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REVIEW ARTICLE

Liver Transplantation for Peri-hilar Cholangiocarcinoma

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Abstract

Background Liver transplantation for peri-hilar cholangiocarcinoma (pCCA) following neoadjuvant chemoradiation achieves excellent long-term survival in carefully selected patients with early-stage unresectable pCCA and patients with primary sclerosing cholangitis (PSC)–associated pCCA. Strict adherence to selection criteria, aggressive neoadjuvant therapy, operative staging prior to transplantation, and several technical accommodations during the transplant operation are necessary for success. In this review, we provide a contemporaneous overview of liver transplantation for pCCA, including selection criteria, neoadjuvant therapy, operative staging, and technical aspects of liver transplantation unique to patients with pCCA and an irradiated operative field. We also discuss several evolving trends intended to improve patient outcomes.

Results and Conclusion Intention-to-treat and patient outcomes after liver transplantation for PSC-associated pCCA are superior to de novo pCCA. Outcomes between living donor liver transplantation (LDLT) and deceased donor liver transplantation are similar for patients with PSC-associated pCCA. However, LDLT for de novo pCCA shows a trend toward more disease recurrence and worse patient survival. A period of waiting time before transplant may be beneficial in selecting for patients with superior outcomes after transplant. Compared with liver transplantation for other indications, there is an increased risk of late arterial and portal vein complications, presumably due to the radiation. However, with close follow-up and prompt intervention for vascular complications, graft loss can be avoided. Neoadjuvant therapy and liver transplantation can achieve results comparable with resection for patients with early-stage unresectable pCCA and is the treatment of choice for patients with pCCA arising in the setting of PSC.

Keywords Perihilar cholangiocarcinoma · Liver transplantation · Neoadjuvant therapy

Introduction

Cholangiocarcinoma (CCA) is the second most common form of primary liver cancer, arising from the biliary epithelial cells and showing markers of cholangiocyte differentiation.[1] It is typically classified into three types based on anatomical location: peri-hilar, intrahepatic, and extrahepatic. Peri-hilar CCA (pCCA) arises in the region between the second-degree bile ducts and the insertion of the cystic duct into the common bile duct. Worldwide, the incidence of CCA ranges from 0.3 per 100,000 person-years in Western populations to 85 per 100,000 person-years in parts of Thailand where the liver fluke *Opisthorchis viverrini* is endemic.[2–4] Within the USA, extrahepatic CCA is a comparatively rare tumor with an incidence of 1.02 per 100,000 person-years. This incidence has been relatively stable, in contrast to intrahepatic CCA which has been gradually increasing over time.[5]

The most common form of CCA is pCCA (50%), followed by extrahepatic CCA (42%) and intrahepatic CCA (8%).[6] Peri-hilar CCA can arise in the background of primary sclerosing cholangitis (PSC). It can also arise de novo, in the absence of underlying liver pathology. Other risk factors include congenital biliary cystic disorders, parasitic infections, cirrhosis, and hepatolithiasis.[1,7] pCCA is a malignancy that has a poor response to chemotherapy. It is insidious and often detected late in the course of the disease process with local progression and metastatic disease precluding potentially curative treatment. Surgical resection and transplantation are the only potential curative treatment options for early-stage disease. Surgical resection is particularly challenging for pCCA

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as it requires partial or extended hepatectomy with en bloc resection of the gallbladder, common hepatic and bile ducts with preservation of the vasculature to the contralateral liver. It is often difficult to achieve a tumor-free (R0) resection. Anything less than a R0 resection provides little, if any, benefit to the patient.[8] Surgical resection in well-selected patients can yield survival rates of 35–44% at 5 years and 17–30% at 10 years.[9,10]

Liver transplantation as a single modality (i.e., without neoadjuvant chemoradiation) to treat CCA has a dismal outcome with 1-, 3-, and 5-year survival rates of 72, 35, and 23%, respectively.[11,12] In 1993, the liver transplant team at the Mayo Clinic partnered with their colleagues in radiation therapy and medical oncology to develop a protocol to treat patients with unresectable early-stage pCCA arising de novo or early-stage pCCA arising in PSC. The Mayo Clinic protocol includes strict diagnostic and patient selection criteria followed by aggressive neoadjuvant chemoradiation and operative staging prior to transplantation.[13] Between 1993 and 2018, we have enrolled 349 patients, with 79% (n=277) proceeding to the staging operation and 60% (n=211) undergoing liver transplantation. Intention-to-treat analysis (from the start of neoadjuvant therapy, including patients who did not undergo transplantation) yielded 1-, 5-, and 10-year survival rates of 80, 51, and 46% (Fig. 1a). Survival rates after transplantation are 91, 69, and 62% at 1, 5, and 10 years (Fig. 1b).

There is a distinct difference in the outcomes of patients with pCCA arising in the setting of PSC compared with those with arising de novo. Survival after the start of therapy (intention-to-treat analysis) for patients with PSC-associated pCCA is 78, 60, and 52% at 1, 5, and 10 years compared with 83, 39, and 32% for patients with pCCA arising de novo (p = 0.03; Fig. 2a). Survival after transplantation for patients with PSC-associated pCCA is 92, 76, and 70% at 1, 5, and 10 years compared with 90, 58, and 49% for patients with de novo pCCA (p = 0.02; Fig. 2b). Various selection methods and neoadjuvant protocols are employed at other institutions. These have achieved similar results with survival rates of 75–88% at 1 year,[14] 55–60% at 2 years, and 32% at 5 years after transplantation.[15–18] It is important to note the percentage of patients with PSC-associated pCCA versus pCCA arising de novo when comparing results between centers. The differences in outcomes for both intention-to-treat survival and survival after transplantation are so different that we encourage everyone to report these results separately. A recent study of 10 institutions in the USA reported improved outcomes after transplantation compared with resection (among patients that met transplant criteria) with survival rates of 54% vs. 44% and 54% vs. 29% at 3 and 5 years.[19] These results affirm the role and effectiveness of neoadjuvant chemoradiation protocol followed by liver transplantation in the treatment of pCCA. We will discuss later in this review that these results do not demonstrate that transplantation is better than resection for patients with (resectable) de novo pCCA.

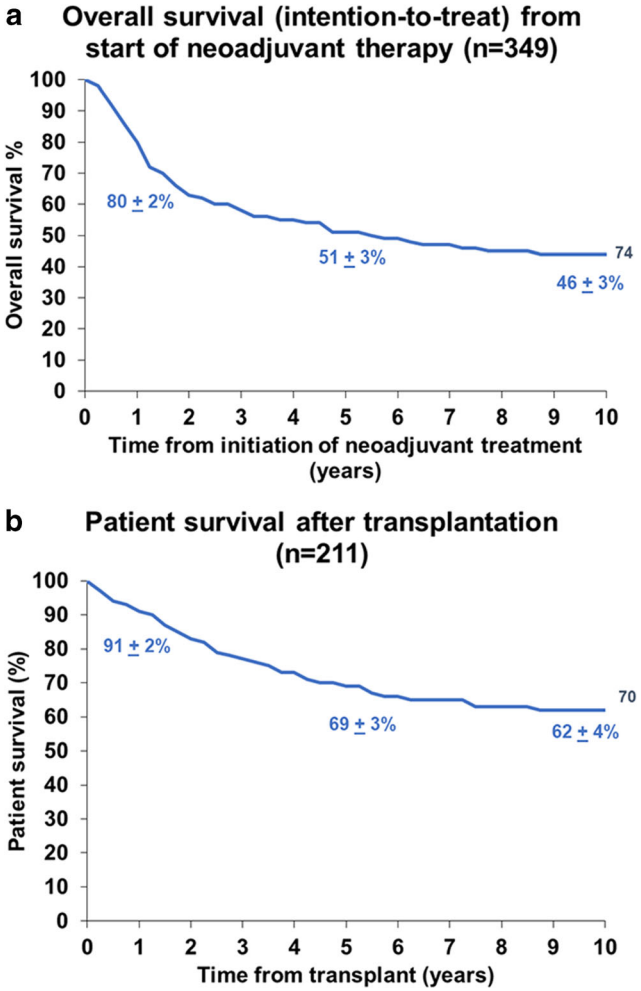

Fig. 1 **a** Overall survival (intention-to-treat) from start of neoadjuvant therapy (n = 349). **b** Patient survival after transplantation (n = 211)

Selection Criteria and Neoadjuvant Therapy

The critical prerequisite in achieving good outcomes is strict adherence to the selection criteria, which have been previously described.[20] The diagnostic criteria for pCCA require the presence of a malignant-appearing stricture on cholangiography with at least one of the following: (1) endoscopic intraluminal brushings or tissue biopsy that is positive or strongly suspicious for CCA; (2) a CA 19-9 level >100 U/ml in the absence of acute bacterial cholangitis; (3) polysomy by fluorescence in situ hybridization or a well-defined mass on cross-sectional imaging at the site of the malignant-appearing stricture. Inclusion criteria require that a mass lesion has a radial (perpendicular to the duct) diameter <3 cm and that the tumor does not extend below the cystic duct. We exclude patients with metastatic disease, prior

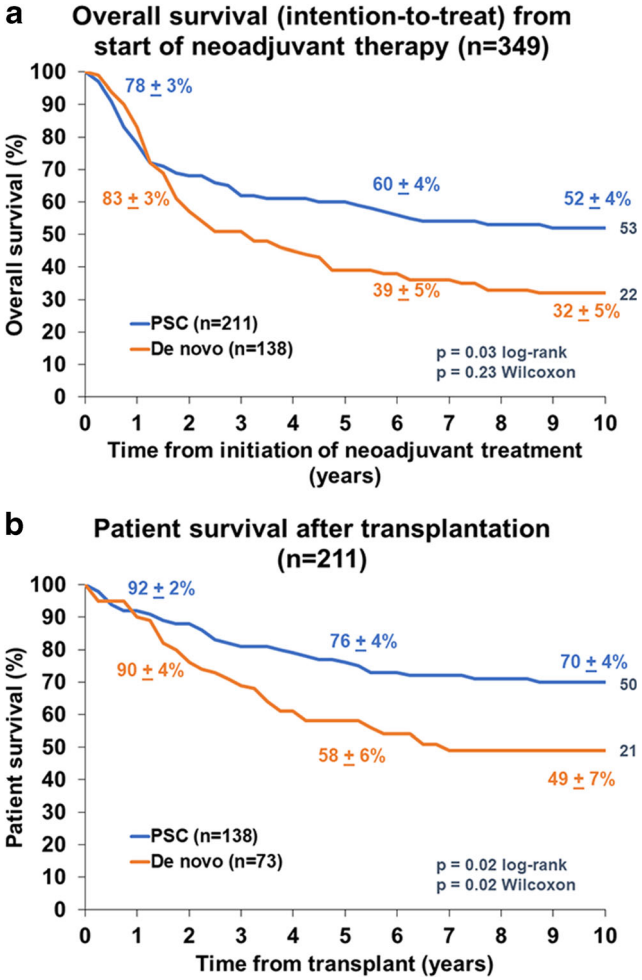

Fig. 2 **a** Overall survival (intention-to-treat) from start of neoadjuvant therapy (PSC-associated vs. de novo pCCA; n = 349). **b** Patient survival after transplantation (PSC-associated vs. de novo pCCA; n = 211)

irradiation of the abdomen precluding additional radiation, or a previous attempt at surgical resection. We routinely perform endoscopic ultrasound guided aspiration of the regional hepatic lymph nodes prior to neoadjuvant therapy and exclude patients with lymph node metastases. Endoscopic trans-gastric or percutaneous trans-hepatic biopsies of tumor to establish diagnosis have, in our experience, been associated with the seeding of metastases in the peritoneum and is now an absolute exclusion criterion.[21] Vascular encasement and tumor extension along the duct are not considered contraindications, although portal vein encasement is a negative prognostic marker for residual tumor in the explant.[22] Lastly, the patient must meet other criteria for medical candidacy for liver transplantation that is in accord with our transplant program practice.

Once deemed an appropriate candidate, the patient proceeds to receive neoadjuvant chemoradiation therapy.[23,24] Radio-sensitization is achieved through infusion of 5-fluorouracil throughout the 2 weeks of external beam radiotherapy that delivers an average dose of 4500 cGy. Approximately 1 week after external beam therapy, patients receive a high-dose brachytherapy boost using Iridium-192 (administered through a nasobiliary or trans-hepatic catheter) to deliver a dose of 930–1600 cGy directly to the tumor.[24] If brachytherapy cannot be delivered, a supplemental stereotactic body radiation therapy dose of 3000 cGy or proton-beam therapy is administered as an alternative. Thereafter, the patient is placed on maintenance oral capecitabine.

All patients undergo operative staging prior to transplantation, usually as a separate procedure performed as the time nears for deceased donor liver transplantation (DDLT) or the day before living donor liver transplantation (LDLT). The staging operation includes a complete exploration of the abdominal cavity, routine biopsy of regional lymph nodes (the lymph node overlying the common hepatic artery at the take-off of the gastroduodenal artery and a lymph node along the common bile duct, in addition to any suspicious lymph nodes), evaluation of the caudate lobe to assess whether caval-sparing hepatectomy will be possible (necessary for LDLT), and biopsy of any other suspicious lesions. We now utilize a hand-assisted laparoscopic approach to minimize the incision. We also liberally apply Seprafilm (Sanofi-Aventis) to prevent adhesions for patients that stage negative and are awaiting a DDLT. Any findings of metastatic disease or tumor extension to adjacent tissues preclude transplantation. Occasionally, a patient is too sick to undergo the staging operation as a separate procedure. These patients usually have underlying PSC or other chronic liver disease resulting in a high Model for End-stage Liver Disease (MELD) score and/or ascites—staging is performed at the time when a donor liver is available. Combining the staging and transplant operations requires close coordination with the organ procurement organization. This also necessitates having a back-up patient in the event the staging procedure yields findings that prohibit transplantation. The likelihood that findings preclude transplantation is different for patients with PSC-associated pCCA than for patients with de novo pCCA. The drop-out rate at staging is approximately 15% for patients with underlying PSC and 28% for those with de novo pCCA. The estimated median survival for patients who eventually drop out (for any reason) is 12 months from the time of cancer diagnosis and approximately 6 months from the staging operation.[25]

Special Considerations

There are several problems and complications that can arise during, and after neoadjuvant therapy and liver transplantation for patients with pCCA that are unique compared with liver transplantation for other indications.

Pre-transplant

Upon completion of neoadjuvant chemoradiation, patients may have to wait for a significant length of time before they receive a deceased donor organ. During this time, they may develop gastroduodenal ulceration with bleeding, perforation, and/or obstruction; acute cholecystitis; and complications due to progression of their underlying liver disease. Due to the burdens of disease and treatment, they may become malnourished from poor appetite and oral intake. Thus, it is important that patients and their coordinators stay in regular contact to recognize progressive weight loss to enable prompt intervention. These patients may require placement of a nasogastric or nasojejunal tube for enteral tube feeding.

Recurrent cholangitis is very common due to biliary obstruction, indwelling biliary stents, radiation-induced ductal injury, and underlying PSC. Most patients require frequent endoscopic retrograde cholangiograms with exchange of stents to maintain adequate biliary drainage. This may mean frequent exposure to multiple courses of antibiotics and, as a result, may harbor multi-drug-resistant bacteria. Cholangitis may become increasingly difficult to treat. Due to this colonization and the need for Roux-en-Y biliary-enteric anastomosis during liver transplantation, patients are at increased risk for intra-abdominal infections. The infection risk is as high as 43%.[26] Having a dedicated infectious disease team on board to guide anti-microbial therapy is crucial as postoperative abdominal infections are associated with increased mortality rates. Patients with pCCA are also prone to develop deep vein thrombosis (DVT), especially after the staging operation, and we suggest thrombo-prophylaxis for all patients during prolonged hospital stays and after operative staging.

Peri-transplant

The technical aspects of liver transplantation for patients with pCCA include avoiding the use of the irradiated native hepatic artery for arterial inflow to reduce the risk of hepatic arterial thrombosis during DDLT. We prefer using a donor iliac artery as an infra-renal aortic jump graft for all patients, even for those with healthy-appearing arteries. This technique did not work for LDLT due to the large size mismatch, so we reverted to using the native common hepatic artery along with close observation and early intervention for patients that developed hepatic artery stenosis.[27] The portal vein and common bile duct are divided as close to the pancreas as possible. The resultant short portal vein is usually not a problem with DDLT as the donor portal vein usually has more than adequate length. Living donor portal vein length, however, is often inadequate, and we frequently use a segment of deceased donor iliac vein as an interposition graft between the donor and recipient portal veins. The use of cold-stored donor vein grafts, while inevitable, is associated with an increased hazard ratio of 22.1 for portal vein stenosis.[28] The extra length, however, comes in handy should portal vein stenosis occur, as intervention through stenting can be achieved safely without occluding the intrahepatic portal vein branches. Biliary reconstruction always requires a choledocho-jejunostomy. Malignancy clearance requires low division of the common bile duct which precludes a duct-to-duct anastomosis. Although we often perform a choledocho-duodenostomy for patients undergoing transplantation for PSC without pCCA, this anastomosis would not be safe in pCCA patients due to the duodenum being in the irradiated field. Patients with pCCA arising in PSC may have microscopic involvement of the common bile duct, and we routinely check the margin with frozen section at the time of hepatectomy. If the common bile duct margin does show involvement (approximately 10% of the time), we have either re-excised the duct (all three patients developed recurrence) or performed a pancreatico-duodenectomy. The pancreato-duodenectomy is performed prior to the anhepatic phase of the transplant, and reconstruction is done after reperfusion of the donor liver. We have not done a pylorus-preserving resection due to concern for the pylorus being in the irradiated field. Reconstruction is done in a standard fashion during DDLT. We recently started using a separate Roux limb for biliary reconstruction during LDLT due to the high rate of biliary leaks. Lastly, several patients with gastric outlet obstruction have required a gastro-jejunostomy during or after transplantation. We have also tried to avoid the use of donor livers procured after circulatory arrest due to the increased risk of biliary and hepatic artery complications in pCCA patients.

Post-transplant

Due to the increased risks for arterial thrombosis and DVT, we start anti-coagulation postoperatively as soon as the INR is less than 2. Patients are maintained on aspirin following discharge indefinitely. Compared with liver transplantation for other indications, there is increased risk of late arterial (21%) and portal venous (22%) complications, presumably due to the irradiation. With close follow-up including Doppler ultrasound surveillance, we have been able to achieve prompt intervention for vascular problems and avoid graft loss.[27,28] In addition to regular post-transplant follow-up, serum tumor markers, chest and abdominal CT are performed at 4 months and annually thereafter for cancer surveillance. Factors associated with post-transplant cancer recurrence include perineural and lymphovascular invasion, elevated CA 19-9 at time of transplant, encasement of the portal vein, and the extent of residual tumor on the explant specimen.[24,29] These factors help identify patients who are at high risk of recurrence and may benefit from additional therapy (adjuvant chemotherapy).

Future Developments

Neoadjuvant therapy followed by liver transplantation has been shown to be an effective therapy for patients with early-stage unresectable pCCA arising de novo and pCCA arising in the setting of PSC. As with transplantation for other indications, the main limitation of this therapy is the availability of donor organs.[30] Intention-to-treat survival data from Mayo Clinic and several other centers demonstrate efficacy with excellent 5- and 10-year survival after start of therapy. Survival after transplantation exceeds 50% at 5 years for both pCCA arising in PSC and de novo pCCA, and these results justify both deceased and living donor liver utilization. Since initiation of this treatment in 1993, there has been a significant increase in the time interval between completion of neoadjuvant therapy and liver transplantation. This interval varies widely by blood type, transplant center location, and living donor availability. We have observed that a longer time interval between neoadjuvant therapy and transplantation is associated with less disease recurrence.[31] Longer intervals select for patients with a better oncologic profile, who are less likely to develop disease progression after neoadjuvant therapy, and less likely to develop recurrence after transplantation. However, patients with prolonged intervals also develop more radiation-induced fibrosis resulting in more difficult staging and transplant operations. LDLT may circumvent these issues by obviating the need to waitlist for a deceased donor, and allows for optimal timing of transplantation. Thus far, we have performed 76 LDLTs for pCCA, and the outcomes between LDLT and DDLT for pCCA arising in PSC are similar. LDLT for de novo pCCA, however, seems to be associated with more disease recurrence and slightly worse patient survival compared with DDLT. Although the differences are not significant, we are concerned that some patients should be observed for disease progression after neoadjuvant therapy for a period to select out those patients who are destined to fall out due to disease progression in order to avoid recurrences after transplantation.

Several studies have suggested that liver transplantation is more effective than resection, and that the indications for neoadjuvant therapy and liver transplantation should be expanded to include patients with resectable pCCA. Based on our highly favorable experience, we have advocated for this approach for patients with pCCA arising in PSC, and we have transplanted many such patients. The role of neoadjuvant therapy and liver transplantation for patients with *potentially resectable* pCCA arising de novo, however, is highly controversial. Our early data were equivocal, and we were unable to determine if patients with de novo pCCA would benefit from liver transplantation over resection from an intention-to-treat perspective.[32] The consensus statement released by the American Hepato-Pancreato-Biliary Association in 2015 thus recommended that resection should be standard therapy for patients with resectable de novo pCCA.[33] The recent publication by Ethun et al. found that liver transplantation, compared with resection for patients who would have met criteria for transplantation, had better survival than observed after resection—72% vs. 45% and 64% vs. 31% at 3 and 5 years ($p < 0.001$).[19] Subset analysis of patients with pCCA unrelated to PSC continued to show superiority of transplant over resection with survival rates of 54% vs. 44% and 54% vs. 29% at 3 and 5 years, respectively ($p = 0.03$).[19] As pointed out in the accompanying editorial by the senior author of this review, the intention-to-treat analysis shows 5-year overall survival of 41% for patients enrolled in the neoadjuvant therapy/transplant protocol versus 27% for those who underwent resection, a difference of only 14%.[34] We contend that this difference is too small to justify the use of a donor liver for resectable pCCA unrelated to PSC. Furthermore, the results with resection reported in the same study are somewhat lower than results commonly reported in the literature which may reflect a lower threshold to proceed with an attempt at resection when there is no other alternative potentially curative therapy. Mayo Clinic data demonstrate 39% and 32% survival at 5 and 10 years from the start of therapy, results comparable with those achieved with resection of resectable disease.[34] An ongoing randomized, intention-to-treat multi-center trial in France TRANSPHIL (NCT02232932) comparing neoadjuvant chemoradiation and liver transplantation versus surgical resection will further elucidate critical information on this controversial topic.

In summary, liver transplantation has proven in the past two decades to play a significant role in the treatment of early-stage unresectable pCCA and pCCA arising in PSC. Excellent outcomes can be achieved by adherence to strict patient selection criteria, administration of high-dose neoadjuvant therapy, and operative staging prior to transplantation. Neoadjuvant therapy and liver transplantation can achieve results similar to resection for patients with early-stage unresectable pCCA and is the treatment of choice for patients with pCCA arising in the setting of PSC.

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