Editorial

Refining selection criteria to further increase survival benefit in liver transplantation for unresectable colorectal liver metastases

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Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Comment on: Dueland S, Syversveen T, Solheim JM, *et al.* Survival following liver transplantation for patients with nonresectable liver-only colorectal metastases. Ann Surg 2020;271:212-8.

Submitted Oct 28, 2019. Accepted for publication Nov 25, 2019.

doi: 10.21037/hbsn.2019.11.10

View this article at: http://dx.doi.org/10.21037/hbsn.2019.11.10

Liver transplantation (LT) for hepatocellular carcinoma (HCC) was characterized in its early experience by high recurrence rates due to extensive tumor burden (1). Only after the adoption of Milan criteria (2), LT was recognized as a standard treatment for HCC (3). Besides HCC, other hepatic malignancies were proposed to be treated in the past with LT but due to the poor results observed (4), these indications were abandoned. Among them, colorectal liver metastases (CRLM) were considered an absolute contraindication until recently.

In June 2019, Dueland and colleagues published in *Annals of Surgery* a case series of 15 LT for unresectable CRLM with an estimated 5-year overall survival (OS) of 83% (5). This trial was named SECA-II and followed the previous SECA-I study (6). SECA-I was published 6 years before and showed a 5-year OS of 60% in 21 patients submitted to LT for unresectable CRLM. Four independent predictors of survival were identified, the so-called "Oslo criteria": maximal tumor diameter <5.5 cm, time from primary cancer surgery >2 years, carcinoembryonic antigen (CEA) levels <80 µg/L and no progressive disease under chemotherapy. By applying these criteria in SECA-II, patients of the second trial had at the time of LT a significantly lower number of metastatic lesions (5 *vs.* 8), size of largest liver lesion (24 *vs.* 45 mm), preoperative CEA levels (2 *vs.* 15 µg/L) and longer time between primary tumor resection and LT (22.6 *vs.* 16.8 months) compared to SECA-I patients. However, if we look to table 2, radiological tumor features were significantly worse at diagnosis. The final tumor burden was the consequence of a partial response to neo-adjuvant therapies: patient in SECA-II trial had a 30% response according to RECIST criteria after chemotherapy or less (10–20%) in case of bridging treatments as transarterial chemoembolization or radioembolization. Response to chemotherapy in CRLM seems to be fundamental in selecting a more or less aggressive disease from the biological point of view, especially if a long waiting time before LT has to be expected. Similar is the prognostic value of the dynamic response to locoregional treatments, together with alpha-fetoprotein (AFP) and morphologic characteristics, to predict survival and recurrence in HCC patients (7). Such a refinement of selection criteria also in LT for CRLM turned into better OS as well as longer disease-free survival (DFS) in SECA-II: 1-year DFS increased from 35% to 53% with 4 patients (26.7%) having no recurrence 31 to 49 months after LT. Moreover, most of recurrences occurred in the lung (n=6) and were amenable of resection in almost all cases (5 out 6). Tumor growth was again controlled through the antiangiogenic activity of sirolimus (mTOR inhibitor) but, compared to SECA-I, it was introduced only after 4–6 weeks of tacrolimus, likely due to the occurrence of a high rate of hepatic artery thrombosis and rejection [reported in the literature to be associated with the administration of mTOR inhibitors (8)] in the first trial.

The good results showed by Dueland *et al.* can also

be attributed to the low number of right-sided primary tumors (n=1) and KRAS mutations (n=1) included in the final study population, both of them already recognized as the two the most important prognostic factors for survival after liver resection (9,10). However, the impact of KRAS/BRAF mutation status on survival after LT is unknown, since mutational analysis was not performed at the time of SECA-I trial. On the other hand, a surrogate marker of tumor biology, the liver 18FDG-PET uptake rate, was lower in SECA-II compared to SECA-I. Only time of detection of hepatic metastases was reported to be more unfavourable in SECA-II (synchronous disease in 93% *vs.* 81% of cases).

The major challenge of LT for CRLM is represented by the shortage of organ donors which limits the wide application of this approach. New strategies are under investigation in the field of LT to expand the donor pool such as hypo/normothermic perfusion to restore borderline liver grafts or novel surgical techniques using auxiliary liver grafts, implanted either orthotopically or heterotopically (11,12). However, if allocation of organs for HCC patients should be based on the concept of transplant benefit (13), i.e., allocating the one available organ to the patient with the largest difference in posttransplant and waiting list lifetime, the survival gain obtained by LT is potentially greater in the setting of unresectable CRLM, given that the only alternative therapy for these patients is represented by palliative chemotherapy with 5-year OS of about 10% (14). Therefore, in theory, CRLM and HCC could equally compete each other given also that OS obtained by the Scandinavian group has been demonstrated to be similar or even higher than that one observed in HCC patients (11).

We do not know whether it is time to push the boundaries of liver transplant for unresectable CRLM but for sure, research should aim to refine selection criteria to further increase survival benefit of these patients who otherwise do not have any other chance of cure. Future studies, including prospective or randomized controlled multicenter trials, are awaited while others are already ongoing.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/hbsn.2019.11.10). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Serenari M, Ravaioli M. Refining selection criteria to further increase survival benefit in liver transplantation for unresectable colorectal liver metastases. HepatoBiliary Surg Nutr 2020;9(4):490-492. doi: 10.21037/hbsn.2019.11.10

