Liver Transplantation for Colorectal Cancer Metastasis: An Evolving Option With Hope in Selected Patients

Spurred by development of the Milan criteria, the field of transplant oncology, as coined by Thomas Starzl as the "unequivocal indication for the operation of liver replacement," has quickly catapulted into representing a discrete indication for liver transplantation (LT). Unfortunately, while transplantation for hepatocellular cancer and hilar cholangiocarcinoma is widely accepted and facilitated by exception point policies to materialize offers, metastatic liver disease lags behind. It was only within the past decade that LT for nonresectable, liver-only, colorectal hepatic metastases (CRLM) was deliberated, based on advances in chemotherapy and strict recipient selection to ensure acceptable oncologic success. This offers significant utility given that 20% of patients present with synchronous metastases and 30% develop liver metastases within 3 years of diagnosis. It quickly developed into an effective treatment, offering R0 resections with unbeatably wide margins, while increasing overall (OS) and disease-free (DFS) survival.

The road to real consideration of LT for CRLM was not without obstacles. First pioneered in the 1980s, LT was quickly thereafter abandoned when 5-year OS rates fell dismally short of 20%.[1] It was not until decades later that the indication was reappraised. Frustrated by 5-year OS of <10% with palliative chemotherapy treatment and the fact that mortality from initial cases was related to transplant complications and not recurrence, a Norwegian group set out to resurrect LT for CRLM.[2] Inspired further by decades of promising progress in transplant outcomes and increased chemotherapy efficacy, the SECA-I trial studied 21 heterogeneous patients with varying extents of disease, chemotherapy, and treatment responses (Table 1). Inclusion required successful primary tumor resection, good performance status, and chemotherapy duration of more than 6 weeks. Initial results were encouraging, with 5-year OS of 60%, although 90% developed recurrence within 6 months. Factors associated with decreased survival included tumor diameter >5.5 cm, carcino-embryonic antigen (CEA) >80 μg/L, progression on chemotherapy, and a short interval between primary resection and transplantation. These factors were converted into a prognostic Oslo Score with each factor allocated 1 point. The SECA-II trial built on this information, narrowing selection to include only those with Oslo scores of 0 or 1 (Table 1).[3] This stricter criterion improved 5-year OS after LT to 83%, and survival after recurrence was conserved (73%), suggesting less aggressive biology.

Importantly, survival rates of the SECA trials were equivalent to treatment with resection for CRLM as well as with matched patients with hepatocellular cancer who underwent LT.[4,5] These results began to cement LT as a real treatment paradigm for select cases and further studies continued to add evidence. Compared with chemotherapy alone, matched patients with CRLM who underwent transplantation had far superior OS (40% difference).[6] Long-term follow-up of SECA-I participants cited promising 5- and 10-year OS of 44% and 26%, respectively[7] (Table 1). And unsurprisingly, stratification by Oslo Score was noteworthy. Patients with 0 or 1 point had 10-year OS of 75% and 50%, whereas those with 3 or 4 points were deceased by 86 months. Other prognostic factors began to emerge, including use of positron emission tomography (PET) scans to measure metabolic tumor volume. Tumor burdens <70 cm^3 were found to have significantly improved OS.[8] Focus on DFS has continued with promising results for patients with <24 months between primary tumor resection and transplant and CEA <80 μg/L before transplantation.[9]

This groundwork led to a global push for randomized multi-center trials. Currently underway or recently completed, SECA-III, SOULMATE, and TRANSMET trials are filling this role.[10–12] Even with considerable overlap between trials, each will be uniquely paramount for decisive guidelines. First, the Norwegian SECA-III trial is investigating the difference in OS in patients with progressive disease on chemotherapy between LT and other therapy modalities that include transarterial chemoembolization, radiotherapy, and chemotherapy. SOULMATE is underway in Sweden and evaluates OS after LT with extended criteria allografts and adjunct therapies compared with best medical therapy alone. Finally, TRANSMET, based in France, evaluates whether LT with adjuvant chemotherapy improved OS in resected patients with 1) partial response or stability on up to 3 lines of chemotherapy for >3 months, 2) no *BRAF* mutation, 3) CEA <80 ng/mL or a 50% decrease from baseline, and 4) satisfactory lab values (Table 1).[13] Other inclusion criteria included an Eastern Cooperative Oncology Group performance of 0 to 1 and normal renal function, and exclusion criteria included contraindications to LT such as substance abuse, active infection, lack of psychosocial support, and other malignancies. Patient eligibility was determined by an independent multi-disciplinary expert committee of oncologists, radiologists, and surgeons. Across 20 centers in Europe over nearly 3 years, 94 patients were evaluated and randomized evenly between the LT plus chemotherapy group and the chemotherapy-alone group. In an intention-to-treat analysis, the trial revealed that LT with chemotherapy significantly improved 5-year OS (73% vs 9%; $P < .0001$) as well as 5-year DFS (20% vs 0%; $P < .0001$). The significant different in OS for LT with chemotherapy was postulated to be due to 3 factors: strict patient selection, use of an independent expert committee to evaluate for trial eligibility, and expeditious prioritization of finding grafts for

Table 1. Key Changes in Patient Criteria for Treatment With Liver Transplantation

Criteria	Outcomes
SECA-I 1) Considerable heterogeneity a. Varying disease extent b. Varying chemotherapy regimen (minimum of 6 wk) c. Varying treatment response	1) 5-y OS 60% 2) 1-y DFS 35% Conclusion: Oslo Score development
SECA-II 1) Oslo score of 0 or 1 a. Tumor diameter <5.5 cm b. CEA <80 μg/L c. No progression on chemotherapy d. Short interval between primary resection and transplantation (<24 mo) 2) >10% response rate 3) At least 1-y interval between diagnosis and inclusion on transplant list	1) 5-y OS 83% 2) 1-y DFS 53% Conclusion: Stricter patient selection improved survival
Long-term follow-up of SECA-I	1) 5-y OS 43.5% 2) 10-y OS 26.1% 3) Oslo 0–1 a. 5-y OS 75% b. 10-y OS 50% Conclusion: Selected patients have potential to be cured
OPTN transplant oncology exception points 1) All hepatic lesions <10 cm 2) Stability or regression of disease for >6 mo (12 mo if synchronous) 3) Primary tumor resection >6 mo from diagnosis 4) Chemotherapy for >6 mo after primary resection	Approved June 18, 2024. Conclusion: Will need at least 12 mo after implementation for meaningful outcome assessment
Toronto Management LDLT trial 1) Primary resection >6 mo before LDLT 2) No progression on systemic chemotherapy for >6 mo 3) Informed consent of potential living donor 4) Bi-lobar, un-resectable liver metastases without vascular invasion 5) Laparotomy 1 wk before LDLT with negative porta hepatis nodes and no evidence of extra-hepatic disease	1) 3-y OS 100% 2) 3-y DFS 69% Conclusion: LDLT offers a favorable option in highly selected patients
TRANSMET 1) No progression on systemic chemotherapy for >3 mo 2) No extrahepatic disease 3) No *BRAF* mutation 4) CEA <80 μg/L or 50% decrease from baseline 5) Platelet count >80 6) White blood cell count >2.5 $\times$ 10^9/L	1) 5-y OS 57% 2) 5-y DFS 20% Conclusion: Transplant with chemotherapy improves survival vs chemotherapy alone
SECA-III (in progress) 1) Progressive disease on first-line chemotherapy or treatment held owing to toxicity 2) No extra-hepatic metastases within 6 wk of faculty meeting except resectable lung lesions <15 mm 3) Transplant within 3 mo of listing 4) No progressive disease during time on waiting list	1) 5-y OS 2) 5-y DFS 3) Quality of life at 1 and 2 y
SOULMATE (in progress) 1) Curative intent not possible with surgery or ablation 2) No progression on systemic first- or second-line chemotherapy for >2 mo with >10% response rate 3) At least 1-y interval between diagnosis and inclusion on transplant list 4) Platelet count >75 5) White blood cell count >23.0 $\times$ 10^9/L	1) 2-y OS 2) 2-y DFS

DFS, disease-free survival; CEA, carcino-embryonic antigen; LDLT, living-donor liver transplantation; OPTN, Organ Procurement and Transplantation Network; OS, overall survival.

the LT group. In fact, the majority of patients (79%) received LT within 2 months of chemotherapy completion through use of exception points, living donors, and partial grafts.

Given these studies and results, the United States, similarly to the rest of the world, has seen an increase—albeit small—in transplant cases for CRLM since 2017. And although outcomes are consistent with these original trials, overall volume remains exceedingly low. In fact, only 46 cases were performed out of 165,000 new cases of CRLM diagnosed annually. This rarity of transplantation for CRLM is owed not only to stringent patient selection and graft scarcity, but also importantly to mindset. Given the novelty of these results, change in practice is unsurprisingly lagging behind. Quick and automatic consideration of transplantation as a treatment option for select patients with CRLM has yet to be cemented in oncology. And as such, many appropriate referrals are bypassed or referred late to transplant centers. Increased outreach, conference attention, awareness, and time should help ameliorate this problem.

Strict patient selection in the setting of CRLM is based on the belief that transplantation should be considered only for those would who derive greatest benefit with promising tumor biology in the setting of such scarce resources. This is particularly poignant because unlike other hepatic malignancies, indication for LT for CRLM is not for curative intent but rather to increase OS and DFS. To create a consensus for selection and decrease center heterogeneity, the International Hepato-Pancreato-Biliary Association commissioned the Liver Transplantation for Colorectal Liver Metastases 2021 working group to establish guidelines.[14] These recommendations provide a rigorous framework for case consideration that includes but is not limited to performance status, criterion standard primary tumor resections, no extra-hepatic disease, and partial or stable responses to chemotherapy. Furthermore, in June 2024, the Organ Procurement and Transplantation Network (OPTN) proposed and approved new updates to allocate exception points to patients with CRLM who meet specific criteria[15] (Table 1).

Fortunately, besides limiting patient selection, centers can also increase available grafts for expanded transplant oncology indications by 1) living donor LT (LDLT), 2) boundary evolution with normo-thermic machine pump (NMP), 3) boundary evolution with normo-thermic regional perfusion (NRP), 4) resource utilization with split-LT (SLT) and pediatric recipient pairing, and 5) administrative maximization with expedited offers and use of aggressive center lists (Table 2). Starting with LDLT, a prospective clinical trial based in Toronto found it to be a promising option for patients with low Oslo scores meeting the following criteria: 1) resection of primary tumor at least 6 months earlier, 2) disease stability on systemic chemotherapy for more than 6 months, and 3) informed consent of at least 1 potential living donor (Table 1).[16] Similarly to previous studies, their

Table 2. Recommended Surgical Strategies to Improve Graft Availability for Recipients With Colorectal Adenocarcinoma Liver Metastases

Boundary evolution with normo-thermic perfusion pump (NMP)
1) Accept DCD grafts for NMP with:
   a. Functional WIT limit <60 min (SBP <80 mm Hg)
   b. Age <60 y
   c. No macro-steatosis (<10%)
2) Accept DCD grafts for NMP with:
   a. Functional WIT limit <60 min (SBP <80 mm Hg)
   b. Age <50 y
   c. Macro-steatosis <30%
3) Accept DBD grafts for NMP with:
   a. Macrosteatosis >30% but <50%

Boundary evolution with normo-thermic regional perfusion (NRP)
1) Accept DCD grafts for NRP with:
   a. Age <70 y
   b. Functional WIT limit <60 min
   c. Macro-steatosis <30%
   d. Rise in ALT <500 U/L over 2 h
   e. Down-trending lactate (preferably <5 mmol/L)
   f. Correction of acidosis
   g. Sufficient bile production/quality
      i. Delta pH >0.1
      ii. Glucose <3.0 mmol/L
      iii. Delta bicarbonate >5 mmol/L

Resource utilization
1) Pair pediatric recipients with transplant oncology recipients
   a. Split-LT with acceptance of both grafts
   b. Opportunity for NMP utilization for the partial graft allocated to the transplant oncology recipient so as to improve logistics

Administrative maximization
1) Mark transplant oncology patients for expedited offers
2) Notify organ procurement organizations to place center on the "aggressive center list" for all blood groups of listed transplant oncology patients

Living-donor LT
1) Establishment of living-donor LT programs
   a. Aim for 1 case/mo to maintain center proficiency
   b. Consider surgeons skilled at minimally invasive hepatectomy
   c. Establish at transplant centers with pediatric split liver expertise and appropriate recipient lists

NOTE. With the exception of living-donor LT, all described strategies are used successfully by our center.
ALT, alanine transaminase; DBD, donation after brain death; DCD, donation after cardiac death; SaO_2, oxygen saturation; SBP, systolic blood pressure; WIT, warm ischemia time.

results demonstrated significantly improved survival after transplant when compared with resection (Table 1). Unfortunately, LDLT still makes up only a small proportion of transplants in the US and cannot currently resolve this dilemma for most centers. Reasons for lack of implementation stem from the donor operation, which is unique in that it does not medically benefit the donor and in fact risks physical harm, and the time and effort required to create and build a program.

Other strategies that can be used to fill this void include NMP and NRP. Historically, liver preservation has been dependent on ischemic cold storage, exposing graft to progressive injury while impeding functional hepatobiliary evaluation. With the establishment of NMP and NRP, procurement practice and utilization have begun to markedly shift.[17] NMP provides a homeostatic haven with oxygenated blood, medicines, and nutrients, while simultaneously monitoring physiologic and biochemical parameters. This allows for tempering of ischemic insults while replenishing metabolic energy, improving outcomes.[17] In fact, our center gravitated quickly toward using NMP for all donation after cardiac death (DCD) allografts, widening boundaries encircling acceptance criteria. Interim evaluation of our first 50 DCD NMP livers revealed improved utilization by 10-fold, with similar recipient outcomes. Furthermore, within 6 months, we transplanted 3 patients with CRLM and Model for End-Stage Liver Disease (MELD) 3.0 scores <10, who otherwise had no offers. One recipient's allograft was rejected by all centers on the Eastern coast, and our graft acceptance was possible only because of NMP.

Similarly beneficial, NRP, which was first described in 1997, reestablishes in situ circulation with heparinized oxygenated blood through normo-thermic extra-corporeal membrane oxygenation. This circulation restoration halts the ischemic insult that occurs during withdrawal and asystole that is only slowed, not arrested, with classic cold perfusion. NRP also allows for the capacity to assess the liver in real time by trending lactate, enzymes, and bile pH. NRP use can increase donor pools by nearly 50% with rescue of grafts otherwise declined.[18] While still relatively new to controlled DCD procurement, preliminary studies have shown improved short-term outcomes with lower rates of ischemic cholangiopathy, early allograft dysfunction, 30-day graft loss, and primary nonfunction.[19]

Other strategies that can be used to increase graft availability fall within resource utilization. SLT offers an attractive option for donor expansion, providing grafts for 2 recipients from 1 liver. Limited by critically ill recipients needing whole grafts and center expertise, SLT is used infrequently; fewer than 2% of grafts are split, with potentially "split-able" livers exceeding pediatric waitlist deaths.[20] As such, there is ample opportunity to increase SLT adoption. Our center suggests pairing children with adult patients who lie within MELD "purgatory," often missing windows of opportunity owing to restrictive criteria.

The final recommended strategy involves executing allocation administration to maximal benefit. Often overlooked, being cognizant of nuances in procurement and allocation can add real benefit to center's lists. Awareness and use of the out-of-sequence expedited placement pathway is one such strategy. Intended to enable placement of organs that would otherwise be discarded because of lack of local recipients, the expedited pathway permits organ procurement organizations (OPOs) to circumvent regional match lists and allocate out of sequence to any center. Analysis of expedited placement grafts demonstrates excellent short-term function yet witnesses considerable regional asymmetric distribution. As such, ensuring that all transplant oncology patients are marked for expedited offers creates additional channels to increase probability for allocation. Similarly, we recommend that transplant centers notify their OPO to be placed on the local "aggressive center" list. This allows preferential relationships for quick placement of grafts, particularly when needed for expedited placement and likely explains the observed asymmetric allocation.

Although an estimate on these alternative allografts using the outlined strategies is near impossible, we can hazard a guess. Per the last OPTN/Scientific Registry of Transplant Recipients report, there were 1305 DCD livers offered in 2021.[21] Of those, 392 were discarded. In addition, and for the same year, 10% of all donation after brain death grafts recovered were discarded, adding another 562 livers retrieved but not used. In theory, the majority of these discarded livers could have been salvaged if NMP was used. On the other hand, an alternative to controlled DCD is uncontrolled DCD with donation after unanticipated but witnessed cardiac arrest. In scenarios like this, organ preservation is optimized after death with the use of NRP. Used minimally in the US, estimates of this potential pool reach 10,000 grafts.[22] SLT grafts are also minimally used, with only 2% of all US livers split. Over 3 years, nearly 9000 donors met optimal split criteria, yet only 384 underwent SLT.[23] Furthermore, 16% of livers meant to be split are paired down and discarded. Thus, over a 1-year period, there are at least 20 livers that are paired down instead of split and 2600 livers that could have been split but instead were transplanted whole. Extrapolating living donor data from countries with high utilization, US volume corresponds to only 6% of all transplant cases, with 569 cases, whereas South Korea's volume is 75% of their total liver volume with 1200 cases. After adjusting for population, there are at least 20 times more potential living donors in the US then currently being used. Finally, non-used expedited livers are another source of discard. When "rescue allocated," 85 livers were placed with outcomes equivalent to primary allocation.[24] Addition of all these discarded grafts yields a staggering estimate of more than 25,000 grafts not used each year.

The history of LT as treatment for CRLM when R0 resection is not technically attainable has and continues to demonstrate real survival benefit. However, given scarcity of organs and differences in survival benchmarks between unresectable liver-only metastatic disease and cirrhosis or hepatocellular carcinoma, there is continued controversy

surrounding selection and graft allocation. As such, centers need to consider aggressive strategies to increase the graft pool, which include adoption of living related LT, widening the application and broadening the controlled DCD criteria for acceptable-risk liver grafts with the use of NMP and NRP, doubling resource utilization with the use of SLT, marking patients for expedited pathways, and alerting local OPOs to the "aggressiveness" of their adjacent transplant centers. Doing so can and will create new opportunity for otherwise unresectable CRLM, pushing the promising field of transplant oncology even further forward.

MARIA BAIMAS-GEORGE
Division of Abdominal Transplantation
Department of Surgery
Carolinas Medical Center
Atrium Health
Wake Forest University School of Medicine
Charlotte, North Carolina

MARK RUSSO
Division of Hepatology
Carolinas Medical Center
Atrium Health
Wake Forest University School of Medicine
Charlotte, North Carolina

JOSE RAUL SOTO
LON ESKIND
DAVID LEVI
DIONISIOS VROCHIDES
Division of Abdominal Transplantation
Department of Surgery
Carolinas Medical Center
Atrium Health
Wake Forest University School of Medicine
Charlotte, North Carolina

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