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EDITORIAL – GASTROINTESTINAL ONCOLOGY

Update to 'A Contemporary Systematic Review on Liver Transplantation for Unresectable Liver Metastasis of Colorectal Cancer'

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ABSTRACT Colorectal cancer is the second most common cause of cancer-related death worldwide, and half of patients present with colorectal liver metastasis (CRLM). Liver transplant (LT) has emerged as a treatment modality for otherwise unresectable CRLM. Since the publication of the Lebeck-Lee systematic review in 2022, additional evidence has come to light supporting LT for CRLM in highly selected patients. This includes reports of >10-year follow-up with over 80% survival rates in low-risk patients. As these updated reports have significantly changed our collective knowledge, this article is intended to serve as an update to the 2022 systematic review to include the most up-to-date evidence on the subject.

We would first like to commend Lee et al. for their 2022 manuscript titled 'A Contemporary Systematic Review on Liver Transplantation for Unresectable Liver Metastasis of Colorectal Cancer' and their work on the topic of liver transplantation (LT) for colorectal cancer liver metastasis (CRLM).[1] As the authors note, colorectal cancer is a deadly disease, representing the third most common malignancy and the second most common cause of cancer-related death worldwide.[2,3] Up to half of patients present with liver metastasis,[2,4,5] and as many patients suffer from unresectable disease, there is an urgent need to address the benefit of LT in this context.

Although Lee et al. comprehensively describe all the evidence showing the benefits of this therapeutic option at the time of their publication, they concluded that "*the role for LT for CRLM is exploratory and should be limited to the clinical trial setting*.[1] However, while this study is of importance summarizing the literature, we do feel that key publications have come to light since its publication that warrant an updated perspective on the issue. Lee et al. noted the need for additional prospective data in their study, some of which are now available. Hence, the rapid expansion of the literature on the subject in the last 2 years has proven that this therapeutic alternative is no longer exploratory and is being performed in clinical practice, albeit in a highly selected patient population. Recent studies by Hernandez-Alejandro et al. and Sasaki et al. have demonstrated overall survival (OS) of >50% 3 years after transplant, and confirmed this approach is being performed in more than 10 centers across the US.[6,7] These studies are limited to <3 years of follow-up, but do provide promising results over this shorter time frame. Perhaps most convincingly, long-term follow-up from the Norwegian studies has also been published, noting a 10-year survival of 88.9% with an Oslo Score of 0, and 80% with a Fong Clinical Risk Score (FCRS) of 1, although

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survival is significantly worse in those with less reassuring risk scores.[8–10] A summary of recent publications and key findings is available in Table 1. In comparison, 5-year OS, as shown by Lee et al., is just 14% without resection and just 30–50% after resection. Furthermore, only 20% of patients have resectable disease, meaning most patients considered for LT would have less than a one in four chance of surviving 5 years without LT.[1] Although Lee et al. could not be faulted for not presenting these data (some of these studies were published after the Lee et al. systematic review), the importance of this topic is such that we feel it is essential to place their findings in a broader context.

Lee et al. felt that a major reason to consider LT exploratory in this context was the lack of prospective data comparing resection and transplantation. While this was accurate at the time of publication, most transplants are performed specifically for unresectable CRLMs, which inherently prevent this comparison. Furthermore, the cited studies (Lanari et al.[11]) demonstrated a survival benefit over liver resection, including, as noted by Lee et al., an OS of 69.1% in the LT cohort versus 14.6% in the resection cohort for patients with an Oslo score of ≤2. In addition, since publication of their study, Rajendran et al. described the University of Toronto experience on the subject, which represents a prospective comparison of patients with CRLM, who were all referred for transplant evaluation.[12] They ultimately received a living donor liver transplant (LDLT; $n = 7$), resection ($n = 22$), or non-operative management ($n = 48$). The 1-year disease-free survival (DFS) in this population was demonstrated to be significantly better after LDLT compared with resection (85.7% vs. 11.4%). This trend persisted on long-term follow-up at 3 years (68.6% vs. 11.4%; $p = 0.012$). The OS was similar between groups at 100% and 93.8% after LDLT and resection, respectively. These prospective data demonstrate potential benefit for transplantation over resection in the proper patient population, although we acknowledge that this is far from definitive. Furthermore, a review of published pretransplant images for some patients transplanted for this indication at our own institution shows that resection may not be a reasonable comparison group for a truly randomized study, since the nature of treatment-induced underlying liver disease necessitates transplant in many of these patients.[13] Many patients undergo a very aggressive, liver-directed therapy for CRLM prior to transplant evaluation, and thus treatment-induced liver failure is an important factor in transplant consideration and one that would not be addressed with liver resection. Additionally, explant histopathology from LT for CRLM has demonstrated a very high rate of preoperatively undiagnosed intrahepatic metastasis that would be untreated by liver resection alone, further supporting the need for LT in certain patients.[14] In summary, data are available to suggest that LT may have a benefit over resection with respect to DFS and offers additional benefits of addressing impaired liver function in patients who have undergone aggressive therapies. LT may also help treat micrometastatic disease and disappearing liver metastasis, although we again acknowledge that definitive comparison of LT versus resection has not been performed. In fact, we feel that a more reasonable comparison may be LT for CRLM versus for other indications, as limited liver grafts

TABLE 1 Survival results for key studies published after, or otherwise not included in, the Lee et al. systematic review

Study	Study design, sample size, and follow-up	Number of centers	Survival after transplant
Hernandez-Alejandro et al. [7]	Design: Prospective Sample size: 10 Follow-up: 1.5 years	3	1.5-year OS: 100% 1.5-year DFS: 63%
Sasaki et al. [6]	Design: SRTR Database Centers: 10 Sample size: 46 Follow-up: 3 years	10	1-year OS: 89.0% 2-year OS: 60.4% 3-year OS: 60.4%
Dueland et al. [9]	Design: Prospective Centers: 1 Sample size: 61 Follow-up: 10 years	1	10-year OS (all patients): 54.7% 10-year OS (Oslo 0): 89% 5-year OS (Oslo 0–2): 63.4% 10-year OS (Oslo 0–2): 45.7%
Wehrle et al. [13]	Design: Retrospective Centers: 1 Sample size: 5 Follow-up: Median 2.67 years	1	OS: 100% DFS: 80%
Rajendran et al. [12]	Design: Prospective Centers: 1 Sample size: 7 LTs, 22 resections Follow up: 3 years	1	3-year OS: 100% 3-year DFS: 68.6%

Only articles presenting, to our knowledge, ≥50% of new patient data are included in this table

LT liver transplantation, *OS* overall survival, *DFS* disease-free survival

mean we weigh the pros and cons of giving an organ to one recipient versus another. Such a comparison has not yet been reported but we feel it would be valuable to the subject.

We agree wholeheartedly with Lee et al. in their conclusion that rigorous patient selection is of paramount importance. The recent, relatively large study published by Dueland et al. demonstrated 5- and 10-year OS of only 8.3% and 0%, respectively, in patients with an Oslo Score of 3 or 4 points.[9] As Lee et al. concluded, these results are quite dismal and patients who do not meet stringent criteria should not be considered for this approach. Additional considerations, such as the FCRS, and, notably, the positron emission tomography metabolic tumor volume (PET-MTV), may play crucial roles in determining ideal candidates. For example, the PET-MTV-low group (MTV <70 cm^2) demonstrated a 5-year OS of 66.7% compared with just 26.6% in the high group (MTV >70 cm^2).[9] We further agree that these criteria are currently established and refined and that further studies will continue to elucidate the best candidates for this approach. Additional factors such as genomic analysis, either tissue or using liquid biopsy, may begin to play a role as we learn more about this approach.[13] However, evolving selection criteria are present in most, if not all, indications for LT, and thus this factor alone should not limit this treatment option to a clinical trial setting. The Norwegian group initially described the Oslo criteria (Table 2) for this purpose, consisting of four clinical variables to predict outcomes of LT for CRLM.[15] Maspero et al. recently outlined the ongoing landscape of this condition, including guiding principles of patient selection that may help to guide surgeons and oncologists.[17] Our group supports this work from Italy in identifying proper candidates.

LT for CRLM first arose in European countries, including Norway, where the SECA I and II trials were conducted in the early 2000s, and was considered exploratory at that time. However, since then, its adoption has increased and is being performed in many US centers, as evidenced by Sasaki et al., who showed that patients were listed for LT for CRLM at 19 centers, and the procedure was performed at 15 unique centers in the US with excellent survival results.[6] While the Oslo group and other European countries have been pioneers in this field, studies as cited have shown increasing uptake across the US, and we feel that this practice is being adopted, with appropriate caution, in this country. Furthermore, international consensus guidelines were released by the International Hepato-Pancreato-Biliary Association (IHPBA) in 2021, describing a common standard for evaluation, outcomes reporting, graft selection, and immunosuppression, and highlighting the international uptake of the approach.[16] The wider rise of LDLT in this context, as described by Hernandez-Alejandro et al., offers some clear benefits, including logistical benefits of scheduling the case at optimal timing for systemic therapy, and in not reducing the donor pool for other transplant indications by using an organ that may have gone to another recipient.[7] LDLT also offers additional benefits of reducing ischemic reperfusion injury, which has been shown to increase tumor recurrence in other hepatic tumors.[17] Finally, the increasing use of marginal grafts with the rise of ex situ machine perfusion, and the reduction in the need for hepatitis C virus (HCV)-associated LT, may help mitigate the impact of a new indication for LT on the availability of donor organs.

The landscape of LT for CRLM is changing rapidly and is likely to continue its evolution. As mentioned, selection criteria will continue to evolve and new techniques such as PET-MTV and liquid biopsy may begin to play stronger roles.[13,18–20] The exact role for neoadjuvant locoregional therapy (LRT) has not been established, but LRT as a treatment is able to reduce tumor burden, which has been described as a positive predictor of RFS when using PET-MTV as a marker.[18] Our center favors aggressive neoadjuvant LRT but this does not have an established role and studies should investigate whether this approach is beneficial. Finally, the ideal management of patients after transplant remains unknown and the role of empiric adjuvant chemotherapy is similarly not established. The ideal management of immunosuppression, balancing rejection and oncologic risk, is also not well established. All these factors should continue to be studied as LT for CRLM is pursued.

We finally aim to place this discussion in the context of organ shortages and graft allocation. With a graft-recipient supply-demand mismatch, it is essential that we ensure we are providing the best use for each possible graft. One- and 5-year survival approaching 90%, as reported in the long-term Norwegian follow-up, actually do approach the survival rates in all-comers after LT, which is reassuring that LT for CRLM is an appropriate use of a liver.[8–10,21] However, as we continue to investigate proper selection criteria, the use of living donor (LDLT) and/or cardiac death (DCD) grafts can provide improved access to treatment for those with advanced CRLM without using grafts that could go to

TABLE 2 The now well-established Oslo score for predicting risk of recurrence after liver transplant for CRLM

Oslo score
Largest tumor size >5.5 cm
Progressive disease at the time of LT
Preoperative CEA >80 ug/L
Less than 2 years from primary tumor resection and liver transplant

One point is assigned for each applicable variable and the score is the sum of these points, with a maximum value of 4. Scores of 0–2 are increasingly indicative of more positive outcomes after LT for CRLM [8,9]

CRLM colorectal cancer liver metastasis, *LT* liver transplant, *CEA* carcinoembryonic antigen

other recipients. The allocation policy for CRLM remains an underexplored topic that will need nationwide attention as this practice continues.

In conclusion, we aim to present the most recent data regarding the role of LT for CRLM. While Lee et al. pointed out that the DFS was not clearly improved in all available studies, OS was significantly better in nearly all studies on the topic in appropriately selected patients. The emphasis on survival as an outcome highlights an important point regarding outcomes in transplant described by Llovet et al. and Maspero et al., namely that *"while being cancer-free is certainly important to patients and to their quality of life, ultimately what determines a successful organ utilization are patient and graft survival"*.[19,22] With demonstrated 10-year DFS >20% in the recently published study by Dueland et al., there is now prospective evidence with very long-term follow-up supporting reasonable survival in selected cases after LT for CRLM. With proper patient selection, LT has the potential to lengthen lives and cure patients, and thus should be considered as part of clinical practice, as recommended by current international consensus guidelines.[16]

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