Editorial

Liver transplantation for hilar cholangiocarcinoma (h-CCA): is it the right time?

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Provenance: This is a Guest Editorial commissioned by Section Editor Guwei Ji, MD, PhD (Liver Transplantation Center, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Comment on: Ethun CG, Lopez-Aguiar AG, Anderson DJ, *et al.* Transplantation Versus Resection for Hilar Cholangiocarcinoma: An Argument for Shifting Treatment Paradigms for Resectable Disease. Ann Surg 2018;267:797-805.

Received: 07 June 2018; Accepted: 22 June 2018; Published: 04 July 2018.

doi: 10.21037/tgh.2018.06.06

View this article at: http://dx.doi.org/10.21037/tgh.2018.06.06

Liver transplantation (LT) is the therapy of choice in selected patients with hepatocellular carcinoma (HCC). In light of the overall excellent results achieved for HCC, LT has been successfully adapted as a therapeutic option for several non-hepatocellular malignancies (1) including unresectable hepatic epithelioid hemangioendothelioma (HEHE) (2), neuroendocrine tumors (NET) (3) or even colorectal metastases in case of liver-only disease (4).

Hilar cholangiocarcinoma (h-CCA) represents another malignant entity potentially curable by LT. h-CCA is a rare but highly aggressive malignancy accounting for approximately 60% of all cholangiocarcinomas (5). The etiopathogenesis of h-CCA is insufficiently understood, yet chronic bile duct inflammation and primary sclerosing cholangitis (PSC) seem to promote its development (6).

To date, radical resections is the standard of care for localized h-CCA without metastatic disease since it is the only curative treatment option for h-CCA (7). R0 resection can result in 5-year survival rates of 20–40% (5,8). When R0 resection is not achieved, however, the 5-year survival rate drops to almost 0% (5). A considerable fraction of h-CCA is staged unresectable at diagnosis and is therefore not eligible for curative-intent resection (7). Chemotherapy, stenting or endoluminal radiofrequency ablation are palliative treatment options with a median survival of about 12 months (9).

To tackle these unsatisfying results, the Mayo Clinic group in Rochester initiated an LT-specific protocol intended to treat patients with unresectable h-CCA or h-CCA (tumor size <3 cm, no evidence for metastases) arising in the setting of PSC. Prior to waitlisting, 5-fluorouracil (5-FU) is given during a course of radiation therapy, followed by capecitabine administered until transplantation (10). Their early experience revealed an actuarial survival of 88% at 1 year and 82% at 5 years after LT (11,12). They later published similar results after expanding the number of enrolled patients to 90 (10). After adoption by other US Centers, Darwish *et al.* reported the outcomes of 287 patients treated between 1993–2010. The authors highlight a 65% rate of recurrence-free survival at 5 years after LT. All in all, the collective experience indicates that LT is an effective therapy in this select group of patients since it outperforms the alternatives by far (13).

While the convincing results may in part be attributed to the strict selection criteria and/or the neoadjuvant therapy, the proof of principle stands (14). However, no sufficient evidence indicating the applicability of this treatment to treat newly diagnosed resectable h-CCAs exists. The superiority of LT over resection has not yet been established and the adjustment of tumor size, lymph node metastasis and patient age remain an important criterion in this exercise (15).

In May 2018, Ethun *et al.* specifically addressed this condition by mining the US Extrahepatic Biliary Malignancy Consortium database. Building on data from 10 US academic centers, they conducted a retrospective analysis of all patients with h-CCA undergoing resection and/or exploratory laparotomy between January 2010 and March 2015. The primary endpoint of the study was patient survival following curative resection *vs.* neoadjuvant therapy and consecutive LT in an intention-to-treat approach. The Mayo protocol was adopted in all 3 centres offering LT as treatment option for h-CCA (12). The large number of transplant patients was achieved by pooling the data from 10 individual institutions.

In total, 304 patients with h-CCA met the defined inclusion criteria and were included in the analysis. Two hundred and thirty-four patients (77%) underwent surgery for resection, 70 (23%) were enrolled into a transplant protocol. Of the 234 patients undergoing conventional surgery, 191 patients eventually received a resection. Of the 70 patients enrolled in a transplant protocol, 41 completed the neoadjuvant chemo-radiation and were subsequently transplanted.

Patient age was significantly lower in the transplant group (54 years compared to 67 years) and the PSC rate was higher. Transplantation was associated with less frequent R1 resection (10% *vs.* 30%), and lower percentages of lymphatic and perineural invasion. Postoperative morbidity was not significantly different in regard to major complications, postoperative liver failure and 90-day mortality while transplanted patients showed a lower overall complication rate. Importantly, the recurrence free survival rate did not differ between the two groups.

The authors found an improved overall survival (OS) rate for patients with h-CCA treated with chemo-radiation and LT compared to patients treated with curative resection. The difference between the two groups remained significant after exclusion of resected patients with tumors >3 cm and nodal manifestations and also after exclusion of patients with PSC. Corresponding with this finding, the intention-to-treat analysis showed an improved survival for patients with h-CCA enrolled in a transplant protocol compared to patients undergoing resection. Again, the survival benefit remained significant after exclusion of patients with tumors >3cm and nodal manifestation and PSC.

Rare diseases such as h-CCA often remain poorly understood for decades without major advances in the therapeutic approach simply due to a lack of appropriate case loads which allow their investigation. This fact highlights the importance of national as well as international registries as well as collaboration in order gather the data necessary to achieve optimal patient care and survival for rare diseases entities.

Noteworthy, the transplant centers included in the analysis by Ethun *et al.* relied on the principles of the Mayo Clinic protocol which dates back to the 1980s. Novel chemotherapeutics, biological drugs and advancements in LT and postoperative transplant patient care holds potential to further improve the results.

The obvious limitation towards expanding this treatment to a larger group of patients is the donor organ shortage. Further to this, the retrospective nature and the imperfection of the comparison warrants more data. Ideally, a prospective controlled trial may help to eventually answer the remaining question and provide more scientific substrate for a proper allocation towards resection *vs.* transplantation. Given an observed 5-year OS of 64% *vs.* 18% following resection (P<0.001), however, it is reasonable to consider these patients and indications for transplantation in clinical trials. Rather than shying away from this indication, the community shall feel all the more motivated to work towards increased donor rates rather than accepting the suggested inferiority of the current standard. Recent developments in organ preservation such as hypothermic or normothermic machine perfusion may help to reduce the discard rate. Furthermore, changes in allocation policies toward a patient-oriented allocation may represent a further option to serve the need of afflicted patients.

In conclusion, the findings by Ethun *et al.* substantially nurture the notion that LT could represent a valuable and effective treatment option for h-CCA, at least in the setting of clinical studies. However, prospective trials with an intention to treat approach now seem warranted.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/tgh.2018.06.06
Cite this article as: Resch T, Esser H, Cardini B, Schaefer B, Zoller H, Schneeberger S. Liver transplantation for hilar cholangiocarcinoma (h-CCA): is it the right time? Transl Gastroenterol Hepatol 2018;3:38.

