct. If the original cytology was normal, then those patients were not re-evaluated with repeat cytology but were followed clinically at a 6-month interval. The patients were rebrushed if they were considered for transplantation or they deteriorated clinically. If the reference cytology contained atypical cells, then a follow-up cytologic examination was obtained approximately 6 to 12 months after the reference ERCP. If the reference cytology contained dysplasia, then a follow-up cytologic examination was obtained in 1 to 3 months. If the index cytology showed adenocarcinoma, then multiple (at least 2 brushes from each segment) brush specimens were obtained from each segment for staging. Endoscopic ultrasound examination (EUS) became available in 1996 and was then used at the time of the confirmatory ERCP/brushing to aid in staging.31,32

Thus, clinical staging was based on the localized ERCP brushing cytology and EUS. With these techniques, the proximal and distal boundaries of the tumor were delineated, and abnormal cells in other areas of the ductal system were identified. In all patients, metastases were excluded by chest, abdomen, and pelvic CT scans and by a bone scan.

Cytological Diagnosis of CC

All cytological specimens were examined by pathologists experienced with biliary cytology. To confirm the diagnosis of CC, all cytological specimens were re-evaluated by 3 cytologists from our institution with established expertise in hepatobiliary cytology using published and validated cytological criteria.26,27,33 as illustrated in Fig. 2. Patients were considered to have early-stage CC if any cytological specimen was positive for adenocarcinoma or carcinoma in situ.

Preoperative Radiation Therapy

Patients found to have early hilar CC were given 4400 cGy via 10 MV photons delivered in 22 fractions 5 days per week for approximately 4 weeks. At 14 to 21 days after completion of the external-beam irradiation, the common bile duct and areas in the hepatic ducts from which positive brushings were obtained were irradiated with 3000 cGy at 0.5 cm delivered with an endoduodenal iridium 192 implant placed via ERCP.

Surgical Procedure

Patients with PSC and stage I or stage II CC24 underwent a staging laparotomy when a donor liver became available. If no evidence of extrabiliary disease was detected during laparotomy, OLT-Whipple was per-
formed. This entailed an en bloc total hepatectomy–
pancreaticoduodenectomy, with intact removal of the
entire biliary system. For all liver transplants, the cava-
plasty triangulated outflow anastomosis was performed
without the use of venovenous bypass. The ana-
tomic extent of resection is demonstrated in Fig. 3. No
prophylactic lymph node dissections were performed. A
pylorus sparing technique was used.

Postoperative Follow-Up

No postoperative radiotherapy or chemotherapy was
given, nor was antibody immunosuppression induction
therapy used. Posttransplant immunosuppression con-
sisted of cyclosporine or tacrolimus and prednisone.
Our oncologic follow-up protocol for these patients con-
sisted of serum tumor marker (CA 19-9 and CEA) analy-
ysis and abdomen, pelvis, and chest CT scans at 3, 6,
and 12 months post-transplant and yearly thereafter.
Survival data were calculated through March 31, 2007.

RESULTS

Between 1988 and 2001, 119 PSC patients underwent
273 ERCP brushing cytologic evaluations at the Univer-
sity of Iowa Hospital and Clinics (average: 2.3 ERCPs
per patient; range: 1-7 per patient). Among them, 77
patients’ original cytologies were normal, and therefore
these patients were not automatically re-evaluated; in-
stead, they were followed clinically. None of these pa-
tients went on to develop CC in the study period. Forty-
two (35%) were found to have abnormalities on their
initial cytologic examinations and therefore were fol-
lowed according to the surveillance cytology described
previously. CC was found on the initial brushings in 3
patients. In another 5 patients whose initial brushings
showed atypical cells or dysplasia, CC was subse-
quently discovered on cytology. Thus, 8 of the 42 pa-
tients with abnormal reference cytologies were eventu-
ally found to have CC. Brushing of 2 patients revealed
that CC was located in areas of regional wall thickening
demonstrated on EUS, and this made them stage II.
However, in all 8 patients, screening CT scans and bone
scans were negative for metastases. No patients were
found to have advanced staged disease with this proto-
col.

One patient with localized disease underwent resec-
tion. Another patient refused OLT and died 35 months
after radiotherapy because of tumor recurrence. The
other 6 PSC patients with early-stage CC completed the
radiotherapy and OLT-Whipple treatment protocol (Ta-
ble 1). All patients but one were alive without CC recur-
rence at last follow-up. Of those, 5 were male; their
median age was 37 (range: 18-56). Three had concom-
itant Child’s class A cirrhosis of the liver, whereas the
other 3 were not cirrhotic. All 6 patients had long-
standing chronic inflammatory bowel disease prior to
the diagnosis of PSC (median: 13; range: 4-20 years).
The diagnosis of PSC preceded the diagnosis of CC by a
median of 5.3 years (range: 0.5-10 years), whereas the
median duration from initial abnormal brushing to di-
agnosis of CC was 9.5 months (range: 0.4-47.6
months). Four were diagnosed with stage I disease. The
other 2 patients had a mass seen on EUS (Fig. 4) and,
therefore, had stage II disease. None had preoperative
(or subsequent) evidence of nodal involvement. Biliary
stenting was necessary for decompression in 4 patients
between time of diagnosis of CC and OLT-Whipple.
There were no episodes of pancreatitis or cholangitis
despite multiple ERCPs used for surveillance in these
patients. The median time between the diagnosis of CC
and OLT-Whipple was 144 days (range: 65-207 days),
whereas the median interval from the completion of
radiotherapy to OLT-Whipple was 87 days (range:
7-151 days; Table 1).
On explant, histological evidence of the radiation effect was present in all areas of the resected bile duct specimens. This consisted of denudation of the biliary epithelium, which was complete in the areas of maximum radiation exposure (both external beam and brachytherapy) where the tumor was initially found. Also on explant, multifocal dysplastic changes in the biliary epithelium were frequently detected at considerable distances from the areas of maximal targeted radiation therapy; however, no CC was found at these distant sights. Because of the extensive focal radiation damage due to the radiation therapy, no CC was identified in the explants.

All patients tolerated the radiation therapy and surgery well. There was no perioperative mortality. Total operative time ranged from 6 to 7 hours. The median intraoperative blood requirement was 3.5 units of red blood cells (range: 0-13 units). The median postoperative length of stay was 21 days (range: 16-138 days). Surgical morbidity included intra-abdominal infections, which resolved after conservative treatment (n = 2), and one instance of a pancreatic leak requiring revision of the pancreatocjejunostomy (n = 1), which prolonged the length of stay to 138 days. One patient developed a pancreatic duct stricture proximal to the anastomosis 22 months after the OLT-Whipple because of preexisting chronic pancreatitis. This resolved with stenting. Another patient developed chronic renal failure secondary to calcineurin inhibitor nephrotoxicity and underwent kidney transplantation 40 months after the OLT-Whipple. One patient, who was diabetic prior to transplantation, died from diabetic ketoacidosis 55 months later without evidence of tumor recurrence. The other 5 patients resumed full-time employment post-transplantation. No patient had detectable recurrent CC at last follow-up: 55, 68, 84, 104, 105, and 121 months after the OLT-Whipple.

**DISCUSSION**

Herein we report extensive long-term survival after the OLT-Whipple combined radiotherapy for PSC patients with early-stage CC. This aggressive approach was applied to PSC patients with evidence of diffuse disease or disease in the central extrahepatic biliary tree. The objective of the study protocol, to eliminate the possibility of seeding and local recurrence by the performance of an intact resection of the entire biliary tree after obliteration of the tumor with local and regional radiation therapy, appears to have been achieved. All 6 treated patients remained free of CC recurrence at last follow-up.

A principle concept behind this therapy is that the entire biliary epithelium is at risk in PSC patients with evidence of diffuse or central disease. Suzuki et al. demonstrated a dysplastic zone surrounding a focus of hepatobiliary bile duct carcinoma in the preponderance of their cases. Likewise, Bergquist et al. found bile duct dysplasia in liver tissue apart from the actual CC in more than 60% of patients with PSC. Dysplastic epithelium is at significant risk for malignant degeneration. Thus, in PSC, biliary epithelial neoplasia can be a diffuse disease (essentially a field effect), and the entire biliary tree is at risk for the development of CC. Because of this, the current staging system based on
the index lesion would underestimate the burden of disease in patients with diffuse disease.\textsuperscript{30}

Given that PSC can be a diffuse disease and that biliary dysplasia is likely a precancerous lesion, treatment with bile duct excision alone may be inadequate. Jarnagin et al.\textsuperscript{10} found that concomitant partial hepatectomy improved long-term survival for CC, regardless of the margins. Even so, bile duct excision with partial hepatectomy still may not be enough for patients with diffuse or central disease. Recurrences of CC after curative surgery, such as total hepatectomy, may have occurred from foci of CC or dysplasia in the remaining bile duct epithelium.\textsuperscript{36,40} Thus, total excision of the biliary system may be needed.

The patients in the present series had diffuse disease or had disease in the central bile duct. One patient presented with a hilar tumor above the cystic duct, 2 presented with tumors extending below the cystic duct, and 3 presented with tumors above the cystic duct accompanied by atypical cells below the cystic duct. Accordingly, a standard hepatectomy-OLT would have left behind bile duct at risk for containing CC or premalignant tissue.

Our patients have not had tumor recurrence through the 5.7- to 10.1-year follow-up period. There was one death from diabetic ketoacidosis 55 months post-transplant (the diabetes was present prior to CC treatment). The other patients are working (one has retired) and have done well.

Rea et al.\textsuperscript{21} performed OLT-Whipple in combination with chemotherapy and radiation therapy for early-stage CC. Their protocol was similar to ours, except that we did not employ chemotherapy. In this series, 82% of the 32 patients with PSC and stage I or II CC who underwent liver transplantation and the 4 patients who underwent OLT-Whipple were alive at 5 years. Three of 4 patients with distal bile duct CC who had an OLT-Whipple remained tumor-free at 24- to 72-month follow-up.\textsuperscript{21,25} Tumor recurrence occurred post-transplant in only 13%. In a similar series, Shimoda et al.\textsuperscript{17} also observed promising tumor-free survival at a median follow-up of 39.5 months in 4 patients who had extrahepatic CC confined to the bile duct and underwent an OLT-Whipple. These series with promising results, along with ours, may indicate that the combination of OLT and Whipple can effect complete extirpation of premalignant regions of the biliary system in PSC patients with diffuse abnormal cytological involvement of the common bile duct.

The results with OLT-Whipple for late-stage CC in patients with PSC have not been as good. Patients with higher stage CC were included in the OLT-Whipple protocol reported by Neuhaus et al.\textsuperscript{34,35} In their series, tumor recurrence occurred in 8 of 15 patients after OLT-Whipple plus extended lymphadenectomy, resulting in a 5-year survival rate of 38%. This was despite negative microscopic margins (R0 in 14 of 15 patients). The suboptimal survival was thought to be due to the advanced stage of tumors at presentation (10 of 15 patients had stage IV tumors). As might be expected for advanced-stage CC, the extent of lymph node involvement correlated with the extent of primary tumor extension. Interestingly, lymph node micrometastases that were missed by routine hematoxylin and eosin staining did not appear to affect survival in their patients with otherwise node-negative hilar CC.\textsuperscript{41} Because this protocol restricted OLT-Whipple to patients with stage I or stage II disease, extended lymphadenectomy was not necessary and, therefore, was not performed.

The early detection of CC in patients with PSC is a critical challenge. Patients with PSC are at significant risk for CC (incidence range of 6%-36%).\textsuperscript{24} Because hilar CC is difficult to detect at early stages with standard studies and because, when discovered at an advanced stage, it is essentially untreatable, there must be protocols for early detection. To address this in our patients, our multidisciplinary team of pathologists, gastroenterologists, and transplant surgeons developed the present protocol. As described in the Patients and Methods section, our surveillance consisted of extensive cytological brushings performed every 1 to 12 months in patients with PSC found to have atypia or dysplasia in their initial biopsies. Patients without atypia were not restudied, unless they developed symptomatic strictures or were listed for transplantation; this decision was based on our finding that those without atypia on presentation were unlikely to develop it later in the absence of symptomatic bile duct disease. In contrast, those with atypia on initial biopsy were found to be at significant risk for developing subsequent dysplasia or CC and, therefore, were followed closely.\textsuperscript{26,29} In summary, once abnormal cytology was detected, patients were screened at regular time intervals (Fig. 1) by serial ERCP-directed bile duct brushings to detect progression to CC.

The present study provokes several important questions regarding the screening of CC in patients with PSC. First, was the screening protocol needed? On the basis of the natural history of PSC and the evidence in the literature, we believe that it was, but because all patients were screened via the ERCP brushing cytological evaluations and therefore there was no control group, we cannot conclude from the present results that it was necessary. Second, was it effective in detecting abnormalities? We believe that it was, as no screened patient who did not have cytological abnormalities subsequently developed CC. Third, and most importantly because the cytopathologic diagnosis of CC was the cornerstone of the application of our aggressive therapy with radiation and OLT-Whipple, did it produce a correct diagnosis? This is an especially important question because of the absence of histological proof in the resected specimen due to the destruction of the tumor by the preoperative radiation therapy. Many studies have shown that brush cytology for early detection of CC is a good diagnostic tool, with sensitivities ranging from 33% to 100% (mean: 97%) and specificities ranging from 87% to 100% (mean: 97%).\textsuperscript{26-28,42-46} The use of repeat brushings significantly increases the detection of dysplasia or CC,\textsuperscript{43-47} and therefore double brushings were employed. Our diagnostic criteria for
the cytological analysis were formalized on the basis of findings (at our institution) from multiple regression analysis of bile duct cytology. To further increase our accuracy and confirm the diagnosis, cytology specimens were retrospectively examined by 3 experienced cytologists. The 7% incidence of CC discovered in our PSC population with our screening protocols is consistent with that of other series.

To increase the accuracy of tumor detection and preoperative staging, EUS, which has a sensitivity of 98%, was used once it became available in 1996. Indeed, another recent study further demonstrated that EUS is highly sensitive, detecting a small mass in 13 of 14 patients with previous negative images on other screening modalities. In the present series, 2 small tumors with invasion of the muscular layer were detected with EUS. These masses were located in the area of the duct corresponding to the region of CC detected on brushing cytology. A similar preoperative staging system has been reported by Rea et al.

Preoperative radiation therapy for the treatment of early-stage CC is likely important. A national Canadian retrospective study of OLT for early-stage CC without neoadjuvant therapy demonstrated poor outcomes. The tumor recurrence rate was 80% within a median of 26 months post-transplant, producing a 3-year survival of 30%. In contrast, our treatment consisted of both local and regional radiation therapy and complete surgical removal. Other groups have used this therapy. Sudan et al. employed brachytherapy at 6000 cGy without the extra-beam radiotherapy (their protocol also included chemotherapy) prior to OLT-Whipple. At a median follow-up of 7.5 years, 45% of patients (5 of 11) with stage III CC were alive without evidence of tumor recurrence. Rea et al. also used only external-beam (4500 cGy) radiotherapy and brachytherapy (2000-3000 cGy) in their OLT-Whipple protocol (they also used systemic chemotherapy). In their series of 38 patients with stage I or stage II CC, 82% achieved 5-year survival. The treatment protocol, consisting of combined regional and local radiotherapy followed by OLT-Whipple for en bloc removal of the entire biliary system, was well tolerated and offered long-term, tumor-free survival. Multicenter studies will be needed to confirm that this extensive surgical therapy is truly required.

REFERENCES

1. Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Plantaditis S, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996; 224:463-473; discussion 473-465.
2. Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer 1995;75(suppl):171-190.
3. Klempnauer J, Ridder GJ, Werner M, Weimann A, Pichlmayr R. What constitutes long-term survival after surgery for hilar cholangiocarcinoma? Cancer 1997;79:26-34.
4. Iwatsuki S, Todo S, Marsh JW, Madriaga JR, Lee RG, Dvorchik I, et al. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. J Am Coll Surg 1998;187:358-364.
5. Miyazaki M, Ito H, Nakagawa K, Ambiru S, Shimizu H, Okaya T, et al. Parenchyma-preserving hepatectomy in the surgical treatment of hilar cholangiocarcinoma. J Am Coll Surg 1999;189:575-583.
6. Gerharz MF, van Gulik TM, de Wit LT, Obertop H, Gouma DJ. Evaluation of morbidity and mortality after resection for hilar cholangiocarcinoma—a single center experience. Surgery 2000;127:395-404.
7. Todoroki T, Kawamoto T, Koike N, Takahashi H, Yoshida S, Kashiwagi H, et al. Radical resection of hilar bile duct carcinoma and predictors of survival. Br J Surg 2000;87:306-313.
8. Tsao JJ, Nimura Y, Kamiya J, Hayakawa N, Kondo S, Nagino M, et al. Management of hilar cholangiocarcinoma: comparison of an American and a Japanese experience. Ann Surg 2000;232:166-174.
9. Blom D, Schwartz SI. Surgical treatment and outcomes in carcinoma of the extrahepatic bile ducts: the University of Rochester experience. Arch Surg 2001:136:209-215.
10. Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodischewicz BJ, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001:234:507-517; discussion 517-509.
11. Nakeeb A, Tran KQ, Black MJ, Erickson BA, Ritch PS, Czubayko EJ, et al. Improved survival in resected biliary malignancies. Surgery 2002;132:555-563; discussion 563-554.
12. Pichlmayr R, Weimann A, Klempnauer J, Oldhafer KJ, Maschek H, Tusch G, et al. Surgical treatment in proximal bile duct cancer. A single-center experience. Ann Surg 1996;224:628-638.

13. Jeyarajah DR, Klintmalm GB. Is liver transplantation indicated for cholangiocarcinoma? J Hepatobiliary Pancreat Surg 1998;5:48-51.

14. Ahrendt SA, Pitt HA, Nakeeb A, Klein AS, Lillemoe KD, Kalloo AN, et al. Diagnosis and management of cholangiocarcinoma in primary sclerosing cholangitis. J Gastrointest Surg 1999;3:357-367; discussion 367-358.

15. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. Transplantation 2000;69:1633-1637.

16. O'Grady JG. Treatment options for other hepatic malignancies. Liver Transpl 2000;6(suppl 2):S23-S29.

17. Shimoda M, Farmer DG, Colquhoun SD, Rosove M, Ghobrial RM, Yersiz H, et al. Liver transplantation for cholangiocellular carcinoma: analysis of a single-center experience and review of the literature. Liver Transpl 2001;7:1023-1033.

18. Lindner P, Norrby J, Olausson M, Rizell M, Cahlin C, Friman S. Survival after liver transplantation for cholangiocarcinoma has increased during the last decade. Transplant Proc 2003;35:811-812.

19. Ghali P, Marotta PJ, Yoshida EM, Bain VG, Mareeau D, Petelkian K, et al. Liver transplantation for incidental cholangiocarcinoma: analysis of the Canadian experience. Liver Transpl 2005;11:1412-1416.

20. Sudan D, DeRooover A, Chinnakotla S, Fox I, Shaw B Jr, McCashland T, et al. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. Am J Transplant 2002;2:774-779.

21. Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, et al. Liver transplantation with neoadjuvant chemoradiation is a safe alternative to venovenous bypass during cavaplasty liver transplantation. Transplantation 2003;76:1724-1728.

22. Suzuki M, Takahashi T, Ouchi K, Matsuno S. The development and extension of hepatobiliary bile duct carcinoma. A three-dimensional tumor mapping in the intrahepatic bile tree visualized with the aid of a graphics computer system. Cancer 1989;64:658-666.

23. Bergquist A, Gluemann H, Persson B, Broome U. Risk factors and clinical presentation of hepatobiliary carcinoma in patients with primary sclerosing cholangitis: a case-control study. Hepatology 1998;27:311-316.

24. Bergquist A, Gluemann H, Stal P, Wang GS, Broome U. Biliary dysplasia, cell proliferation and nuclear DNA-fragmentation in primary sclerosing cholangitis with and without cholangiocarcinoma. J Intern Med 2001;249:69-75.

25. Fleming KA, Boberg KM, Gluemann H, Bergquist A, Smith D, Clausen OP. Biliary dysplasia as a marker of cholangiocarcinoma in primary sclerosing cholangitis. J Hepatol 2001;34:360-365.

26. Neuhaus P, Blumhardt G. Extended bile duct resection—a new oncological approach to the treatment of central bile duct carcinomas? Description of method and early results. Langenbecks Arch Chir 1994;379:123-128.

27. Tojima Y, Nagino M, Ebata T, Uesaka K, Kamiya J, Nimura Y. Immunohistochemically demonstrated lymph node micrometastasis and prognosis in patients with otherwise node-negative hilar cholangiocarcinoma. Ann Surg 2003;249:201-207.

28. Siqueira E, Schoen RE, Silverman W, Martin J, Rabinovitz M, Weissfeld JL, et al. Detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. Gastrointest Endosc 2003;56:40-47.

29. Glasbrenner B, Ardan M, Boeck W, Preclik G, Moller P, Zajko AB, Hassanein T, Shetty B, Bron KM, et al. Liver transplantation for incidental bile duct cancer. A single-center experience. Ann Surg 1996;224:628-638.

30. Moff SL, Clark DP, Maitra A, Pandey A, Thuluvath PJ. Utility of bile duct brushings for the early detection of cholangiocarcinoma in patients with primary sclerosing cholangitis. J Clin Gastroenterol 2006;40:336-341.

31. Johlin FC, Voigt M, Wu Y. Surveillance cytology (SC) in the detection of asymptomatic progression to cholangiocarcinoma (CCC) in patients with primary sclerosing cholangitis (PSC). Hepatology 1998;28(pt 2, suppl):393A.
of biliary brush cytology in primary sclerosing cholangitis. Acta Cytol 2004;48:9-12.

47. Jailwala J, Fogel EL, Sherman S, Gottlieb K, Flueckiger J, Bucksot LG, et al. Triple-tissue sampling at ERCP in malignant biliary obstruction. Gastrointest Endosc 2000; 51(pt 1):383-390.

48. Furmanczyk PS, Grieco VS, Agoff SN. Biliary brush cytology and the detection of cholangiocarcinoma in primary sclerosing cholangitis: evaluation of specific cytomorphologic features and CA19-9 levels. Am J Clin Pathol 2005; 124:355-360.

49. Chang KJ. State of the art lecture: endoscopic ultrasound (EUS) and FNA in pancreatico-biliary tumors. Endoscopy 2006;38(suppl 1):S56–S60.

50. DeWitt J, Misra VL, Leblanc JK, McHenry L, Sherman S. EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results. Gastrointest Endosc 2006;64:325-333.

51. Hassoun Z, Gores GJ, Rosen CB. Preliminary experience with liver transplantation in selected patients with unresectable hilar cholangiocarcinoma. Surg Oncol Clin N Am 2002;11:909-921.

52. D'Angelica M, Martin RC II, Jarnagin WR, Fong Y, DeMatteo RP, Blumgart LH. Major hepatectomy with simultaneous pancreatectomy for advanced hepatobiliary cancer. J Am Coll Surg 2004;198:570-576.

53. Wu YM, Voigt M, Rayhill S, Katz D, Chenhsu RY, Schmidt W, et al. Suprahepatic venacavaplasty (cavaplasty) with retrohepatic cava extension in liver transplantation: experience with first 115 cases. Transplantation 2001;72:1389-1394.