Breakthroughs Beyond the Journal

JOURNAL OF HEPATOLOGY

One year after the TransMet trial: Transplant oncology at a turning point

Adam R, Piedvache C, Chiche L *et al.* Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): results from a multicentre, open-label, prospective, randomised controlled trial. Lancet 2024; 404: 1107-1118. https://doi.org/10.1016/S0140-6736(24)01595-2.

Background and context

Colorectal cancer is the third most common malignancy worldwide and the second leading cause of cancer-related mortality.[1] The liver is the most frequent site of metastatic spread. While surgical resection is the only potentially curative option for colorectal liver metastases, many patients present with disease that is technically unresectable or associated with unfavorable oncological features.[2–4] Permanently unresectable liver-only metastatic colorectal cancer has therefore long been considered a palliative condition, treated exclusively with systemic chemotherapy, with 5-year survival rarely exceeding 10–15%.[5,6]

In this context, liver transplantation (LT) emerged as a potential therapeutic strategy. This approach was initially explored in Norway, a setting less constrained by donor scarcity, where the landmark SECA I and SECA II pilot studies demonstrated that a highly selected subset of patients could achieve survival outcomes far exceeding those of historical controls.[7–9]

However, confirmation in a randomized controlled trial was required to address potential selection bias, assess feasibility in organ-constrained allocation systems, and compare outcomes with contemporaneous standard-of-care patients. The TransMet trial was therefore designed to definitively answer a simple but disruptive question: can LT, combined with chemotherapy, improve survival compared with chemotherapy alone in patients with permanently unresectable liver-only colorectal metastases (CRLM)[10]?

Objectives, methods, and findings

TransMet was a multicenter, open-label, randomized controlled trial conducted in specialized European centers between 2016 and 2021.[10] Eligible patients were aged 18–65 years, had histologically confirmed colorectal adenocarcinoma with complete resection of the primary tumor, liver-only metastatic BRAF wild-type colorectal cancer deemed permanently unresectable by an independent international multidisciplinary validation panel, and sustained disease control after at least 3 months of chemotherapy during three or less lines of chemotherapy. In the transplantation arm, access to transplantation was secured through a dedicated prioritization process ensuring LT within 2 months after the last chemotherapy cycle.

The primary endpoint was 5-year overall survival (OS) in an intention-to-treat analysis, with secondary endpoints including progression-free survival (PFS), perioperative outcomes, recurrence patterns, and quality of life.

Among 157 screened patients, 94 were randomized (47 per group). In the transplantation arm, 36 patients ultimately underwent LT, with exclusions mainly due to disease progression. In the standard-of-care (SOC) arm, seven patients underwent secondary resection and two received LT. Baseline characteristics were well balanced: 98% of patients had synchronous metastatic disease, and the median interval between diagnosis and randomization was 15.9 months in the transplantation arm *vs.* 13.5 months in the SOC arm. The primary tumor originated from the left colon or rectum in 85% of patients; approximately 80% had pT3–T4 tumors, and more than 85% presented with a high hepatic tumor burden (>10 metastases, largest lesion ≥50 mm). Nodal involvement was reported in 55% *vs*. 66%, and RAS mutations in 36% *vs*. 28% of patients in the transplantation and control groups, respectively. Response to first-line chemotherapy was comparable, with partial response observed in 57% of patients.

After a median follow-up of approximately 5 years, 5-year OS was 56.6% in the LT arm compared with 12.6% in the SOC arm (hazard ratio 0.37, $p = 0.0003$). In the per-protocol population, 5-year OS reached 73.3% among transplanted patients from the transplantation arm *vs.* 9.3% in the SOC arm (hazard ratio 0.16, $p < 0.0001$). PFS was significantly prolonged, with a median exceeding 17 months in the LT arm *vs.* approximately 6 months in the SOC arm. Recurrence after transplantation was frequent but often delayed and amenable to further oncological treatments, resulting in a median secondary PFS of 35.4 months. Perioperative morbidity and mortality were consistent with standard LT practice, and long-term quality of life was not significantly impaired.

Significance of findings

TransMet is the first randomized controlled trial to demonstrate a substantial survival benefit of LT in carefully selected patients with unresectable CRLM. The magnitude of benefit far exceeds that achieved by systemic therapies in this setting and, importantly, meets accepted thresholds for graft utility, a core principle in scarce resource allocation, with 5-year OS comparable to outcomes observed in established indications for LT.[11,12] Accordingly, for a subset of patients previously considered incurable, LT offers long-term survival and the realistic prospect of cure, fundamentally challenging long-standing conceptual boundaries between transplant medicine and oncology.

However, these results do not support indiscriminate expansion of this indication. Eligibility in TransMet was highly

restrictive, disease progression precluded LT in a substantial proportion of candidates, and organ scarcity remains the major ethical constraint. Compared with other recently emerging indications for LT – such as perihilar or intrahepatic cholangiocarcinoma, or alcohol-associated hepatitis in patients meeting strict addiction-related criteria – the potential impact of CRLM on graft allocation may be even greater given the high prevalence of CRLM, the relatively young age of affected patients, and the frequent absence of major comorbidities. While the exact number of patients who could ultimately be referred for this indication remains uncertain, the rigor and quality of the selection process remain paramount.

This principle was central to the TransMet design and relied on independent expert validation through an international multidisciplinary panel. In the trial, approximately 40% of patients initially considered eligible were ultimately excluded by this panel, underscoring its critical role in maintaining stringent selection and preventing indication drift. This approach has already been embraced by regulatory frameworks. In the United States, CRLM has been granted MELD exception status under the oversight of the National Liver Transplant Oncology Review Board. Similarly, most European LT programs surveyed for this manuscript report that, in countries where access to LT for CRLM has been implemented or is being considered, eligibility is strictly regulated and contingent upon centralized approval by all transplant centers and/or independent national boards (*e.g.* France, Spain, Belgium, and the Netherlands). Further implementation in clinical practice would require prioritizing access to LT, with prioritization schemes that may range from urgent listing within 1–2 months to other defined priority pathways.

In the future, the development of transplant oncology will more than ever require expansion of the graft pool. This includes advanced machine perfusion technologies, partial grafts, extended-criteria donors – particularly from donation after circulatory death – and living donor liver transplantation programs. In this context, two recent experiences from the United States have reported particularly promising outcomes in the same indication, reinforcing the potential of these strategies to be validated in large prospective cohorts.[13,14]

Beyond allocation issues, additional challenges remain. Refinement of candidate selection will likely be necessary, as emerging analyses from western cohorts have identified additional predictive factors, including sex, KRAS mutation status, absence of prior liver-directed therapy, and tumor burden, particularly the number of metastatic lesions.[15–17] Moreover, the optimal integration of peri-transplant chemotherapy remains unresolved, including the timing of treatment discontinuation before LT and its resumption thereafter. These questions are currently being addressed by a growing body of ongoing studies – more than 20 to date, predominantly observational, but including four randomized controlled trials. Among these, the awaited SECA-III trial from Norway (NCT03494946), comparing transplantation with chemotherapy, transarterial chemoembolization, or selective internal radiation therapy, and the MELODIC trial from Italy (NCT04870879) are expected to provide critical insights.

In conclusion, LT for CRLM is now a validated therapeutic option, supported by randomized evidence and associated with unprecedented survival outcomes in a strictly selected subgroup of patients. Its success will depend on rigorous selection, responsible allocation, and tight integration with modern oncology practice. The remaining challenges are not only scientific and technical, but also ethical, regulatory, and organizational. If these challenges can be addressed while maintaining strict and transparent criteria, transplant oncology may represent one of the most transformative advances in metastatic colorectal cancer over the coming decade.

Florent Artru
Liver Department, Rennes University Hospital and Rennes University, NuMeCan Institute, UMR INSERM 1317, Rennes Liver Failure Group, Rennes, France

Financial support

No financial support was received to produce this manuscript.

Conflict of interest

The author declares no conflict of interest that pertain to this manuscript. Please refer to the accompanying ICMJE disclosure forms for further details.

Acknowledgment

The author would like to thank Dr. Maximiliano Gelli for his valuable input and critical review of the manuscript, as well as Prof. Sarwa Darwish-Murad, Marina Berenguer, and Valerio Lucidi for answering the mini-survey.

Declaration of AI-assisted technologies in the writing process

During the preparation of this work the author used GPT-5.2 in order to proofread the manuscript. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2025.12.027.

References

Author names in bold designate shared co-first authorship

[1] Colorectal cancer n.d. https://www.who.int/news-room/fact-sheets/detail/colorectal-cancer
[2] Osterlund P, Salminen T, Soveri L-M, et al. Repeated centralized multidisciplinary team assessment of resectability, clinical behavior, and outcomes in 1086 Finnish metastatic colorectal cancer patients (RAXO): a nationwide prospective intervention study. Lancet Reg Health Eur 2021;3:100049. https://doi.org/10.1016/j.lanepe.2021.100049.
[3] Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol 2007;25:4575–4580. https://doi.org/10.1200/JCO.2007.11.0833.
[4] Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644–657. https://doi.org/10.1097/01.sla.0000141198.92114.f6. discussion 657-658.
[5] **Bond MJG**, **Bolhuis K**, Loosveld OJL, et al. First-line systemic treatment strategies in patients with initially unresectable colorectal cancer liver metastases (CAIRO5): an open-label, multicentre, randomised, controlled, phase 3 study from the Dutch Colorectal Cancer Group. Lancet Oncol 2023;24:757–771. https://doi.org/10.1016/S1470-2045(23)00219-X.
[6] Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1065–1075. https://doi.org/10.1016/S1470-2045(14)70330-4.
[7] Hagness M, Foss A, Line P-D, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg 2013;257:800–806. https://doi.org/10.1097/SLA.0b013e3182823957.

[8] Dueland S, Syversveen T, Solheim JM, et al. Survival following liver transplantation for patients with nonresectable liver-only colorectal metastases. Ann Surg 2020;271:212–218. https://doi.org/10.1097/SLA.0000000000003404.

[9] Solheim JM, Dueland S, Line P-D, et al. Transplantation for nonresectable colorectal liver metastases: long-term follow-up of the first prospective pilot study. Ann Surg 2023;278:239–245. https://doi.org/10.1097/SLA.0000000000005703.

[10] Adam R, Piedvache C, Chiche L, et al. Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): results from a multicentre, open-label, prospective, randomised controlled trial. Lancet 2024;404:1107–1118. https://doi.org/10.1016/S0140-6736(24)01595-2.

[11] Samuel D, Colombo M, El-Serag H, et al. Toward optimizing the indications for orthotopic liver transplantation in hepatocellular carcinoma. Liver Transpl 2011;17(Suppl 2):S6–S13. https://doi.org/10.1002/lt.22423.

[12] European Association for the Study of the Liver. EASL clinical practice guidelines on liver transplantation. J Hepatol 2024;81:1040–1086. https://doi.org/10.1016/j.jhep.2024.07.032.

[13] Byrne MM, Chávez-Villa M, Ruffolo LI, et al. The Rochester Protocol for living donor liver transplantation of unresectable colorectal liver metastasis: a 5-year report on selection, approval, and outcomes. Am J Transpl 2025;25:780–792. https://doi.org/10.1016/j.ajt.2024.09.027.

[14] Jones J, Taner CB, O'Donnell C, et al. Is there a place for deceased donor liver transplantation for colorectal metastases in the United States? Feasibility of a protocol utilizing machine perfusion. Liver Transpl 2025. https://doi.org/10.1097/LVT.0000000000000727.

[15] Adam R, Nheri K, Chiche L, et al. Prognostic factors of survival and recurrence after liver transplantation for unresectable colorectal liver metastases: results from the TransMet trial. J Clin Oncol Official J Am Soc Clin Oncol 2025;43. https://doi.org/10.1200/JCO.2025.43.16_suppl.3561.

[16] Dueland S, Smedman TM, Syversveen T, et al. Long-term survival, prognostic factors, and selection of patients with colorectal cancer for liver transplant: a nonrandomized controlled trial. JAMA Surg 2023;158:e232932. https://doi.org/10.1001/jamasurg.2023.2932.

[17] Vitale A, Lanari J, Cillo U, et al. Sex-based differences in survival after liver transplantation for colorectal cancer liver metastases: a multivariable analysis. JHEP Rep 2025;7:101505. https://doi.org/10.1016/j.jhepr.2025.101505.