

# Safety and feasibility of chemotherapy followed by liver transplantation for patients with definitely unresectable colorectal liver metastases: insights from the TransMet randomised clinical trial



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## Summary

**Background** Despite the increasing efficacy of chemotherapy (C), the 5-year survival rate for patients with unresectable colorectal liver metastases (CLM) remains around 10%. Liver transplantation (LT) might offer a curative approach for patients with liver-only disease, yet its superior efficacy compared to C alone remains to be demonstrated.

**Methods** The TransMet randomised multicentre clinical trial (NCT02597348) compares the curative potential of C followed by LT versus C alone in patients with unresectable CLM despite stable or responding disease on C. Patient eligibility criteria proposed by local tumour boards had to be validated by an independent committee via monthly videoconferences. Outcomes reported here are from a non-specified interim analysis. These include the eligibility of patients to be transplanted for non resectable colorectal liver metastases, as well as the feasibility and the safety of liver transplantation in this indication.

**Findings** From February 2016 to July 2021, 94 (60%) of 157 patients from 20 centres in 3 countries submitted to the validation committee, were randomised. Reasons for ineligibility were mainly tumour progression in 50 (32%) or potential resectability in 13 (8%). The median delay to LT after randomisation was 51 (IQR 30–65) days. Nine of 47 patients (19%, 95% CI: 9–33) allocated to the LT arm failed to undergo transplantation because of intercurrent disease progression. Three of the 38 transplanted patients (8%) were re-transplanted, one of whom (3%) died post-operatively from multi-organ failure.

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**Interpretation** The selection process of potential candidates for curative intent LT for unresectable CLM in the TransMet trial highlighted the critical role of an independent multidisciplinary validation committee. After stringent selection, the feasibility of LT was 81%, as 19% had disease progression while on the waiting list. These patients should be given high priority for organ allocation to avoid dropout from the transplant strategy.

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**Keywords:** Colorectal liver metastases; Liver transplantation; Chemotherapy; Randomised clinical trial

#### Research in context

##### Evidence before this study

PubMed was searched on 14 April 2022 for articles published since 1 January 1990, without language restrictions, using the search terms “liver transplant” or “liver transplantation” and “colorectal liver metastases” in the title. The retrieved articles were manually screened for relevance and their reference lists were examined for additional sources of relevant information. Patients with unresectable colorectal liver metastases did not appear to benefit from liver transplantation until recent pilot studies from Norway suggested a paradigm shift. The current standard of care for unresectable CLM is systemic therapy. Phase 3 evidence of the benefit of LT in this setting is still lacking, as is the safety and feasibility of LT for this indication in countries with organ shortages.

##### Added value of this study

This study reports on the safety and feasibility of LT for unresectable CLM in the TransMet trial. The initial safety of

the procedure is comparable to that of LT for other indications. The selection process of potential candidates highlighted the critical role of an independent multidisciplinary validation committee. In fact, 40% of the patients deemed eligible in the specialised centres were not selected, either because of tumour progression (50 patients, 32%) or potential resectability (13 patients, 8%). Another important finding is that 19% (9 patients) of the patients selected for LT were dropped out due to tumour progression during the waiting period.

##### Implications of all the available evidence

On an intention-to-treat basis, strict selection criteria for LT for unresectable CLM are not sufficient to lead patients to transplantation and strict control of the selection process is mandatory. In addition to a meticulous selection process, prioritisation of organ allocation is critical to avoid disease progression and failure to achieve transplantation.

## Introduction

The incidence of colorectal cancer (CRC) is increasing worldwide, with nearly two million new cases diagnosed each year.<sup>1</sup> Mortality from CRC is also rising, with nearly one million deaths annually.<sup>1,2</sup> Colorectal liver metastases (CLM) are diagnosed in up to 50% of CRC cases<sup>3</sup> and are responsible for a significant proportion of patient deaths.<sup>4</sup>

Although the results of systemic treatments for metastatic CRC have steadily improved since our initial oxaliplatin-based chronotherapy trials,<sup>5</sup> long-term survival remains dismal.<sup>6,7</sup> In patients with isolated CLM, resection leads to superior survival outcomes and is therefore a paramount step in the treatment strategy.<sup>8,9</sup> The definition of resectability of CLM has evolved over time and is now more pragmatic than dogmatic.<sup>10</sup> Age-related as well as tumour-related concerns, such as size and number, do not exclude patients with CLM from the possibility of resection.<sup>11</sup> Furthermore, margin status is not a contraindication per se in selected patients, as R1 resection, performed by necessity in close contact with critical vessels, yields equivalent results

compared to R0 resection,<sup>12</sup> especially when a major response to systemic therapy has been achieved.<sup>13</sup> Consequently, resectability is rather defined as a technical limit of safe and complete tumor resection.

For patients with initially unresectable CLM, tumour shrinkage to induce resectability has become the main objective of the strategy, as complete resection after tumour downsizing still offers a significant survival benefit.<sup>14</sup> Indeed, current guidelines recommend conversion systemic therapy when resection of CLM is a potentially achievable goal.<sup>15</sup> Furthermore, the addition of hepatic artery infusion to systemic treatments may improve the conversion rate of unresectable CLM.<sup>16,17</sup>

However, if resection cannot be achieved despite tumour response to systemic therapy, no treatment with curative intent is available. Local treatments such as ablation and radioembolization of metastases may complement continued systemic therapy to improve patient outcomes.<sup>18,19</sup>

Nevertheless, liver transplantation (LT) may offer a curative approach for these unresectable patients with liver-limited disease. Indeed, Hagness et al.

demonstrated in a pivotal prospective study that LT for unresectable CLM resulted in a 5-year overall survival (OS) of 60%.<sup>20</sup> Although the disease-free survival (DFS) was poor, with 90% recurrence at a median time of 6 months after LT, the significantly improved OS in this study suggested a possible paradigm shift in the field of transplant oncology, as CLM had been considered an absolute contraindication to LT in light of the poor previous results reported by the European Liver Transplant Registry (18% 5-year survival).<sup>21</sup> Despite these apparently improved outcomes, the superior efficacy of LT compared to chemotherapy alone needs to be further demonstrated as there is still equipoise regarding this emerging indication for LT.<sup>22</sup>

The multicenter randomised controlled TransMet trial was therefore designed to compare the 5-year survival of patients treated by C and LT (C + LT arm) versus chemotherapy alone (C arm) in patients with confirmed unresectable liver-only CRC metastases, in the absence of tumour progression on an ongoing C protocol. The primary objective of the randomised trial was to demonstrate a 5-year OS of 50% in the C + LT arm compared to 10% in the C arm (unreported). The rationale of the trial, which was exploratory in nature and had a consensus within the oncology and transplant community, was based on the intention to improve the initial Oslo results of the SECA 1 trial (5-year OS 60%) by implementing more stringent selection criteria.

To reduce selection bias, unresectability criteria and indications for LT were assessed by an independent multidisciplinary steering committee including hepatopancreato-biliary (HPB) and transplant surgeons, oncologists, radiologists and hepatologists. Indeed, the balance between expected outcomes after LT for CLM and organ shortage is a compelling challenge facing the field of transplant oncology.<sup>22</sup> Accordingly, the unresectability of CLM as an emerging indication for LT should be confirmed and risk factors for poor outcomes after LT should be formally excluded.

The objective of our study was to assess the safety and feasibility of combining LT with chemotherapy in the selected population of the TransMet trial, while awaiting the completion of the follow-up event for the core report of the trial.

## Methods

### Study design

The TransMet randomised clinical trial (NCT02597348) compares the curative potential of C with LT versus C alone in a large multicentre cohort of selected patients with unresectable CLM. The trial design assumes that the 5-year OS rate will be at least 50% with C + LT compared to 10% with C alone.

The TRANSMET trial has completed recruitment but has not yet reached the required number of events at the time of the study, to report the results of the end points.

Results were obtained from an extraction performed on 8 February 2022 at a time when all events related to selection for eligibility, transplantability and 3-month morbidity and mortality of transplanted patients have been fully reported. The results presented in this paper stem from an unplanned, non-specified analysis.

Inclusion criteria were: age between 18 and 65 years; ECOG performance status 0–1; histologically confirmed CRC, confirmed unresectable CLM, curative resection of the primary tumour according to oncological principles (negative margins with adequate TNM staging<sup>23</sup>); absence of local recurrence on colonoscopy performed within 12 months prior to enrolment (unless primary tumour resection <12 months); no extrahepatic disease according to CT scan and FDG-PET-CT; stable or partial response on last C protocol according to RECIST criteria lasting  $\geq 3$  months while on  $\leq 3$  C lines; absence of BRAF tumour mutation; serum CEA level <80 ng/mL or  $\geq 50\%$  decrease from baseline; renal function within normal limits, white blood cell count >2500/mL and platelet count >80.000/mL; signed informed consent and expected patient co-operation for treatment and follow-up.

The primary tumour was treated with standard oncological resection at each local centre. For synchronous lesions, chemotherapy was used first (unless the primary tumour was symptomatic and required resection first), followed by resection of the primary tumour after disease control with chemotherapy if the patient was deemed eligible for potential enrollment in the TransMet trial.

In addition to thoracic, abdominopelvic and FDG-PET-CT scans, work-up included liver MRI and complete abdominal exploration at LT with frozen section of lymph nodes if any, at laparotomy.

Non-inclusion criteria were: no signed consent; no health insurance; general contraindication to LT; extrahepatic malignancy; active alcohol or substance abuse; active infection or uncontrolled sepsis; lack of psychosocial support or inability to comply with medical treatment; other malignancies either concurrent or within 5 years before planned TransMet inclusion; recommended guidelines for primary CRC surgery not implemented; previous extrahepatic metastases or local recurrence; or pregnancy at the time of inclusion.

The eligibility of candidates proposed by the tumour board at each centre had to be validated by an independent committee of international expert oncologists, hepatologists, radiologists and liver surgeons via monthly videoconference.

This selection through the TransMet trial was the only potential access to liver transplantation in the participating countries, as the indication for liver transplantation has not yet been validated. Patients enrolled in this trial were given high priority for organ allocation by the organ procurement organisation in each country to avoid excessive delays on the waiting

list, with a recommendation to perform LT within two months of stopping chemotherapy. Chemotherapy was stopped when patients were listed for liver transplantation, and if progression occurred before LT, chemotherapy was restarted and the patient was removed from the transplant list until disease control was achieved. This priority was equivalent to patients with severe end-stage liver disease and a high MELD score of up to 35. Tailored immunosuppression and post-transplant chemotherapy were recommended for LT patients. The initial immunosuppressive regimen consisted of steroids, tacrolimus and mycophenolate mofetil, with a recommendation to reduce the dose of tacrolimus, to switch mycophenolate mofetil to everolimus 2 months after LT and taper the steroids during the first 6 months. The safety assessment was set at 3 months after LT to capture the early outcomes of the procedure.

### Non-specified outcomes

We evaluate in this multicentric study the selection process for the eligibility of patients to be transplanted for non resectable colorectal liver metastases, as well as the feasibility and the safety of liver transplantation in this indication. Feasibility was defined as the effective realization of LT in the absence of tumor progression in the waiting time for transplant, and of any intraoperative contraindication due to unexpected extrahepatic tumor deposit at laparotomy on the day of LT. Safety was assessed by the rate of severe complications (Clavien-Dindo grade IIIb) within 90 days after LT.

### Ethics statement

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. This study was conducted after local and national ethics committee approval.

### Statistical analysis

As previously mentioned in the study design, the TRANSMET trial has completed recruitment but has not yet reached the required number of events at the time of the study, to report the results of the end points. Results were obtained from an extraction performed on 8 February 2022, at a time when all events related to selection for eligibility, transplantability and 3-month morbidity and mortality of transplanted patients have been fully reported. The trial was overseen by a Clinical Research Unit, which centralised and controlled all the data collected by the research teams at each of the participating centres.

Descriptive statistics were reported: mean (standard deviation) and/or median (interquartile range) for quantitative variables, frequency (percent) for categorical variables. Clopper-Pearson method was used for calculation of 95% confidence intervals for percentage. Kaplan–Meier curves were plotted and Kaplan–Meier

method was used to estimate the OS. All statistical analyses were performed with SAS version 9.4 (Cary, NC 27513-2414, USA). Survival in the randomised and non-randomised groups was calculated from the time of submission to the validation committee. The most comprehensive assessment of post-transplant complications was reported according to the Clavien-Dindo classification.

### Role of the funding source

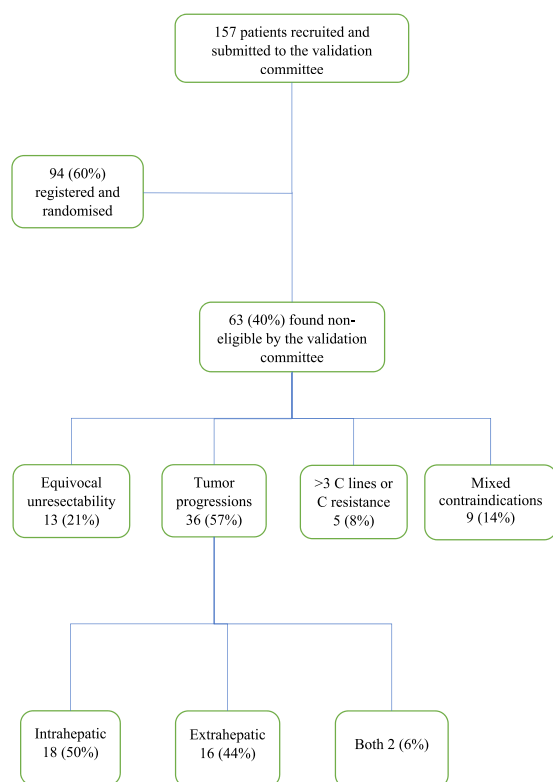
Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this research and by delegation, the Clinical Research and Development Department (DRCD) carries out the research's missions in accordance with Article L.1121-1 of the French Public Health Code and article 5 of ICH GCP. Assistance Publique - Hôpitaux de Paris reserves the right to halt the research at any time for medical or administrative reasons. All authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication. The following co-authors had access to the final dataset reported in this manuscript: René Adam, Céline Piedvache, Lamiae Grimaldi, Nadja Boukhedouni, Maximiliano Gelli, Francis Levi and David Badrudin. The decision to publish was taken by the principal investigator of the TransMet trial and corresponding author, René Adam.

### Results

From February 2016 to July 2021, 157 patients from 20 centres in France, Belgium and Italy were submitted to the validation committee. Ninety-four patients (60%) were included and randomised, 47 in each treatment arm. The main reasons for ineligibility were intrahepatic (n = 18) or extrahepatic (n = 16) tumour progression or both (n = 2) despite C; equivocal unresectability (n = 13); >3 C lines or C resistance (n = 5) and miscellaneous causes (n = 9). The selection process is shown in Fig. 1. Of the 13 patients excluded due to potential resectability as determined by the independent validation committee, 7 underwent interventions (4 liver resections, 3 ablations) and the other 6 did not. All seven resected patients were alive at 12 months. One died at 24 months. In comparison, the survival of the 36 patients who were not included due to tumour progression on C was 71% at one year and 26% at two years.

After randomisation, 38 out of 47 patients (81%) were transplanted after a median delay to LT of 51 days (IQR 30–65). As access to liver transplantation was provided by national organ sharing organisations, there was no significant difference in delay between centres. Altogether, the organs used in the TransMet trial represented less than 2% of all organs transplanted across all three countries during the study period.

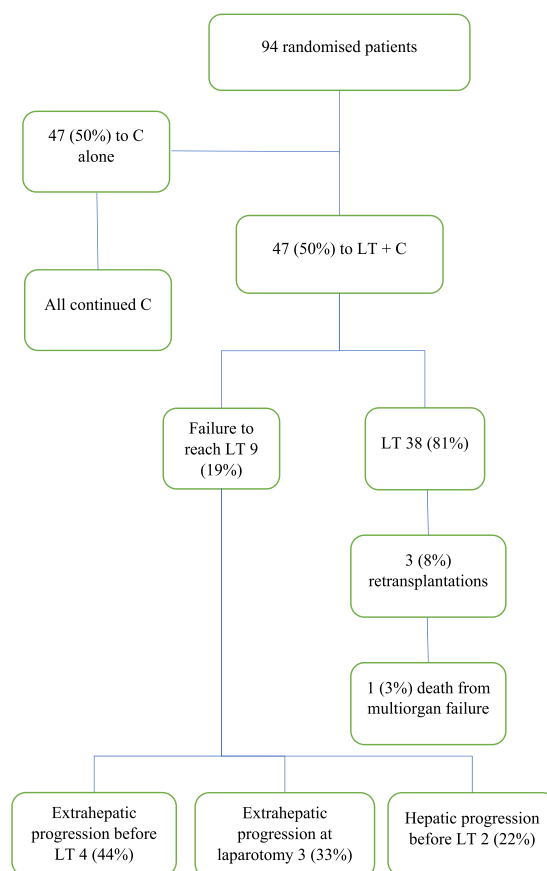
Among transplanted patients, 30/38 (79%) underwent transplantation within 2 months after the last cycle of chemotherapy. However, 9/47 patients



**Fig. 1:** Flowchart of the exclusion process in the TransMet Trial. n (%), number (percentage); C, chemotherapy.

(19%, 95% CI: 9–33) allocated to the C + LT arm failed to be transplanted because of intercurrent hepatic (n = 2) or extrahepatic progression either before LT (three pulmonary progressions and one concomitant prostate cancer) or at laparotomy for LT because of unexpected discovery of metastatic lymph nodes at the hepatic hilum or celiac axis (n = 3). The median time to progression for the six patients who progressed while waiting for liver transplantation was 35 days (IQR 14–48). The waiting times of the 3 patients excluded at laparotomy for LT were 15, 26 and 168 days. All non-transplanted grafts were re-allocated if a contraindication to LT was identified at laparotomy. Three of the 38 transplanted patients (8%) were re-transplanted either because of primary non-function, post-transplant discovery of gallbladder cancer in the graft, or caval obstruction related to a large for size liver graft, one of whom (3%) died post-operatively of multi-organ failure. Postoperative mortality rate was 2% among the 41 patients who underwent laparotomy with the intent of LT, and 3% in the 38 patients who actually underwent a transplantation. After LT, 26 patients (68%) received adjuvant chemotherapy with a median delay of 71 days (44–109) after transplantation.

The remaining patients (32%) did not receive adjuvant chemotherapy either because complications or



**Fig. 2:** Completion of assigned treatments. n (%), number (percentage); C, Chemotherapy; LT, Liver Transplantation.

inadequate performance status after LT. However, one centre abstained from delivering chemotherapy due to insufficient evidence supporting its efficacy.

In the C arm, all patients continued chemotherapy. As data from the TransMet trial are not yet finalised, a comparison of outcomes between arms is not yet available. [Fig. 2](#) shows the completion of assigned treatments in both arms of the trial.

Patient demographics are shown in [Table 1](#). The median age was 52 (47–59) and 55 (47–59) years in the C + LT and C groups, respectively, with a male predominance and similar tumour characteristics in both arms. Rectal tumours accounted for 28% (26 patients), while right colon tumours represented 15% (14 patients) and left colon tumours 57% (54 patients) of the total 94 patients in this study. All patients were diagnosed with synchronous CLM except 2 patients who were diagnosed with early metachronous disease (at 43 and 53 days after diagnosis of primary, respectively).

The median delay between primary tumour diagnosis and LT enlistment was 17 months (12–26), with 73% of patients waiting more than one year.

|                                                                      | Randomisation arm                                                       |                                 |
|----------------------------------------------------------------------|-------------------------------------------------------------------------|---------------------------------|
|                                                                      | Liver transplantation with perioperative chemotherapy (LT + C) (n = 47) | Chemotherapy alone (C) (n = 47) |
| <b>Age at randomisation (years)</b>                                  |                                                                         |                                 |
| n                                                                    | 47                                                                      | 47                              |
| Mean (SD)                                                            | 52 (8)                                                                  | 53 (9)                          |
| Median (IQR)                                                         | 52 (47–59)                                                              | 55 (47–59)                      |
| Range                                                                | 35–65                                                                   | 31–65                           |
| <b>Gender, n (%)</b>                                                 |                                                                         |                                 |
| Male                                                                 | 27 (57%)                                                                | 28 (60%)                        |
| Female                                                               | 20 (43%)                                                                | 19 (40%)                        |
| <b>(p)T3-T4, n (%)</b>                                               |                                                                         |                                 |
| No                                                                   | 6 (14%)                                                                 | 9 (19%)                         |
| Yes                                                                  | 37 (86%)                                                                | 38 (81%)                        |
| Missing                                                              | 4                                                                       | 0                               |
| <b>(y)pN+, n (%)</b>                                                 |                                                                         |                                 |
| No                                                                   | 21 (45%)                                                                | 16 (34%)                        |
| Yes                                                                  | 26 (55%)                                                                | 31 (66%)                        |
| <b>KRAS mutation, n (%)</b>                                          |                                                                         |                                 |
| No                                                                   | 36 (77%)                                                                | 34 (74%)                        |
| Yes                                                                  | 11 (23%)                                                                | 12 (26%)                        |
| Missing                                                              | 0                                                                       | 1                               |
| <b>NRAS mutation, n (%)</b>                                          |                                                                         |                                 |
| No                                                                   | 40 (87%)                                                                | 45 (98%)                        |
| Yes                                                                  | 6 (13%)                                                                 | 1 (2%)                          |
| Missing                                                              | 1                                                                       | 1                               |
| <b>BRAF mutation, n (%)</b>                                          |                                                                         |                                 |
| No                                                                   | 46 (100%)                                                               | 47 (100%)                       |
| Missing                                                              | 1                                                                       | 0                               |
| <b>Micro satellites, n (%)</b>                                       |                                                                         |                                 |
| Stability (MSS)                                                      | 36 (77%)                                                                | 41 (87%)                        |
| Unknown                                                              | 10 (21%)                                                                | 5 (11%)                         |
| ND                                                                   | 1 (2%)                                                                  | 1 (2%)                          |
| <b>Number of nodules, n (%)</b>                                      |                                                                         |                                 |
| <10                                                                  | 14 (30%)                                                                | 17 (38%)                        |
| Between 10 and 20                                                    | 20 (43%)                                                                | 16 (36%)                        |
| >20                                                                  | 13 (28%)                                                                | 12 (27%)                        |
| Missing                                                              | 0                                                                       | 2                               |
| <b>Diameter of largest nodules (mm)</b>                              |                                                                         |                                 |
| n                                                                    | 43                                                                      | 41                              |
| Mean (SD)                                                            | 31 (16)                                                                 | 33 (21)                         |
| Median (IQR)                                                         | 27 (15–42)                                                              | 26 (16–45)                      |
| Range                                                                | 4–73                                                                    | 5–90                            |
| <b>Carcinoembryonic antigen (ng/mL) (At diagnosis of metastases)</b> |                                                                         |                                 |
| n                                                                    | 47                                                                      | 47                              |
| Mean (SD)                                                            | 902 (2089)                                                              | 1200 (2661)                     |
| Median (IQR)                                                         | 305 (33–762)                                                            | 81 (20–530)                     |
| Range                                                                | 3–11,868                                                                | 1–13,033                        |
| <b>CA 19-9 (U/mL) (At diagnosis of metastases)</b>                   |                                                                         |                                 |
| n                                                                    | 35                                                                      | 34                              |
| Mean (SD)                                                            | 1567 (3467)                                                             | 1447 (3112)                     |
| Median (IQR)                                                         | 93 (20–800)                                                             | 160 (17–1905)                   |
| Range                                                                | 2–14,910                                                                | 2–13,683                        |

(Table 1 continues on next page)

|                                                                                                                                                                                                         | Randomisation arm                                                       |                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|---------------------------------|
|                                                                                                                                                                                                         | Liver transplantation with perioperative chemotherapy (LT + C) (n = 47) | Chemotherapy alone (C) (n = 47) |
| (Continued from previous page)                                                                                                                                                                          |                                                                         |                                 |
| <b>Carcinoembryonic antigen (ng/mL) (At inclusion)</b>                                                                                                                                                  |                                                                         |                                 |
| n                                                                                                                                                                                                       | 47                                                                      | 47                              |
| Mean (SD)                                                                                                                                                                                               | 12 (22)                                                                 | 37 (101)                        |
| Median (IQR)                                                                                                                                                                                            | 3 (2–11)                                                                | 3 (2–22)                        |
| Range                                                                                                                                                                                                   | 1–120                                                                   | 0–555                           |
| <b>CA 19–9 (U/mL) (At inclusion)</b>                                                                                                                                                                    |                                                                         |                                 |
| n                                                                                                                                                                                                       | 41                                                                      | 40                              |
| Mean (SD)                                                                                                                                                                                               | 134 (525)                                                               | 340 (1893)                      |
| Median (IQR)                                                                                                                                                                                            | 11 (5–34)                                                               | 16 (7–31)                       |
| Range                                                                                                                                                                                                   | 2–3231                                                                  | 2–12,000                        |
| <b>Number of lines of chemotherapy before inclusion</b>                                                                                                                                                 |                                                                         |                                 |
| n                                                                                                                                                                                                       | 47                                                                      | 47                              |
| Mean (SD)                                                                                                                                                                                               | 2 (1)                                                                   | 2 (1)                           |
| Median (IQR)                                                                                                                                                                                            | 2 (1–2)                                                                 | 2 (1–2)                         |
| Range                                                                                                                                                                                                   | 1–3                                                                     | 1–3                             |
| <b>Number of lines of chemotherapy before inclusion, n (%)</b>                                                                                                                                          |                                                                         |                                 |
| 1                                                                                                                                                                                                       | 19 (40%)                                                                | 22 (47%)                        |
| 2                                                                                                                                                                                                       | 20 (43%)                                                                | 22 (47%)                        |
| 3                                                                                                                                                                                                       | 8 (17%)                                                                 | 3 (6%)                          |
| <b>Previous liver surgery/local ablation, n (%)</b>                                                                                                                                                     |                                                                         |                                 |
| No                                                                                                                                                                                                      | 43 (91%)                                                                | 35 (74%)                        |
| Yes                                                                                                                                                                                                     | 4 (9%)                                                                  | 12 (26%)                        |
| <b>Chronological nature of the liver metastases</b>                                                                                                                                                     |                                                                         |                                 |
| Synchronous (0–1 month)                                                                                                                                                                                 | 47 (100%)                                                               | 45 (96%)                        |
| Early metachronous (1–12 months)                                                                                                                                                                        | 0 (0%)                                                                  | 2 (4%)                          |
| <b>Delay between diagnosis of liver metastases and randomisation (months)</b>                                                                                                                           |                                                                         |                                 |
| n                                                                                                                                                                                                       | 47                                                                      | 47                              |
| Mean (SD)                                                                                                                                                                                               | 19 (10)                                                                 | 16 (10)                         |
| Median (IQR)                                                                                                                                                                                            | 16 (12–26)                                                              | 14 (9–19)                       |
| Range                                                                                                                                                                                                   | 6–44                                                                    | 7–52                            |
| <b>Delay between randomisation and transplantation (days)</b>                                                                                                                                           |                                                                         |                                 |
| n                                                                                                                                                                                                       | 38                                                                      |                                 |
| Mean (SD)                                                                                                                                                                                               | 64 (61)                                                                 |                                 |
| Median (IQR)                                                                                                                                                                                            | 51 (30–65)                                                              |                                 |
| Range                                                                                                                                                                                                   | 8–350                                                                   |                                 |
| <b>Delay between randomisation and transplantation, n (%)</b>                                                                                                                                           |                                                                         |                                 |
| ≤1 month                                                                                                                                                                                                | 10 (26%)                                                                |                                 |
| 1–2 months                                                                                                                                                                                              | 15 (39%)                                                                |                                 |
| >2 months                                                                                                                                                                                               | 13 (34%)                                                                |                                 |
| Missing                                                                                                                                                                                                 | 9                                                                       |                                 |
| n, number; SD, Standard deviation; IQR, Interquartile range; MSS, Microsatellite stable; mm, millimetre; ng/mL, nanogram per millilitre; CA 19–9, Carbohydrate antigen 19–9; U/mL, unit per millilitre. |                                                                         |                                 |

**Table 1: Patient demographics in the two arms.**

The median delay between primary tumour diagnosis and LT was 20 months (14–29), with 84% of patients waiting more than one year.

In the 94 patients, the median number of nodules at diagnosis was 20 (IQR 10–25) with a median diameter

of 53 mm (IQR 37–78). The median interval between CLM diagnosis and randomisation was 16 months (12–26) in the C + LT arm and 14 months (9–19) in the C arm. In the C + LT arm, 28 patients (60%) received 2 or more lines of C prior to randomisation compared to

| Type of complications                                               | N (%)   |
|---------------------------------------------------------------------|---------|
| <b>Hepatic</b>                                                      |         |
| Retransplantation                                                   | 3 (7%)  |
| Early graft dysfunction                                             | 2 (5%)  |
| Hepatic artery thrombosis                                           | 1 (2%)  |
| Hepatic artery stenosis                                             | 1 (2%)  |
| Biliary complications                                               | 8 (20%) |
| Postoperative collections                                           | 3 (7%)  |
| Bleeding                                                            | 2 (5%)  |
| Superficial surgical site infection                                 | 1 (2%)  |
| <b>Pulmonary</b>                                                    |         |
| Pneumopathy                                                         | 2 (5%)  |
| <b>Cardiovascular</b>                                               |         |
| Cardiogenic shock                                                   | 1 (2%)  |
| <b>Mortality</b>                                                    |         |
| Multiorgan failure after retransplantation for primary non-function | 1 (2%)  |

N, number.

**Table 2: 90-day complications (Clavien-Dindo Grade IIIb or higher) of the 41 patients operated with the intent of performing liver transplantation.**

25 patients (53%) in the C arm. The feasibility of liver transplantation did not differ significantly whether patients received 1, 2 or 3 lines of chemotherapy preoperatively: 84%, 75% and 88% respectively.

Ninety-day morbidity and mortality are shown in Table 2. Twenty-four major complications requiring intervention (Grade IIIb or higher) were observed in 14 of the 41 patients (34%) who underwent surgery. Overall, ten patients underwent interventional procedures under general anaesthesia (grade IIIb) for either biliary complications (8 patients), intra-abdominal collections (3), arterial complications (2) or bleeding (1). Three patients experienced multi-organ dysfunction (Grade IV) for either cardiogenic shock secondary to Takotsubo syndrome, early graft dysfunction and large-for-size syndrome. One patient (2%) died from primary dysfunction.

## Discussion

This is the first study to report the safety and feasibility of LT in addition to C for unresectable CLM in a large multicentre randomised trial.

The most notable finding of this study is that the validation committee excluded 63 (40%) of the candidates proposed by the local tumour boards of already expert centres. Another important result is that 9 patients (19%) selected for LT were dropped out because of tumour progression during the waiting time or unexpected finding of extrahepatic tumor at laparotomy.

The completion of our trial within 5 years underlines the importance of this oncological issue and the commitment of medical teams to this potentially curative strategy.

One of the main challenges of this treatment option is patient selection. The first experience reported by the Norwegian team provided a proof of concept demonstrating the efficacy of LT in a non-optimised patient population. Indeed, 19 out of 21 patients in the Norwegian study experienced tumour relapse, which is a highly significant recurrence rate, although mitigated by preoperative staging inaccuracies rather than true recurrences in some patients.<sup>24</sup> Independent risk factors have also been shown to be useful in optimising patient selection and improving survival.<sup>20</sup> Obviously, the selection criteria in our study were more stringent, excluding tumour progression, high CEA levels and BRAF mutation. This evolution has also been subsequently shared by the Oslo group: in the SECA2 study, the 5-year OS after LT was 83% in a more restrictively selected population of patients with unresectable CLM, giving a survival similar to that expected after LT for other indications.<sup>25</sup>

Furthermore, the selection process of potential candidates for LT for unresectable CLM in our trial, highlighted the critical role of an independent multidisciplinary validation committee. In fact, 40% (63 patients) of those deemed eligible in the specialist centres were not selected, either because of tumour progression (50 patients, 32%) or potential resectability (13 patients, 8%). To explain this, it is possible that the local tumour board was not as attentive as the independent committee to ensure that all the criteria were met. The careful analysis of the radiological report by the radiologist of the independent committee has sometimes identified a suspicious lymph node or pulmonary nodule that was not detected by the local team. Similarly, the progression of some liver metastases was not always recognised in local centres. Moreover, resectability is often appreciated differently and is probably better assessed by a group of independent expert surgeons. Finally, the lack of strict adherence to predefined selection criteria by transplant teams could be related to empathy for young patients with no other chance of curative treatment, leading to compassionate indications for LT, known to have poor outcomes.<sup>26</sup> By making an independent decision, the expert validation committee avoided such compassionate indications for LT.

Another critical issue in transplant oncology is access to organ availability. The results of the Oslo group were obtained in a country with an exceptionally high ratio of donors to transplant candidates, resulting in a pre-LT waiting time of only 29 days without dropout from the transplant strategy.<sup>25</sup> The impact of longer waiting times on feasibility and survival after LT deserved further investigation, as the majority of countries worldwide suffer from organ shortages. This was the case in the three countries whose centres contributed to the study. Despite the prioritisation of organ allocation, the objective of performing LT within 2 months of randomisation was not achieved in 13 (34%) of transplanted

patients. Furthermore, the feasibility of LT after selection was only 81% (38 patients), illustrating the difficulty of disease control in advanced unresectable CLM despite the improved efficacy of systemic treatments. Indeed, six patients on the waiting list were excluded from LT due to tumour progression, while three showed tumour progression at laparotomy for LT, suggesting that transplant programmes should implement an organ reallocation policy in these scenarios. Their median time to progression on the waiting list was not significantly different from the waiting time of patients who actually underwent transplantation. This suggests that the delay to LT was not exclusively responsible for the failure to achieve transplantation and that the selection process itself could benefit from improvements. Certainly, intention-to-treat results should remain the primary objective for outcome analysis, rather than results obtained after effective LT, as is the case for all types of transplanted liver malignancies. These patients should therefore be given high priority for organ allocation to avoid harmful delays. In this changing landscape, strategies to address organ shortages and expand the LT donor pool for unresectable CLM, such as the use of extended criteria grafts and living donor LT, are gaining favour.<sup>27</sup>

Finally, an assessment of the initial safety of the procedure was of concern. Early mortality was intuitively expected to be lower than in conventional indications for LT due to the normality of liver function and the absence of portal hypertension. Nevertheless, we reported 3 retransplantations and one postoperative death. These results are in line with those recently reported from the United States, with three postoperative deaths in 46 LT for CLM (7% mortality),<sup>28</sup> and with the 5–10% 3-month mortality after LT for all indications described in large studies from Europe and North America.<sup>29,30</sup>

Our study has some limitations. Indeed, our study could benefit from improved granularity of data with a longer follow-up and an exhaustive completion of the database. However, this does not affect the early outcome after LT, nor the robustness of the results regarding the access and feasibility of LT in this indication.

On an intention-to-treat basis, drastic selection criteria for LT for unresectable CLM are not sufficient to lead patients to transplantation. Strict control of the selection process is mandatory, as demonstrated in this study by the crucial role of the independent validation committee. In addition to a meticulous selection process, prioritisation of organ allocation is critical to avoid disease progression and failure to transplant. Accordingly, this study is the first to provide a true assessment of transplantability in “organ shortage countries” that do not use living donor transplantation. The forthcoming final results of the TransMet trial are expected to help validate or not the indication for LT in unresectable CLM.

#### Contributors

René Adam, Maximiliano Gelli and Francis Levi contributed to the following: conceptualisation, investigation, methodology, project management, resources, supervision, visualisation, writing—original draft, writing—review and editing.

Céline Piedvache, Nadja Boukhedouni and Lamiae Grimaldi contributed to the following: data curation, formal analysis, methodology, resources, supervision, validation, visualisation, writing—review & editing.

David Badrudin contributed to: visualisation, writing—original draft, writing—review & editing.

The other co-authors all contributed to: investigation, resources, writing—review & editing.

All authors read and approved the final version of the manuscript.

#### Data sharing statement

The individual participant data, as well as the study protocol and statistical analysis plan are available after de-identification (text, tables, figures and appendices) on request to the corresponding author.

Where applicable, data generated or analysed during this study are included in this published article (and its supplementary information files). The raw data supporting the conclusions of this manuscript will be made available by the authors without undue restriction to any qualified researcher who provide a methodologically sound proposal immediately following publication with no end date.

#### Declaration of interests

No sources of support or funding for this study to disclose. There are no ethical problems or conflicts of interest related to the study reported in this paper. ICMJE conflict of interest forms are provided for each author.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclim.2024.102608>.

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