Editorial Commentary

Liver transplantation for colorectal liver metastasis: the exception, not the rule

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Approximately half of individuals diagnosed with colorectal cancer (CRC) will develop colorectal liver metastasis (CRLM) during the course of their disease (1,2). Liver resection is the only potentially curative treatment for patients with CRLM, yet less than 20% of individuals are candidates for resection due to the extent or location of liver disease, underlying liver function and/or presence of extrahepatic metastases (1,2). In addition, the oncologic benefit of liver resection for CRLM is limited by recurrence rates than can be as high as 70% (3). Liver transplantation (LT) for CRLM was initially proposed as an alternative treatment strategy in the early 1990s but was abandoned due to the initial poor outcomes (3,4). The concept of transplantation for CRLM was later revisited in the 2000s by a group in Oslo, Norway that reported promising results in the SECA-I pilot study (5). Since the completion of the SECA-I study, the Norwegian group has also published other promising data from the SECA-II study (6). In addition, other notable outcomes have been reported in the RAPID study (7), as well as another study from specialized centers in North America (8), both of which have revitalized the concept of LT for CRLM.

In a recent *JAMA Surgery* article, Dueland *et al.* summarized their experience with patients who underwent LT for CRLM at Oslo University Hospital from 2006 to 2020 (9). The authors pooled data from three clinical trials (SECA-I, SECA-II, and RAPID studies) to define long-term outcomes following LT for CRLM and proposed appropriate selection criteria for LT in this patient population (9). Over the course of 14 years, 72 patients with CRLM were listed for a LT with 61 individuals ultimately undergoing LT (9). The vast majority of patients (n=47, 78.3%) had a relapse after LT with a median time to relapse of 9.0 months. One patient died from complications shortly after LT (1.4 months after LT) and was, therefore, excluded from further analyses. Although the median disease-specific survival (DFS) for the entire cohort was 11.8 months, 5-year overall survival (OS) following LT for CRLM was 50.4%. A total of 13 patients remained disease-free at last follow up and one patient remained alive 165 months after LT for CRLM (9). The authors suggested several criteria that were associated with a very good prognosis (5-year OS: >80%) after LT for CRLM: time from diagnosis to LT >3 years (9 patients, 5-year OS: 100%), metachronous disease (more than 12 months from diagnosis of primary tumor to detection of liver metastases) (5 patients, 5-year OS: 100%), Oslo score of 0 (10 patients, 5-year OS: 88.9%) and Fong Clinical Risk Score of 1 (5 patients, 5-year OS: 100%) (9).

Proponents of LT for CRLM cite an overall 5-year survival of more than 50% for selected patients and the potential for long-term cure as evidenced by the

13 individuals who remained disease-free at the end of follow-up in the latest study by Dueland *et al.* (9). In turn, the identification of patients with favorable clinicopathologic characteristics who are most likely to benefit from LT for CRLM is a research area of great interest. While Dueland *et al.* cited a 5-year OS over 80% for certain subpopulations (i.e., Oslo score 0, Fong score 1, metachronous disease, etc.), other subgroups of patients [i.e., Oslo score 3–4, largest lesion >5.5 cm, carcinoembryonic antigen (CEA) >80 μg/L, time from diagnosis to LT <3 years, etc.] had poor survival and did not appear to benefit from LT. These individuals could have perhaps avoided a significantly morbid operation, been transitioned to alternative therapies and have potentially avoided use of a scarce resource (i.e., a donor liver).

The major limitation to the broader adoption of LT in the setting of CRLM is the need for strict patient selection. Despite the promising results, patients who benefited the most from LT for CLRM represented a subpopulation of an already highly selected patient cohort with CRLM. Indeed, over 14 years, only 61 patients received LT for CRLM in Norway with a median of 21 months from diagnosis to LT (9). Such a prolonged interval with liver only disease and no significant disease progression over a nearly 2-year period demonstrates the high select nature of the patient cohort. These patients likely represent a cohort of individuals with less aggressive, indolent liver only disease who likely have a better prognostic profile than the average CRLM patient irrespective of treatment modality received. As such, patient selection alone can skew the survival data and make LT patients appear more favorable than non-LT patients. In turn, defining the right denominator/comparator cohort is key for objective interpretation of the true utility of LT in the setting of CRLM.

Another critical point of discussion is the allocation of donor organs, especially in countries with limited organ availability. Contrary to Norway, the North American perspective differs dramatically with 2,000–3,000 patients dying annually while awaiting LT (10). Competing interests for well-established indications of LT for end-stage liver disease have increased the challenge to access grafts for indications that have not been well defined. In addition, given the scarcity of donor livers, ethical considerations arise regarding the prioritization of patients and allocation of organs. Introducing patients with CRLM into the transplant pool could potentially strain the already limited supply of organs, disadvantaging patients with potentially curable diseases. Opportunities for expansion of the donor pool and technical innovation exist and can perhaps allow for a larger number of grafts to become available for patients with CRLM in the future. Living donor LT (LDLT) represents an opportunity to overcome the lack of deceased-donor grafts (8). In fact, centers from the US and Canada have already reported their initial experience with LDLT for liver-confined, unresectable CRLM demonstrating promising results [relapse-free survival (RFS) and OS of 62% and 100% at 1.5 years, respectively] (8). The availability of LDLT may, however, shorten the time to LT, which could paradoxically result in less patient selection. In the future, an equitable and evidence-based allocation framework will be necessary to ensure fair access to transplantation for eligible patients.

Another point that warrants further investigation is the oncological safety and the optimal management of immunosuppression post-transplantation. Immunosuppressive therapy is a critical component of post-transplant care to prevent organ rejection. At the same time, long-term immunosuppression can create a favorable environment for residual cancer cells to proliferate (10). The SECA investigators reported that the immunosuppression protocol consisted of induction with basiliximab, sirolimus, or tacrolimus the first 4 to 6 weeks and then conversion to sirolimus (11). Of note, certain immunosuppressive agents have anti-tumor effects, such as the mammalian target of rapamycin (mTOR) inhibitor sirolimus in hepatocellular carcinoma (12), as well as antiangiogenetic properties in experimental models of CRLM (13); in turn, this immunosuppressive agent may be favored over other agents. Nevertheless, data to compare different immunosuppressive agents in this patient population are lacking. While administration of adjuvant chemotherapy for systemic control appears logical, none of the patients in the SECA-I and SECA-II studies received adjuvant chemotherapy post-transplant and currently no data exist to support this strategy. As such, optimizing immunosuppressive therapy and systemic chemotherapy in the setting of LT for CRLM is another area that warrants further research.

The biology of CRLM is a major determinant of oncologic outcomes. Among 61 individuals who received LT for CRLM in the study by Dueland *et al.*, 58 patients had data on *KRAS* status; 15 (25.9%) had a *KRAS* mutation whereas 43 (74.1%) had wild type *KRAS* (9). There was no difference in OS among patients with *KRAS* mutated versus wild type *KRAS* tumors (9). Nevertheless, mutated *KRAS* status has been negatively associated with oncologic

outcomes among surgically resected patients (3). This effect has largely been noted among patients with the G12 *KRAS* variant, while other variants have not been associated as often with long-term survival (14). Further data on specific *KRAS* variants, with a particular focus on G12 *KRAS* mutations, are needed to understand better the biological status of patients who underwent LT for CRLM. Apart from *KRAS* status, other genes such as *BRAF*, *PIK3CA* and *TP53* have also been associated with oncologic outcomes (3). With the evolution of transplant oncology, mutational status will likely become increasing relevant to the selection of patients with CRLM for LT.

Preliminary results from the TRANSMET prospective multicentric randomized trial were recently presented at the 2024 American Society of Clinical Oncology (ASCO) meeting (15). Between 2016 and 2021, 94 patients were assigned to LT plus chemotherapy (n=47) or chemotherapy alone (n=47) arms (15). In the intention-to-treat analysis, 5-year OS was 57% in the LT + chemotherapy arm versus 13 in the chemotherapy alone arm [hazard ratio (HR) 0.16, 95% confidence interval (CI): 0.07–0.33]. Median progression-free survival (PFS) was 17.4 months in the former versus 6.4 months in the latter arm (HR 0.34, 95% CI: 0.20–0.58), which strongly suggested a role for LT in select patients with liver-only unresectable CRLM (15). The full data including details on study design, protocol compliance, as well as chemotherapy regimen and treatment of recurrent tumors are eagerly awaited. Randomized trial data that quantify the clinical utility of LT in the setting of CRLM are critical. To date, the promising results from LT have been noted among highly selected cohorts of CRLM patients with otherwise favorable clinicopathologic characteristics (i.e., liver only disease, low CEA, low Fong score, time from diagnosis to metastasis >3 years, etc.). Future, national and international collaborations should focus on accruing patients to randomized trials to demonstrate the true value of LT in the treatment armamentarium of patients with CRLM. Until then, LT for CRLM should be considered the exception and not the rule.

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