LIVER ADVISORY GROUP

Liver transplantation for hilar cholangiocarcinoma (phCCA): time for change in the UK

Early reported experience of LT for phCCA was disappointing. Recent updates reported from several centres worldwide have suggested that with careful patient selection, rigorous protocols of neo-adjuvant therapy including radiation, chemotherapy and timely access to LT acceptable outcomes can be achieved. A number of questions have not been answered with regard to the definition of resectability, survival on an intention to treat basis and the ability to treat patients with available infrastructure in an appropriate time frame.

The Mayo Clinic group reported 71 patients in the transplant treatment protocol of whom 38 underwent LT for hilar CCA. One, 3 and 5 year survival rates were 92%, 82% and 82% after LT. Once recurrence and survival rates were analyzed, they found better outcomes in transplanted patients compared to patients undergoing resection [Rea et al]. The Mayo Clinic protocol involves careful selection of patients with unresectable *de novo* phCCA or phCCA in the setting of PSC without intrahepatic or extrahepatic metastases. Positive lymph nodes are an absolute contraindication. Criteria for anatomical unresectability include bilateral segmental ductal extension, encasement of the main portal vein, unilateral segmental ductal extension with contralateral vascular encasement and unilateral atrophy with contralateral segmental ductal or vascular involvement. There are no longitudinal limits for bile duct involvement [Rosen et al]. A pancreaticoduodenectomy combined with OLT is justified to reach a R0 resection. The upper limit of tumor size is 3 cm when a mass is visible on cross sectional imaging studies. Patients initially receive external-beam radiation (45 Gy in 30 fractions, 1.5 Gy twice daily) and continuous infusion of 5-flurouracil administered over 3 wk. Brachytherapy (20 Gy at 1 cm in approximately 20-25 h) is administered 2 weeks following completion of external beam radiation therapy. After that, patients are treated with oral capecitabine, administered until the time of transplantation. An exploratory laparotomy is performed to exclude metastatic disease in all patients. Staging laparotomies are performed as patients come close to being on the top of the waiting list for deceased

donor liver transplantation, or the day before, in the setting of live donor liver transplantation [Heimbach et al, Rosen et al, Rosen and Gore].

The Mayo Clinic group also published an update to their series with the aim of identifying prognostic factors. They found that older recipient age, prior cholecystectomy, CA-19.9 more than 100 at the time of OLT, visible mass on cross-sectional imaging and prolonged waiting times were related with worse prognosisRosen et al]. This group attributed their success to both patient selection and neoadjuvant treatment. Currently, 10-20 patients are enrolled in the neoadjuvant therapy and LT transplantation per year in this centre [Gore and Rosen].

The survival for transplanted patients with phCCA arising in the setting of PSC is better than for patients with *de novo* phCCA. It could be explained due to close follow-up in PSC patients, making an earlier diagnosis compared to patients with *de novo* CCA [Rosen et al, Darwish et al]. The same authors observed that pretreatment pathological confirmation was not associated with a statistically significantly higher risk for recurrence after OLT and they concluded that pathological confirmation before therapy is desirable, but it should not be a requirement for enrolling into their protocol [Rosen et al].

Encouraged by the Mayo Clinic outcomes, in 2009, the United Network of Organ Sharing/Organ Procurement and Transplantation Network approved the allocation of a standard Model of End-stage Liver Disease (MELD) exception score for patients with phCCA who completed a standardized neoadjuvant therapy protocol [Rosen et al, 41]. Due to the lack of data, the MELD score was set to equal the current standard assigned score for HCC.

Other studies have confirmed the good outcomes of OLT for phCCA following this protocol. Darwish Murad et al [40] presented a multicenter study including 12 large volume centers in the United States. Centers with three or more cases performed between 1993 and 2010 were included. They found that patients with phCCA who were treated with neoadjuvant therapy followed by OLT had a 65% 5 year disease-free survival and the intention-to-treat 5 year survival was 53%. The drop-out rate after 3.5 mo of treatment was 11.5%. Forty-three patients (20%) developed

recurrence after OLT. This figure is very low compared with recurrence in patients who were transplanted without the use of any neoadjuvant protocol, which ranged from 53% to 84%. They concluded that this therapy was highly effective and that the MELD exception was appropriate [Darwish et al].

The use of a multimodality oncologic approach including neoadjuvant chemo radiotherapy with subsequent OLT achieves excellent results for patients with localized, regional lymph node-negative phCCA. Patient survival after OLT is comparable to the results of OLT for other causes. OLT for phCCA should be considered an option in patients diagnosed of an un-resectable phCCA, in centers where the pre-transplant treatment of these patients is optimal. One of the main challenges of this protocol is to determine what patients are unresectable as this can differ between centers.

Taken from Liver transplantation for cholangiocarcinoma: Current status and new insights. Sapisochín et al. World J Surgery 2015 Oct 8; 7(22): 2396–2403.

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Proposal for pilot for liver transplantation for phCCA on background of PSC (?without)

Selection of candidates?

Sclerosing cholangitis

Fit for chemo-radiation

Negative lymph nodes

Anatomical unresectable include bilateral segmental ductal extension, encasement of the main portal vein, unilateral segmental ductal extension with contralateral vascular encasement and unilateral atrophy with contralateral segmental ductal or vascular involvement. No longitudinal limits for bile duct involvement.

Upper limit of tumor size of 3 cm if visible on cross sectional imaging studies.

For discussion

- Pilot programme
- PSC or PSC and cholangiocarcinoma without
- Centres/patient pathway
- Definition of unresectable
- Infrastructure
- As part of ITT/trial
- Timely access to appropriate liver grafts