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REVIEW ARTICLE

Surgery for cholangiocarcinoma: the role of liver transplantation

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Abstract
Liver transplantation alone for unresectable hilar cholangiocarcinoma (CCA) is fraught with frequent recurrence and poor long-term survival. The Mayo Clinic developed a novel therapeutic protocol combining neoadjuvant chemoradiation and orthotopic liver transplantation (OLT) in 1993 to treat patients with unresectable hilar CCA or CCA arising in the setting of PSC. *Aim.* We recently reviewed our experience over the past 14 years with the specific aim to evaluate the long-term outcomes of CCA patients treated according to our study protocol. *Methods.* We analyzed data from all patients enrolled in the Mayo Clinic liver transplant protocol since 1993. Statistical data analysis of recurrence and survival rates was performed using the Kaplan-Meier method. *Results.* 148 patients were enrolled in the protocol. Of 90 patients who completed neoadjuvant therapy and subsequent OLT, 71 are alive and 19 have died – only 8 due to recurrent CCA. Nineteen patients are awaiting OLT and 39 were removed from the protocol owing to disease progression or death. Overall, 1-, 3-, and 5-year patient survival was 82%, 63%, and 55%, respectively; 1-, 3-, and 5-year survival after OLT was 90%, 80%, and 71%. *Conclusions.* Neoadjuvant chemoradiation and OLT achieves significantly lower recurrence and higher long-term survival rates than resection, OLT alone, or medical treatment in hilar CCA. Additional experience at independent transplant centers is necessary to confirm these encouraging results, address the role of neoadjuvant therapy and liver transplantation versus conventional resection, determine appropriate inclusion/exclusion criteria, and define the risk of disease progression while awaiting transplantation.

Key Words: *Hilar cholangiocarcinoma, liver transplantation, neoadjuvant therapy*

Introduction

Cholangiocarcinoma (CCA) may occur as an intrahepatic mass or as an obstructing tumor involving the major intrahepatic and/or extrahepatic bile ducts. Intrahepatic CCA is best treated by liver resection. Liver transplantation for intrahepatic CCA is fraught with rapid metastases and has been abandoned at most centers [1].

Liver transplantation 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.

Surgical resection has been the mainstay of treatment for periductal CCA arising in the hilus of the liver. Unfortunately, extensive perineural and lymphatic invasion, bilateral liver involvement, and vascular encasement frequently preclude potentially curative resection [2]. CCA arising in the setting of PSC is even more difficult to treat either due to advanced tumor stage or liver disease, and resection in the setting of PSC is essentially futile [3].

Liver transplantation alone

Orthotopic liver transplantation appeared promising as it would easily achieve a tumor-free margin within the liver, accomplish a radical resection, and treat underlying PSC when present. Despite this sound rationale, actual experiences have been very poor. The Cincinnati Transplant Tumor Registry reported 28% 5-year survival with a 51% tumor recurrence rate [1]. Eighty-four percent 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 survival.

Three recent multicenter series corroborate the registry findings. A Scandinavian series reported 30% 5-year survival for patients with early stage

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CCA (no mass lesions) arising in the setting of PSC [4]. The Spanish liver transplant centers reported a similar experience, 30% 3-year survival for 36 patients [5]. Even CCA incidentally found in liver explants portended a poor prognosis, as reported in a multicenter Canadian experience [6]. Three-year survival for 10 patients was identical to the Spanish series – 30%, and the median time to recurrence was 26 months.

The University of Pittsburgh pioneered a radical approach with cluster abdominal transplantation, but results were equally poor, i.e. 20% 3-year survival and a 57% recurrence rate [7]. As a result of these experiences, CCA has become widely recognized as a contraindication to liver transplantation [8].

Neoadjuvant therapy and liver transplantation

Despite the overall poor results with liver transplantation alone, a few patients with negative margins and absence of regional lymph node metastases did do well after transplantation [9]. 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 [10].

Based on the known palliative efficacy of radiotherapy for CCA and the knowledge that CCA resection failures are usually due to locoregional recurrence rather than distant metastases [11], 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 [12]. Although there were significant complications attributed to 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 [13], and an update in 2004 reported 82% 5-year survival for 28 patients [14].

Mayo clinic protocol

The Mayo Clinic protocol involves careful selection of patients with early stage CCA which is either unresectable or arising in the setting of underlying PSC. Vascular encasement of the hilar vessels is not a contraindication to transplantation. The upper limit of tumor size is 3 cm, and there must be no evidence of intra- or extrahepatic metastases. The protocol specifically excludes patients with intrahepatic CCA or gallbladder involvement.

Neoadjuvant therapy includes 4000 to 4500 cGy administered by external beam, followed by 2000 to 3000 cGy transcatheter irradiation with iridium. 5-FU is given during the radiation treatment and capecitabine is then administered until transplantation. Prior to transplantation, patients undergo a staging abdominal exploration. Regional lymph node metastases, peritoneal metastases, or locally extensive disease preclude transplantation.

Mayo Clinic experience

One-hundred-and-forty-eight patients have begun neoadjuvant therapy at the Mayo Clinic Rochester since 1993, and 90 have had favorable findings at the staging operation and subsequent liver transplantation [unpublished data through October 2007]. Five-year actuarial survival for all patients that began neoadjuvant therapy is 55%, and 5-year survival after transplantation is 71%.

Factors that adversely affect prognosis are: older patient age, prior cholecystectomy, CA-19.9 >100 at time of transplantation, visible mass on cross-sectional imaging, and prolongation of waiting time [15]. Explanted livers with residual cancer >2 cm, high tumor grade, and/or perineural invasion are also associated with tumor recurrence.

Controversy and discussion

Despite the extensive Mayo Clinic experience, liver transplantation for CCA raises several controversial issues: 1) Does liver transplantation following neoadjuvant therapy have efficacy in the treatment of CCA? 2) Do results warrant use of a donor liver for patients with CCA? 3) Would transplantation with neoadjuvant therapy be better treatment than resection for patients with potentially resectable disease? and 4) What is the appropriate prioritization for patients with CCA awaiting a deceased donor liver?

Efficacy of neoadjuvant therapy and transplantation is demonstrated by comparing results with the natural history of the disease. Untreated CCA has a 50–70% mortality rate within 12 months [16,17], which is much lower than 55% 5-year survival for patients entered in the Mayo Clinic protocol and 71% 5-year survival after transplantation. However, only two centers (Mayo Clinic and the University of Nebraska) have published their experiences with this approach. Confirmation of efficacy by other centers is necessary prior to widespread adoption of this approach to the treatment of hilar CCA.

The Mayo Clinic reported that neoadjuvant therapy and liver transplantation achieves results similar to transplantation for other chronic liver diseases and hepatocellular carcinoma [14]. Thus, it would seem appropriate that patients with CCA be considered appropriate recipients for scarce donor livers. Indeed, neoadjuvant therapy and transplantation is their only opportunity for prolonged survival.

The Mayo Clinic 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 [18]. However, there were significant differences between the two groups; the transplant group was younger and more likely to have underlying PSC (and perhaps earlier stage disease despite being unresectable). 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 to prior experiences with resection [19].

Liver transplantation following neoadjuvant therapy does not appear to be an inferior cancer operation compared to resection. Transplantation affords a more radical extirpation of CCA than does resection with absolute certain avoidance of hepatic duct margin involvement. Liver transplantation is technically feasible despite aggressive neoadjuvant therapy, which is necessary to achieve success. Indeed, neoadjuvant therapy and transplantation may be considered a "new paradigm" in the treatment of CCA [20].

Prioritization for deceased donor liver allocation is highly controversial and has been discussed in detail by an international group of transplant surgeons and physicians [MELD Exception Study Group, Chicago, 1–2 March 2006]. The MELD Exception Study Group concluded that current data justify priority for patients enrolled in clinical trials provided: 1) Transplant centers submit formal patient care protocols to the UNOS Liver and Intestinal Committee; 2) candidates satisfy accepted diagnostic criteria for CCA and be considered unresectable on the basis of technical considerations or underlying liver disease (e.g. PSC); 3) tumor mass, when visible on cross-sectional imaging studies, be less than 3 cm in diameter; 4) imaging studies to assess patients for intra- and extrahepatic metastases be repeated prior to interval score increases; 5) regional hepatic lymph node involvement and the peritoneal cavity be assessed by operative staging after completion of neoadjuvant therapy and prior to transplantation; and 6) transperitoneal aspiration or biopsy of the primary tumor be avoided because of the high risk of tumor seeding associated with these procedures [21].

Conclusions

The results of liver transplantation alone for either intrahepatic or hilar CCA are poor; patient survival is less than 30% at 5 years. Widespread experience (registry data, multicenter and single center reports) warrants avoidance of liver transplantation for patients known to have CCA. Indeed, hilar and intrahepatic CCA are well accepted contraindications for liver transplantation.

The University of Nebraska and the Mayo Clinic have demonstrated that excellent survival can be obtained for highly selected patients with early stage hilar CCA treated with aggressive neoadjuvant therapy prior to liver transplantation. 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 primary sclerosing cholangitis. Additional experience at independent transplant centers will be necessary to confirm these encouraging results, address the role of neoadjuvant therapy and liver transplantation versus conventional resection, determine appropriate inclusion/exclusion criteria, and define the risk of disease progression while awaiting transplantation.

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