Editorial Commentary

Liver transplantation for non-resectable colorectal metastases—an evolving paradigm in transplant oncology

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A better understanding of colorectal liver metastasis (CRLM) onco-genomics and the improvement of systemic treatments, including targeted and immune therapies, have shifted the paradigm of CRLM prognosis over the past two decades. While 40% of the patients with colorectal cancers are likely to develop CRLM [and 50% of them to be non-resectable (nCRLM)], current oncologic management allows for the identification of a subset of CRLM patients with controlled diseases likely to highly benefit from curative resections and, perhaps, liver transplantation (LT). Indeed, the Norwegian SECA I trial in 2013 (1) triggered a growing interest in LT as a curative treatment for non-resectable colorectal liver metastasis (nCRLM). This strategy is supported by several pilot studies reporting up to 80% of 5-year estimated overall survival (OS) after LT for CRLM, in contrast to the poor results obtained in the early 80's series.

The international consensus guidelines published by Bonney *et al.* identify several key components for the safe implementation of LT for nCRLM (2). This remarkable collaborative work proposes a standardized nomenclature as well as several important statements regarding patient selection, biological tumor evaluation, and graft- and recipient-related considerations. These guidelines state that LT for nCRLM is an acceptable indication providing favorable long-term survivals [5-year overall survival (OS) >50%] and superiority in comparison to palliative chemotherapy. The proposed guidelines prioritize stringent patient selection for long-term results optimization. Whether transplanted patients for nCRLM actually experienced these endpoints (3) has not fully been elucidated yet. Most of our knowledge is inferred from pioneer, yet small-sized, pilot-study populations, therefore the results are extrapolated from the same and "in-protocol" patients; they are likely to be amended in future large-scale LT series, although recent short-term data from the United Network for Organ Sharing registry (1- and 2-year OS of 89.0% and 60.4%) seem to align with SECA I results (3). The matched comparison of SECA I to NORDIC VII populations suggests a better OS in the LT group (*vs.* chemotherapy) due to the removal of hepatic diseases (5-year OS of 56% *vs.* 9%) (4). However, this study has limitations, as acknowledged in the guidelines. Ongoing comparative trials are awaited to clarify how nCRLM patients/health care systems could benefit from LT, especially when compared to modern chemotherapy alone in terms of oncological results but also regarding additional endpoints, such as quality of life and cost-effectiveness.

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In contrast to other cancers (especially HCC), where LT is indicated for early-stage diseases, nCRLM is already a metastatic/systemic disease with a substantial tumor burden. The guidelines suggest that morphologic criteria might be inadequate for nCRLM candidates' selection while being liberally (size especially) considered in several ongoing clinical trials. The authors suggest excluding candidates with acknowledged unfavorable histological and molecular features such as undifferentiated adenocarcinoma, signet ring cell carcinoma and BRAFV600E mutation. A threshold of CEA dosage (<80) has been set, while its variations in response to chemotherapy might have a better significance. However, some other acknowledged factors such as performance status (sarcopenia assessment is however mentioned) and sidedness of the primary tumor are lacking the guidelines spectrum (1). From a practical point of view, it is unlikely that nCRLM patients with unfavorable oncologic criteria would experience the required favorable evolution to compete with LT indications. Disease history (synchronous *vs.* metachronous) and response to systemic treatment are distinctively the most well-defined factors in selecting LT nCRLM candidates. For example, the authors advocate that sustained response to bridging chemotherapy ≥6 months (more than most of the ongoing protocols) is required: a reasonable and safe statement that nonetheless emphasizes our inability to anticipate colorectal cancer behavior using the current criteria. As underlined in the guidelines, new tools to assess CRLM molecular and mutational profiles are required to refine the concept of biological non-transplantability and avoid futile LT (5,6).

On the other hand, the "curative intent" of LT for nCRLM is somehow discredited by the mitigated disease-free survivals (DFS) observed even in well-selected nCRLM recipients [SECA II; 1-, 2-, and 3-year DFS =53%, 44%, and 35% (7), SECA I; 100% of recurrence, median DFS =10 months (1)]. The discrepancy between post-transplant OS and DFS of nCRLM recipients justifies that these guidelines accept LT as a local, however life-altering, treatment of nCRLM (4). Therefore, overall survival and quality of life become the most relevant patient-centered endpoints (especially compared to standard chemotherapy). The boundaries of the selection could be reasonably challenged in the future based on the availability of liver grafts. The ideal selection strategy should certainly preclude futility without necessarily seeking "best performers" recipients only. The dogma of 50% required 5-year survival could be questioned without donor shortage or availability of living donor grafts. While SECA 1 has been repeatedly criticized for its heterogeneous population, the latter experiences impressive actuarial survivals (actuarial 5- and 10-year OS after LT were 43.5% and 26.1%) (1). Furthermore, post-LT recurrences are mainly pulmonary lesions with a favorable prognosis, unresponsive to immunosuppression, and likely to exist before LT (8,9). These observations support the consideration of nCRLM patients with a history of pulmonary metastasis in LT protocols, especially if accessible to local treatment. Likewise, patients with sustained stability to the bridging treatments could also be considered for LT, especially when morphologic criteria (RECIST and Chun criteria) are combined with metabolic imaging modalities (10). In contrast, alternative options (destruction of active lesions only) could be an option in listed nCRLM patients with sustained very good responses to chemotherapy (10). Access to LT for patients with resectable CRLM should remain an open debate, especially for surgically unfavorable candidates, such as the presence of a high tumor burden, advanced surgical strategies, repeatedly recurring liver-only metastases or unlikely to achieve complete margins (expected parenchymal R1) (11). Finally, LT might be an option to prioritize in CRLM patients associated with parenchymal underlying conditions precluding resection or further systemic treatments such as liver failure from chemotherapy-associated liver injuries or biliary ischemia due to hepatic artery infusion pump (3).

Unlike liver resection, LT is a limited resource mainly driven by the local policy of organ allocation, determining the concept of utility in LT for nCRLM. While the actual number of grafts expected to allocate for LT for nCRLM indications is relatively small, the guidelines have already introduced several options to overcome the issues related to brain death organ shortage and expand the donor pool. Extended criteria donors, including cardiac arrest donors, are among the most promising resources, especially considering the ongoing advances regarding dynamic liver regeneration via machine perfusion (12). LDLT (13) and RAPID (14) techniques convey growing interest; however, their oncological outcomes remain unclear. While living donation overcomes the organ shortage considerations, donor risk is another ethical dimension that must be balanced, especially for extended oncologic indications. In addition, current improvements in the management of alcohol- and HCV-related liver decompensation, especially as a result of the advent of direct-acting anti-hepatitis C agents, allow for a considerable amount of delisted patients creating a new source of grafts likely to cover the new indications such as nCRLM candidates (15).

The presented guidelines are an important and necessary consensus framework for the safe implementation of LT as a new valuable option for nCRLM. It provides essential arguments to minimize the risk of futile LT. Dozens of trials are ongoing and will clarify in the next few years the oncological benefit of LT versus chemotherapy (or the best alternative option), the most relevant pre- and post-LT prognostic factors, as well as the role of novel strategies such as LDLT and RAPID. In parallel, options to overcome organ shortage are continuously developed, especially with the advent of organ perfusion technologies and extended criteria graft optimization. In addition, the definition of traditional and extended indications for LT should be based on patient-centered outcomes and might change in the future. LT already appears as a very promising treatment for selected CRLM and might be an established part of the management algorithm for CRLM patients in the future.

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Footnote

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