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REVIEW

Liver transplantation for cholangiocarcinoma

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Summary

Liver transplantation following high dose neoadjuvant radiotherapy with chemosensitization achieves excellent results for patients with early stage, unresectable hilar cholangiocarcinoma or cholangiocarcinoma arising in the setting of primary sclerosing cholangitis.

Introduction

Hilar cholangiocarcinoma (CCA) is a devastating disease. Even though resection is well established as conventional treatment, very few tumors are amenable to complete resection. Unfortunately, 5-year survival is only 20–40% for resectable disease. Liver transplantation alone is equally poor treatment. Until recently, CCA has been considered by most transplant centers to be a contraindication for transplantation. Two transplant centers, the University of Nebraska and the Mayo Clinic, have pioneered a strategy of neoadjuvant radiochemotherapy and subsequent transplantation for patients with unresectable hilar CCA and have demonstrated success. This paper reviews results of liver transplantation with and without neoadjuvant therapy and discusses the current role of liver transplantation in the treatment of hilar CCA.

Cholangiocarcinoma

The incidence of CCA in the United States is rising and currently estimated at 3000–4000 cases per year [1]. The incidence is especially high in patients with primary sclerosing cholangitis (PSC) – up to 10% within the first 10 years after diagnosis [2].

Cholangiocarcinoma may occur as an intrahepatic mass separate from the hilus and major biliary branches or as an obstructing tumor involving the extrahepatic and/or major intrahepatic bile ducts. Intrahepatic CCA is best treated by liver resection. Liver transplantation for intrahepatic CCA (unlike hepatocellular carcinoma) is fraught with rapid recurrence and has been abandoned by most centers [3]. Liver transplantation also has no role in the treatment of periductal CCA that is limited to the extrahepatic duct below the bifurcation of the common hepatic duct; these tumors are best treated by surgical resection.

Until recently, surgical resection has been the mainstay of treatment for periductal CCA arising in the hilus of the liver. Launois proposed radical resection including partial hepatectomy, as a potentially curative operation, and initial results demonstrated improved survival [4]. Since then, there has been a multitude of published experiences with similar results. Five-year patient survival can be achieved for 20–30% of patients with resectable CCA [5–13].

Unfortunately, extensive perineural and lymphatic invasion, bilateral liver involvement, and vascular encasement frequently preclude potentially curative resection [14]. Survival with unresectable CCA is only 12–16 months after onset of symptoms [15].

Approximately, 10% of patients with CCA in the United States also have underlying PSC, and CCA arising in association with underlying PSC is even more difficult to treat. Advanced tumor stage and liver disease lead to high risks for involved margins and hepatic decompensation after the procedure [16].

Liver transplantation alone

Orthotopic liver transplantation was once thought to be an ideal operation for CCA. Liver transplantation easily achieves a tumor-free margin within the liver, accomplishes a radical resection, and also treats underlying PSC when present. Despite this sound rationale, actual experiences during the late 1980s and early 1990s were uniformly poor. Liver transplantation alone was followed by high recurrence rates and poor patient survival. The Cincinnati Transplant Tumor Registry reported 28% 5-year survival with a 51% tumor recurrence rate [3]. Eighty-four per cent of the recurrences were detected within 2 years, with 47% occurring in the liver allograft and 30% in the lungs. Incidentally detected CCA fared no better than other tumors, and adjuvant therapy was not associated with prolongation of survival.

Several additional multicenter series corroborate the registry findings. A Scandinavian series reported 30% 5-year survival for patients with early-stage CCA (no mass lesions) arising in the setting of PSC [17]. The Spanish liver transplant centers reported a similar experience, i.e. 30% 3-year survival for 36 patients [18]. Even CCA incidentally found in liver explants portended a poor prognosis as reported in a multicenter Canadian experience [19]. Three-year survival for 10 patients was identical to the Spanish series – 30%, and the median time to recurrence was 26 months.

A more radical approach with cluster abdominal transplantation reported by the University of Pittsburgh had equally poor results – 20% 3-year survival and a 57% recurrence rate [20]. A similar experience was recently reported by Neuhaus' team in Berlin [21]. Sixteen patients with CCA were treated by combined liver transplantation and pancreatoduodenectomy between 1992 and 1998, and results were compared with those achieved for eight patients without pancreatoduodenectomy. Pancreatoduodenectomy at the time of liver transplantation was associated with significant higher morbidity than transplantation alone. Long-term survival (>4 years) was achieved in only three lymph node negative patients of 20 patients that survived the perioperative period. Neuhaus and colleagues concluded that 'there is no good evidence that more radical resections alone are able to markedly improve long-term results'.

Neoadjuvant therapy

Despite the poor results with liver transplantation alone, some patients with favorable tumors – negative margins and the absence of regional lymph node metastases – did benefit from transplantation [22]. In addition, a small group of patients at the Mayo Clinic treated with primary radiotherapy and chemosensitization alone (without resection) had 22% 5-year survival [23].

Based on the known palliative efficacy of radiotherapy for CCA and knowledge that CCA resection failures are usually due to locoregional recurrence rather than distant metastases [24], the transplant team at the University of Nebraska pioneered a strategy of high-dose neoadjuvant brachytherapy and 5-fluorouracil (5-FU) followed by liver transplantation [25]. Although there were significant complications attributed to the use of high-dose brachytherapy, early results were promising with regard to locoregional control of cancer.

The Mayo Clinic adopted this concept with the development of a similar neoadjuvant therapy/liver transplant protocol in 1993. The protocol combined the benefits of radiotherapy, chemosensitization, liver transplantation, and appropriate patient selection for patients with localized, unresectable hilar CCA. Preliminary results for 11 patients reported in 2000 were encouraging [26], and an update in 2004 reported 82% 5-year survival for 28 patients [27].

Mayo Clinic protocol

The Mayo Clinic protocol involves careful selection of patients (Tables 1 and 2) with early-stage CCA arising in the setting of underlying PSC or deemed anatomically unresectable by an experienced hepatobiliary surgeon. Criteria for anatomical unresectability include bilateral segmental ductal extension, encasement of the main por-

Table 1. Criteria for neoadjuvant therapy and liver transplantation.

Diagnosis of cholangiocarcinoma
Transcatheter biopsy or brush cytology
CA-19.9 > 100 mg/ml and/or a mass on cross-sectional imaging with a malignant appearing stricture on cholangiography
Biliary ploidy by FISH with a malignant appearing stricture on cholangiography
Unresectable tumor above cystic duct
Pancreatoduodenectomy for microscopic involvement of CBD
Resectable CCA arising in PSC
Radial tumor diameter ≤3 cm
Absence of intra- and extrahepatic metastases
Candidate for liver transplantation

CBD, common bile duct; CCA, cholangiocarcinoma; PSC, primary sclerosing cholangitis.

Table 2. Exclusion criteria.

Intrahepatic cholangiocarcinoma
Uncontrolled infection
Prior radiation or chemotherapy
Prior biliary resection or attempted resection
Intrahepatic metastases
Evidence of extrahepatic disease
History of other malignancy within 5 years
Transperitoneal biopsy (including percutaneous and EUS guided FNA)

EUS, endoscopic ultrasound; FNA, fine needle aspiration.

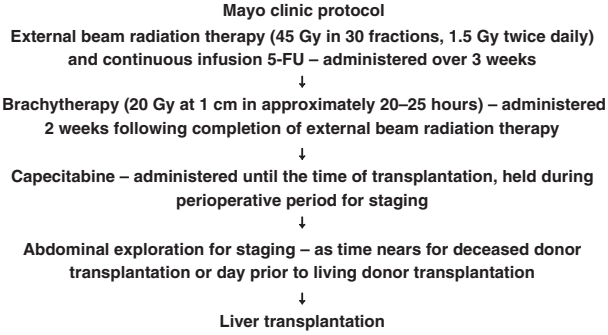

Figure 1 Mayo Clinic neoadjuvant therapy and liver transplantation protocol.

tal vein, unilateral segmental ductal extension with contralateral vascular encasement, and unilateral atrophy with either contralateral segmental ductal or vascular involvement. Because of the difficulty in assessing the extent of disease along the bile duct, there are no longitudinal limits for bile duct involvement. Original criteria required that hilar CCA not extend lower than the cystic duct, but it was subsequently found that early CCA arising in PSC with unsuspected common bile duct involvement found at transplantation was amenable to transplantation with pancreatoduodenectomy. Vascular encasement of the hilar vessels is not a contraindication to transplantation. The upper limit of tumor size is 3 cm when a mass is visible on cross-sectional imaging studies, and there must be no evidence for intra- or extrahepatic metastases by chest CT, abdominal CT or MRI, ultrasonography, or bone scan. The protocol specifically excludes patients with intrahepatic CCA or gall bladder involvement. Surgical intervention and percutaneous or endoscopic ultrasound-directed transperitoneal biopsy or fine needle aspiration have been observed to cause peritoneal seeding and are now considered absolute contraindications to transplantation. Candidates must have received no other treatment prior to neoadjuvant therapy, and have no active infections or medical conditions that would preclude either neoadjuvant therapy or liver transplantation.

The Mayo Clinic protocol and timeline for treatment are outlined in Fig. 1. Neoadjuvant therapy is targeted to the primary tumor and regional lymph nodes. 1.5 Gy is administered twice daily by external beam therapy for a total dose of 45 Gy. Intraluminal brachytherapy is administered by transcatheter irradiation with iridium 2 weeks after completion of external beam therapy. 20 Gy is delivered to a 1 cm radius over approximately 20–25 h through an endoscopically placed biliary tube (or occasionally through a percutaneous transhepatic tube). 5-FU is given during the radiation treatment and capecitabine is then administered until transplantation.

All patients undergo a staging abdominal exploration prior to transplantation. Staging operations are performed as patients near the top of the waiting list for deceased donor transplantation or the day before living donor transplantation. Selected patients without any prior upper abdominal operations (including laparoscopic cholecystectomy) have been more recently staged with hand-assisted laparoscopy. The staging operation involves a thorough abdominal exploration and assessment of the caudate for involvement, which would preclude subsequent caval-sparing hepatectomy. At least one lymph node along the proper hepatic artery and another along the common bile duct are excised even if the regional nodes appear normal. The liver is carefully palpated for evidence of intrahepatic metastases that may have gone undetected by preoperative imaging studies. Regional lymph node metastases, peritoneal metastases, or locally extensive disease precludes transplantation.

Mayo Clinic experience

One hundred eighty-four patients have begun neoadjuvant therapy at the Mayo Clinic Rochester since 1993, and 120 have had favorable findings at the staging operation and undergone liver transplantation – 81 deceased donors, 38 living donors, and 1 domino familial amyloid donor [CB Rosen, unpublished data through August 2009]. Initially, 40–50% had findings at the staging operation that precluded transplantation. With adoption of endoscopic ultrasound (EUS)-directed aspiration of regional hepatic lymph nodes in 2003, most patients destined to fall out at staging are now detected prior to the administration of neoadjuvant therapy. Currently, less than 15% fall out because of findings during the staging operation. Five-year actuarial survival for all patients who begin neoadjuvant therapy is 54%, 61% for patients with underlying PSC and 42% for those with *de novo* CCA. Five-year survival after transplantation is 73%, 79% for patients with underlying PSC and 63% for those with *de novo* CCA. Twenty-one patients (18%) have developed recurrent CCA at a mean interval of 25 months after

transplantation. The longest interval between transplantation and recurrence was 64 months, and 33 of 42 patients with at least five follow-ups are alive and disease-free.

The Mayo Clinic team published an update to their series with an aim to identify prognostic factors [28]. Factors that adversely affect prognosis were older patient age, prior cholecystectomy, CA-19.9 > 100 at the time of transplantation, visible mass on cross-sectional imaging, and prolongation of waiting time. Explanted livers with residual cancer >2 cm, high tumor grade, and/or perineural invasion also were associated with tumor recurrence.

Neoadjuvant therapy is associated with long-term vascular complications rarely seen in patients undergoing liver transplantation alone [29]. Portal vein stenosis with or without thrombosis occurs in 20% of transplanted patients. It is often detected on a follow-up CT performed 4 months after transplantation. The native common hepatic artery is avoided during deceased donor transplantation, but its use in living donor transplantation is associated with a 20% late stenosis/thrombosis rate. Although portal venous and hepatic artery stenoses may develop after transplantation, they are amenable to treatment with transluminal angioplasty and stent insertion. Fortunately, no grafts have been lost because of these late complications.

Controversy and discussion

The Mayo Clinic experience has raised several controversial issues: (i) Are results due to patient selection, treatment, or both? (ii) Does the absence of pathologic confirmation of disease possibly explain the good results? (iii) Do results warrant use of either a living donor or deceased donor liver? (iv) Would transplantation with neoadjuvant therapy be better treatment than resection, even for patients with potentially resectable disease? and (v) What is the appropriate prioritization for patients with CCA awaiting a deceased donor liver?

The Mayo Clinic group attributes their success to both patient selection and treatment. Untreated CCA has a 50–70% mortality rate within 12 months [2,15] which is much lower than the 54% 5-year survival for patients entered in the Mayo Clinic protocol and 73% 5-year survival after transplantation. Selection criteria are quite strict. Over the past 10 years, the number of patients with CCA seen at the Mayo Clinic has increased from approximately 110 to 220 patients per year, and the number of patients enrolled in the neoadjuvant therapy and liver transplantation protocol has increased from 10 to 20 patients per year – approximately 10% of the total number of CCA patients. Many of the patients are not enrolled as a result of intrahepatic CCA, locally advanced disease, and metastatic disease. The Mayo Clinic is also seeing a reduction in patient referrals as other transplant centers adopt the Mayo Clinic protocol. The selection criteria have also undergone data-driven refinement since the initiation of the protocol in 1993. Indeed, patients with transperitoneal biopsy or fine needle aspirations of the primary tumor are now excluded from treatment.

Unpublished results from the Mayo Clinic show that approximately half of the patients transplanted for CCA did not have pathologic confirmation of disease prior to administration of neoadjuvant therapy. Over 40% were found to have residual CCA in the explanted liver compared to 60% residual disease in those patients with pathologically confirmed disease. Most importantly, the CCA recurrence rates are the same for patients with and without pathologic confirmation before the start of therapy. Thus, the absence of a pathologic diagnosis in some patients does not indicate that inclusion of patients with a misdiagnosis of CCA leads to an artificial improvement in survival.

Neoadjuvant therapy and liver transplantation achieve results similar to transplantation for other chronic liver diseases (i.e., hepatitis C virus infection, PSC) and hepatocellular carcinoma [27]. Thus, it would seem appropriate that patients with CCA be considered appropriate recipients of scarce deceased and living donor livers. As these patients are not candidates for resection (either because of being unresectable or having underlying PSC), transplantation is their only opportunity for prolonged survival.

The Mayo Clinic has also reported that survival after transplantation in patients with unresectable CCA or CCA arising in the setting of PSC, exceeded survival in patients who underwent resection during the same period of time [30]. Transplantation affords a more radical extirpation of CCA than resection, and the procedure is technically feasible despite aggressive neoadjuvant therapy. Equally important is certain avoidance of hepatic duct margin involvement. Indeed, neoadjuvant therapy and transplantation may be considered a 'new paradigm' in the treatment of CCA – the rationale and implications of this approach are discussed in detail in a recent article in Surgery [31].

One might consider neoadjuvant therapy and liver transplantation for patients with potentially resectable, *de novo* CCA. However, the most recent Mayo Clinic results now show lower survival for the patients with *de novo* CCA. Indeed, differences in results between resection and neoadjuvant therapy/transplantation are less marked than for patients with *de novo* CCA than those with underlying PSC. Moreover, Neuhaus *et al.* have reported 60% 5-year survival (after censoring perioperative mortality) following resection with portal vein resection and reconstruction, which is a significant

improvement compared with prior experiences with resection [32]. Thus, the benefit of liver transplantation with neoadjuvant therapy for patients with potentially resectable *de novo* CCA is less pronounced than for patients with unresectable CCA or CCA arising in the setting of PSC.

The Mayo Clinic data clearly show better survival for patients with CCA arising in the setting of PSC than for patients with *de novo* CCA. This finding is somewhat at odds with an early paper describing the poor outcome of CCA arising in the setting of PSC [16]. A possible explanation is that PSC patients are followed closely for the development of CCA such that CCA arising in the setting of PSC is detected earlier than CCA arising *de novo*. Indeed, CCA arising *de novo* is associated with adverse prognostic factors such as advanced age and a visible mass on cross-sectional imaging.

Prioritization for deceased donor liver allocation is the most controversial issue of all. This issue was discussed in detail by an international group of transplant surgeons and physicians comprising an *ad hoc* MELD Exception Study Group, which met in Chicago, March 1–2, 2006. The deliberations and recommendations by this group were published in a supplement to Liver Transplantation in December 2006 [33].

The MELD Exception Study Group concluded that the current data justify priority for patients enrolled in clinical trials provided (i) transplant centers submit formal patient care protocols to the UNOS Liver and Intestinal Committee; (ii) candidates satisfy accepted diagnostic criteria for CCA and be considered unresectable on the basis of technical considerations or underlying liver disease (e.g. PSC); (iii) tumor mass, when visible on cross-sectional imaging studies, be less than 3 cm in diameter; (iv) imaging studies to assess patients for intra- and extrahepatic metastases be repeated prior to interval score increases; (v) regional hepatic lymph node involvement and the peritoneal cavity be assessed by operative staging after completion of neoadjuvant therapy and prior to transplantation; and (vi) transperitoneal aspiration or biopsy of the primary tumor be avoided because of the high risk of tumor seeding associated with these procedures. The group also concluded that there was no justification to warrant prioritization of patients with biliary dysplasia to avoid progression to CCA. In 2009, the UNOS Board of Directors voted to implement the allocation changes recommended by this report and to adopt the Mayo Clinic criteria for a MELD score exception adjustment.

Conclusion

Hilar CCA – once a contraindication for transplantation – has re-emerged as an indication for liver transplantation when combined with effective preoperative neoadjuvant therapy. Strict adherence to selection criteria is of paramount importance. The combination of neoadjuvant therapy, operative staging to rule-out regional metastases, and liver transplantation has achieved remarkable success for selected patients with early-stage unresectable CCA and CCA arising in the setting of PSC. Patients with *de novo* CCA should be treated with resection whenever possible. Patients with anatomically unresectable CCA or CCA arising in the setting of PSC should be considered for neoadjuvant therapy and liver transplantation.

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