# 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

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## Summary

**Background** Despite the increasing efficacy of chemotherapy, permanently unresectable colorectal liver metastases are associated with poor long-term survival. We aimed to assess whether liver transplantation plus chemotherapy could improve overall survival.

**Methods** TransMet was a multicentre, open-label, prospective, randomised controlled trial done in 20 tertiary centres in Europe. Patients aged 18–65 years, with Eastern Cooperative Oncology Group performance score 0–1, permanently unresectable colorectal liver metastases from resected *BRAF*-non-mutated colorectal cancer responsive to systemic chemotherapy (≥3 months, ≤3 lines), and no extrahepatic disease, were eligible for enrolment. Patients were randomised (1:1) to liver transplantation plus chemotherapy or chemotherapy alone, using block randomisation. The liver transplantation plus chemotherapy group underwent liver transplantation for 2 months or less after the last chemotherapy cycle. At randomisation, the liver transplantation plus chemotherapy group received a median of 21·0 chemotherapy cycles (IQR 18·0–29·0) versus 17·0 cycles (12·0–24·0) in the chemotherapy alone group, in up to three lines of chemotherapy. During first-line chemotherapy, 64 (68%) of 94 patients had received doublet chemotherapy and 30 (32%) of 94 patients had received triplet regimens; 76 (80%) of 94 patients had targeted therapy. Transplanted patients received tailored immunosuppression (methylprednisolone 10 mg/kg intravenously on day 0; tacrolimus 0·1 mg/kg via gastric tube on day 0, 6–10 ng/mL days 1–14; mycophenolate mofetil 10 mg/kg intravenously day 0 to <2 months and switch to everolimus 5–8 ng/mL), and postoperative chemotherapy, and the chemotherapy group had continued chemotherapy. The primary endpoint was 5-year overall survival analysed in the intention to treat and per-protocol population. Safety events were assessed in the as-treated population. The study is registered with ClinicalTrials.gov (NCT02597348), and accrual is complete.

**Findings** Between Feb 18, 2016, and July 5, 2021, 94 patients were randomly assigned and included in the intention-to-treat population, with 47 in the liver transplantation plus chemotherapy group and 47 in the chemotherapy alone group. 11 patients in the liver transplantation plus chemotherapy group and nine patients in the chemotherapy alone group did not receive the assigned treatment; 36 patients and 38 patients in each group, respectively, were included in the per-protocol analysis. Patients had a median age of 54·0 years (IQR 47·0–59·0), and 55 (59%) of 94 patients were male and 39 (41%) were female. Median follow-up was 59·3 months (IQR 42·4–60·2). In the intention-to-treat population, 5-year overall survival was 56·6% (95% CI 43·2–74·1) for liver transplantation plus chemotherapy and 12·6% (5·2–30·1) for chemotherapy alone (HR 0·37 [95% CI 0·21–0·65]; p=0·0003) and 73·3% (95% CI 59·6–90·0) and 9·3% (3·2–26·8), respectively, for the per-protocol population. Serious adverse events occurred in 32 (80%) of 40 patients who underwent liver transplantation (from either group), and 69 serious adverse events were observed in 45 (83%) of 54 patients treated with chemotherapy alone. Three patients in the liver transplantation plus chemotherapy group were retransplanted, one of whom died postoperatively of multi-organ failure.

**Interpretation** In selected patients with permanently unresectable colorectal liver metastases, liver transplantation plus chemotherapy with organ allocation priority significantly improved survival versus chemotherapy alone. These results support the validation of liver transplantation as a new standard option for patients with permanently unresectable liver-only metastases.

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## Introduction

Complete surgical resection plus systemic chemotherapy represents the best treatment for liver metastases from colorectal cancer to achieve long-term survival (5-year survival ~40%)[1,2] and possible cure. However, less than 30% of patients are considered to have initially resectable metastases and be suitable for up-front surgery,[1] and the potential cure from surgery remains poor.[2]

Tumour downstaging is a primary treatment objective to facilitate secondary resection in patients with initially unresectable colorectal liver metastases. Complete resection after response to chemotherapy was found to be associated with a 5-year survival of 33% in a large retrospective series.[3] Although response rates were high (54–80%) in phase 3 randomised controlled trials using doublet or triplet regimens with targeted therapy,[4,5] only 13–50% of patients had secondary curative-intent surgery. Therefore, systemic chemotherapy represents the standard of care for most patients with permanently unresectable colorectal liver metastases.

In this setting, liver transplantation initially emerged as a promising treatment. However, preliminary results from 50 patients with colorectal liver metastases who underwent liver transplantation in Europe in the 1980–90s had a 5-year survival of only 18%.[6] Because of organ scarcity and high rates of survival in common indications for liver transplantation, colorectal liver metastases were considered a contraindication to liver transplantation. At that time, chemotherapy was based on fluorouracil (≤20% response rate), and a retrospective analysis by one of the authors (RA) of this study showed that 44% of deaths were unrelated to tumour recurrence.[7] In light of this, plus the increasing efficacy of chemotherapy, increased expertise of transplantation teams, improved knowledge of metastatic disease, and improvements in imaging and immunosuppression, we proposed revisiting liver transplantation for colorectal liver metastases in carefully selected patients who responded to chemotherapy. This idea was trialled in Norway, which showed promising preliminary results.[7] These results were supported 3 years later in the first proof-of-concept pilot study of 21 consecutive patients transplanted for colorectal liver metastases with a 60% 5-year survival rate.[8] These findings motivated further research into outcomes after liver transplantation for colorectal liver metastases via alternative routes to cadaveric donation, such as living-donor liver transplantation, and increased the use of liver transplantation in experimental programmes worldwide.

### Research in context

#### Evidence before this study

Complete resection of liver metastases is the best option for long-term survival in patients with liver metastases from colorectal cancer. However, this surgical treatment is only suitable for a small proportion of patients, and systemic chemotherapy remains the standard of care for patients with unresectable liver metastases. Recent advances in liver transplantation, including living-donor transplantation and use of partial grafts, as well as positive findings from pilot, non-controlled studies (NCT01311453 and NCT01479608), have reignited interest in liver transplantation for patients with permanently unresectable colorectal liver metastases.

We searched PubMed from database inception to April 17, 2024, with the search terms "colorectal cancer", "colorectal carcinoma", "rectal cancer", "rectal carcinoma", "colon cancer", "colon carcinoma", "liver metastasis", and "transplant" for randomised trials comparing liver transplantation plus chemotherapy with chemotherapy alone in patients with metastatic colorectal cancer. No randomised controlled trials comparing systemic chemotherapy plus liver transplantation versus chemotherapy alone were identified.

#### Added value of this study

To our knowledge, the TransMet trial is the first randomised study to prospectively compare liver transplantation plus chemotherapy versus chemotherapy alone as the current standard of care in patients with permanently unresectable colorectal cancer and liver metastases. Our findings show that patients with permanently unresectable liver metastases from colorectal cancer have better overall survival after liver transplantation following chemotherapy than patients receiving chemotherapy alone. This is the first comparative study demonstrating a notable benefit of transplantation in liver metastases from an aggressive digestive cancer, expanding the concept of transplant oncology. In the absence of evidence from randomised controlled trials, the role of liver transplantation in addition to systemic chemotherapy in patients with permanently unresectable liver metastases from colorectal cancer has not been scientifically shown. Strong evidence of clinical benefit is especially important in this setting, given the demand for, and scarcity of organs as well as the competition with standard indications.

#### Implications of all the available evidence

The TransMet trial shows that liver transplantation plus chemotherapy considerably improves outcomes, achieving a potential of cure in patients with permanently unresectable colorectal cancer liver metastases compared with chemotherapy alone. These findings support liver transplantation plus chemotherapy as a new standard option for carefully selected patients with permanently unresectable liver metastases from colorectal cancer.

Despite international recommendations,[9] liver transplantation plus chemotherapy versus chemotherapy alone needs to be validated in light of consistent improvements in systemic treatments. Outcomes of liver transplantation plus chemotherapy for colorectal liver metastases should be assessed within validated indications for liver transplantation, in which a 5-year survival rate of 70–80% can be expected. A recent systematic review concluded that further evidence from ongoing prospective trials is needed to determine whether, and to what extent, liver transplantation has a role in liver-only, surgically unresectable, metastatic colorectal cancer.[10] The TransMet trial (NCT02597348) was therefore initiated to assess the potential clinical benefit of liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases.

## Methods

### Study design

TransMet was a multicentre, open-label, prospective, randomised controlled trial that compared curative-intent liver transplantation plus chemotherapy versus chemotherapy alone in selected patients with permanently unresectable colorectal liver metastases. This trial was conducted in 20 tertiary centres in Europe (14 in France, four in Belgium, and two in Italy). A list of study centres, including the principal investigators and number of patients in each, is provided in the appendix (pp 2–3). The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and the relevant French and European laws. The study was approved by the Ethical Committee of Île de France VII. The study protocol amendments are provided in the appendix (p 5). The results of a feasibility study within the TransMet trial have been previously published.[11]

### Participants

Eligible patients were adults (aged 18–65 years) with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1, histologically proven colorectal cancer adenocarcinoma, *BRAF* wild–type colorectal cancer, permanently unresectable colorectal liver metastases centrally confirmed by an independent validation panel, and an objective response (stable disease or partial response) according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria for at least 3 months during the last chemotherapy line. Additional criteria were up to three chemotherapy lines for metastatic disease, carcinoembryonic antigen concentration of less than 80 ng/mL at inclusion or a decrease of 50% or more of the highest serum concentration of carcinoembryonic antigen observed during disease, no extrahepatic disease on CT scan and PET–CT imaging, high standard oncological surgical resection of the primary tumour (ie, safe margins of resection, with adequate TNM staging), absence of local recurrence on colonoscopy performed 12 months or less before enrolment (unless primary tumour resection was performed within the past 12 months), renal function within normal limits, white blood cell count higher than 2500 cells per mL and platelet count higher than 80 000 cells per mL, receipt of informed consent, and expected patient co-operation for treatment and follow-up (appendix p 4). Patients were excluded if they had general contraindication to liver transplantation, had active alcohol or substance misuse, had active infection or uncontrolled sepsis, had no psychosocial support from social services or were unable to comply with medical treatment, had other malignancies, either concomitant or within 5 years before inclusion in TransMet, had not implemented the recommended guidelines for primary colorectal cancer surgery, had previous or concomitant extrahepatic metastases or local recurrence, were pregnant, did not provide signed consent, and had no health insurance. Eligible participants were selected by the local multidisciplinary tumour board at each centre. Eligibility was assessed by an independent multidisciplinary committee of international expert oncologists, radiologists, and liver surgeons via monthly videoconferences in the presence of local investigators. The TransMet trial completed recruitment on July 5, 2021, and the database was frozen on Jan 18, 2024, once the predefined number of events was reached. Patients provided written informed consent.

### Randomisation and masking

Patients were randomly assigned (1:1) to liver transplantation plus chemotherapy or chemotherapy alone, using block randomisation with randomly selected block sizes, and stratified by centre or centre cluster for those with an expected low recruitment rate.[12] An independent statistician prepared the randomisation list with NQuery Advisor (version 7.0) using a pseudo-random numbers generator and randomly assigned patients using an interactive web-response system. Patients were enrolled by their treating physician after validation by the expert panel committee. Investigators, clinicians, participants, caregivers, and the expert panel were not masked to treatment allocation.

### Procedures

Radiological evaluation was centrally reviewed by an expert radiologist (ML). Definitive technical unresectability of colorectal liver metastases was assessed by at least two expert liver surgeons, two expert oncologists, and one radiologist (ML) on imaging at diagnosis, and was confirmed on imaging after chemotherapy, integrating the fact that missing metastases were considered as potentially persistent tumours for defining unresectability. Primary tumour resection (ie, modality and timing) and chemotherapy before inclusion were done according to local practice at participating centres. In selected patients with primary

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See Online for appendix

treatment by chemotherapy, the primary tumour was resected if the patient was eligible for enrolment. Disease control by postoperative chemotherapy for at least 2 months was mandatory to definitively validate patient eligibility. Previous hepatic resection was not a contraindication to eligibility provided there was technical unresectability.

In the liver transplantation plus chemotherapy group, local contributing centres assessed patient transplant eligibility before randomisation. If extrahepatic progression was detected during pre-transplantation evaluation, the patient was ineligible and not included. As colorectal liver metastases were not a validated indication for liver transplantation, the TransMet trial was the only potential access to liver transplantation in the participating countries. Once eligibility for liver transplantation was confirmed, investigators registered patients on organ donor waiting lists via a specific prioritisation process with national organ-sharing organisations. This process ensured liver transplantation within 2 months from the last chemotherapy cycle to reduce the risk of progression while minimising the risk of postoperative complications. In cases of progression while on the waiting list, chemotherapy was restarted, and the patient was temporarily contraindicated to liver transplantation until disease control was achieved. All liver transplantation procedures were preceded by complete abdominal exploration for occult extrahepatic disease, with frozen section of any suspicious deposit or pedicle lymph node. Orthotopic liver transplantations were done using whole cadaveric liver grafts and conventional reconstruction techniques. After liver transplantation, patients were managed in the intensive care unit for 3–4 days and then on hepatology wards for 1–4 weeks. Tailored immunosuppression was recommended for transplant recipients. The initial immunosuppressive regimen (day 0) consisted of methylprednisolone (10 mg/kg intravenously), tacrolimus (0·1 mg/kg via gastric tube), and mycophenolate mofetil (1 g twice a day intravenously). Thereafter, the recommendation was to maintain the tacrolimus dose at trough levels of 6–10 ng/mL during the first 14 days, to switch mycophenolate mofetil to everolimus at trough levels of 5–8 ng/mL within 2 months of liver transplantation, to reduce the tacrolimus dose to 3–5 ng/mL after introduction of mammalian target of rapamycin inhibitors, and to taper the steroid dose during the first 3–6 months. Administration of post-transplantation systemic chemotherapy (usually doublet) regimens, shown to be effective in pre-transplant period, was recommended in the absence of post-liver transplantation complications but not mandatory and at the discretion of the medical oncologist in charge of the patient.

In the chemotherapy group, systemic chemotherapy (mainly doublet) regimens were continued. Chemotherapy type, duration, and modality of administration were at the discretion of the team in charge of the patient according to tumour response and toxicity.

Oncological follow-up was based on thoraco-abdominal CT scan and tumour markers performed every 3 months during the first 2 years, and every 6 months thereafter. Additionally, in the liver transplantation plus chemotherapy group, a PET–CT was performed at 6 months, 12 months, and 24 months, and every year thereafter up to 5 years. This was not performed in the chemotherapy group because it would not have changed the treatment strategy.

Standard transplantation follow-up included physical examination, complete blood cell count, and blood chemical and liver function tests according to local practice in association with the oncological follow-up.

### Outcomes

The primary endpoint was 5-year overall survival, defined as the time from random assignment to death from any cause. Patients alive at the time of database freezing were censored at their last assessment. Secondary outcomes were 3-year overall survival, 3-year and 5-year progression-free survival, 3-year and 5-year recurrence rate, and health-related quality of life. Progression-free survival was defined as the time from random assignment to the first event (ie, disease progression, defined as recurrence in the liver transplantation plus chemotherapy group and progression, according to RECIST version 1.1, in the chemotherapy alone group, or death from any cause). A post-hoc analysis was performed for secondary progression-free survival to assess the effect of curative surgery or local ablation of recurrence following liver transplantation. Secondary progression-free survival was calculated as the time from random assignment to failure of curative-intent treatment of disease progression, by surgery or ablation. In the chemotherapy alone group, a post-hoc exploratory analysis was done to describe overall survival in patients who had undergone resection after random assignment. However, no crossover was allowed in the study.

Postoperative complications in the liver transplantation plus chemotherapy group were assessed within 90 days of surgery according to Clavien–Dindo grading;[13] severe morbidity was defined as grade 3b or higher complications in relation to liver transplantation within 90 days of surgery. Adverse events and serious adverse events were investigator-assessed throughout the study by a member of the central research unit to each participating centre. The seriousness and causal relationship between serious adverse events and the procedures were centrally reviewed during the final analysis. Toxicity related to systemic chemotherapy after inclusion was evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire (QLQ-C30). Global health scores were calculated from the Global Health Status and Quality of Life scale in the QLQ-C30;

a standardised score (range 0–100) was calculated from the item responses. Questionnaires were completed at baseline, months 6, 12, 18, and 24, and years 3, 4, and 5. Translational research, as specified in the protocol, and central analysis of pathological response are ongoing and will be published separately.

### Statistical analysis

The trial was designed to detect a 40% difference in 5-year overall survival rates (from 10% for the chemotherapy alone group to 50% for liver transplantation plus chemotherapy group) with 90% power and a two-sided α level of 0·05. In the survival analysis, the number of participants needed was derived from the number of deaths. Initially, 29 deaths were needed in the combined groups. However, as some patients in the liver transplantation plus chemotherapy group did not undergo liver transplantation, the required number of deaths was re-estimated to 50 deaths at the final analysis to preserve the intended power of the trial.

Overall survival was compared between the two groups using the log-rank test and Cox regression analysis to obtain a hazard ratio (HR) and 95% CI. If the proportional hazards assumption was not met, a restricted mean survival time analysis was performed, although this was not prespecified in the protocol. The difference in restricted mean survival time represents the gain or loss in event-free survival time with 95% CI in the liver transplantation plus chemotherapy group versus the chemotherapy alone group, up to a prespecified clinical point (60 months in this instance).

Analysis of overall survival was done in the intention-to-treat population and per-protocol population, which included patients who received allocated treatment without major protocol deviation (appendix p 6). Patients without major protocol deviation were defined, in the liver transplantation plus chemotherapy group, as those without liver transplant, those with disease progression at pre-liver transplantation CT scan or with 3 months or longer between the last chemotherapy cycle and liver transplantation (appendix p 7), and in the chemotherapy alone group as patients who did not receive chemotherapy or who had undergone liver transplantation or resection after random assignment (appendix p 8). For harmonisation, we considered recurrence (liver transplantation plus chemotherapy group) and progression (chemotherapy alone group) to be equivalent and therefore comparable.

Progression-free survival and quality-of-life analyses were done in the per-protocol population to evaluate the effect of treatments delivered according to the study design. The recurrence rate and secondary progression-free survival (calculated using Kaplan–Meier estimation) were presented in the liver transplantation plus chemotherapy group. Quality-of-life analyses were descriptive. Postoperative complications and post-randomisation chemotherapy-related toxicity were assessed in the per-protocol population according to the type of treatment. Safety was described in the as-treated population, which comprised patients who had liver transplantation and those treated by chemotherapy (without liver transplantation). Descriptive statistics were reported as median (IQR) for quantitative variables and frequency (%) for categorical variables. For statistical significance, a two-tailed p value of less than 0·05 was used. All statistical analyses were done independently using SAS, version 9.4, except for restricted mean survival time, which was calculated using the survRM2 package in R, version 4.3.2.

Data monitoring was done by the Clinical Research Unit of Assistance Publique–Hôpitaux de Paris, Paris-Saclay University, which centralised and controlled, via routine monitoring visits, all data collected by the research teams at each participating centre (eg, patient consent, reliability and completeness of collected data, and checking for serious adverse events). An independent data and safety monitoring board controlled the safety data. The trial is registered with ClinicalTrials.gov (NCT02597348) and accrual is complete.

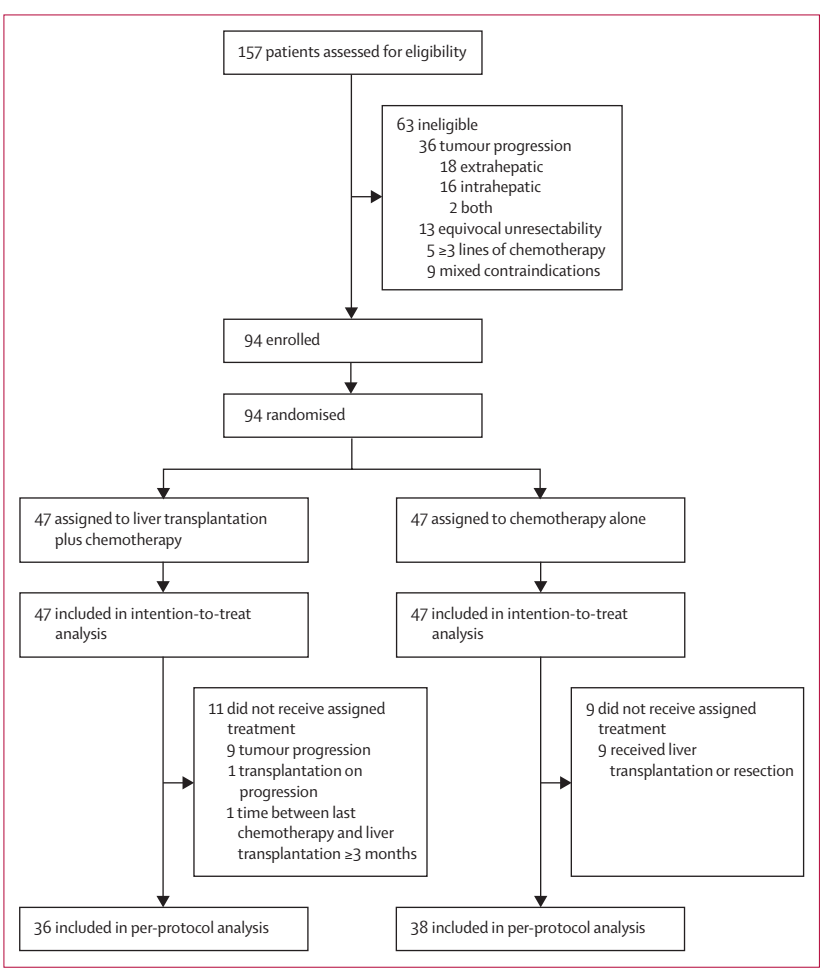


*Figure 1:* **Trial profile**

| | Liver transplantation plus chemotherapy (n=47) | Chemotherapy alone (n=47) |
|---|---|---|
| **Primary tumour** | | |
| Primary tumour site* | | |
| Right | 7 (15%) | 7 (15%) |
| Left | 25 (53%) | 29 (62%) |
| Rectum | 15 (32%) | 11 (23%) |
| (y)pT3-T4 | | |
| Yes | 37 (79%) | 38 (81%) |
| No | 9 (19%) | 9 (19%) |
| Missing | 1 (2%) | 0 |
| (y)pN status | | |
| N0 | 21 (45%) | 16 (34%) |
| N+ | 26 (55%) | 31 (66%) |
| *RAS* mutation status | | |
| Yes | 17 (36%) | 13 (28%) |
| No | 29 (62%) | 32 (69%) |
| Missing | 1 (2%) | 2 (4%) |
| Mismatch repair status | | |
| Proficient mismatch repair | 47 (100%) | 46 (98%) |
| Deficient mismatch repair | 0 | 1 (2%) |
| **Liver metastases at diagnosis** | | |
| Timing of metastases | | |
| Synchronous† | 47 (100%) | 45 (96%) |
| Metachronous | 0 | 2 (4%) |
| Number of colorectal liver metastases | 20·0 (14·0–25·0) | 20·0 (12·0–25·0) |
| <10 | 5 (11%) | 7 (15%) |
| 10–20 | 19 (40%) | 18 (38%) |
| >20 | 23 (49%) | 22 (47%) |
| Diameter of largest colorectal liver metastases, mm | 55·0 (43·0–76·0) | 50·0 (27·0–83·0) |
| CEA level, ng/mL | 305·0 (32·9–762·0) | 81·0 (20·0, 530·0) |
| CA19–9 level, UI/mL | 96·0 (19·7–800·0) | 193·0 (20·9–1949·0) |
| **Systemic chemotherapy after diagnosis** | | |
| Type of chemotherapy (first line) | | |
| Fluorouracil alone | 0 | 0 |
| Oxaliplatin based | 22 (47%) | 22 (47%) |
| Irinotecan based | 9 (19%) | 11 (23%) |
| Triplet chemotherapy | 16 (34%) | 14 (30%) |
| Targeted therapy (first line) | | |
| None | 8 (17%) | 10 (21%) |
| Anti-VEGF only | 21 (45%) | 16 (34%) |
| Anti-EGFR only | 18 (38%) | 21 (45%) |
| Tumour response (first line)‡ | | |
| Complete response | 1 (2%) | 0 |
| Partial response | 27 (57%) | 27 (57%) |
| Stable disease | 14 (30%) | 14 (30%) |
| Progression | 5 (11%) | 5 (11%) |
| Missing | 0 | 1 (2%) |

CA19–9=carbohydrate antigen 19–9. CEA=carcinoembryonic antigen. EGFR=epidermal growth factor receptor. VEGF=vascular endothelial growth factor. Data are n (%) or median (IQR). *Right=primary tumour located proximally to the colic flexure. Left=primary tumour located distally to the colic flexure. Rectum=primary tumour located within 15 cm of the anal verge. †Synchronous is defined as metastases diagnosed within 1 month of diagnosis of the primary tumour. ‡Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumours criteria version 1.1.

***Table 1:*** **Baseline characteristics at diagnosis of colorectal liver metastases in the intention-to-treat population**


## Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.


## Results

Between Feb 18, 2016, and July 5, 2021, 157 patients were assessed for eligibility and 63 were excluded (figure 1). Of four patients whose eligibility was requested before resection of the primary tumour, three were excluded due to extrahepatic tumour (n=2) or potentially resectable colorectal liver metastases (n=1), and one was randomly assigned 4 months after resection of the primary tumour. Consequently, 94 patients were included in the intention-to-treat population, with 47 in the liver transplantation plus chemotherapy group and 47 in the chemotherapy alone group. The per-protocol population included 36 patients from the liver transplantation plus chemotherapy group and 38 from the chemotherapy alone group, after excluding those with major deviations. Details of patients excluded from the intention-to-treat population are in the appendix (pp 7–8). There were no patients with missing data for the primary outcome.

Baseline disease characteristics at diagnosis (table 1) and randomisation (table 2) were similar in both groups. Patients had a median age of 54·0 years (IQR 47·0–59·0), and 55 (59%) of 94 patients were male and 39 (41%) were female. All patients who underwent liver transplantation plus chemotherapy had synchronous metastases versus all but two who received chemotherapy only. The median number of colorectal liver metastases at diagnosis was 20 in both groups. At randomisation, the liver transplantation plus chemotherapy group received a median of 21·0 chemotherapy cycles (IQR 18·0–29·0) versus 17·0 cycles (12·0–24·0) in the chemotherapy alone group, in up to three lines of chemotherapy. During first-line chemotherapy, 64 (68%) of 94 patients had received doublet chemotherapy and 30 (32%) of 94 patients had received triplet regimens; 76 (81%) of 94 patients had targeted therapy. 14 (15%) patients had previous liver resection. The median delay between diagnosis and randomisation was 15·9 months (11·8–25·7) for liver transplantation plus chemotherapy versus 13·5 months (9·0–19·4) for chemotherapy alone. Grade 3 or worse toxicity during the last chemotherapy line before randomisation occurred in six (13%) patients in the liver transplantation plus chemotherapy group and eight (17%) patients in the chemotherapy alone group (table 2). Baseline characteristics of the per-protocol population are presented in the appendix (p 10).

38 (81%) of 47 patients in the liver transplantation plus chemotherapy group underwent liver transplantation at a median of 50·5 days (IQR 30·0–65·0) post-randomisation with 30 (79%) patients having surgery within 2 months from the last chemotherapy cycle. All but one (5%) patient had a low Oslo score in the liver transplantation plus chemotherapy group. Nine patients (19%) in the liver

| | Liver transplantation plus chemotherapy (n=47) | Chemotherapy alone (n=47) |
|---|---|---|
| Age, years | 52·0 (47·0–59·0) | 55·0 (47·0–59·0) |
| Sex | | |
| Male | 27 (57%) | 28 (60%) |
| Female | 20 (43%) | 19 (40%) |
| ECOG performance status | | |
| 0 | 38 (81%) | 37 (79%) |
| 1 | 9 (19%) | 10 (21%) |
| Number of colorectal liver metastases | 14·0 (8·0–25·0) | 15·0 (5·0–25·0) |
| <10 | 12 (26%) | 16 (34%) |
| 10–20 | 20 (43%) | 17 (36%) |
| >20 | 15 (32%) | 14 (30%) |
| Diameter of largest colorectal liver metastases, mm | 27·0 (18·0–42·0) | 27·0 (16·0–45·0) |
| CEA, ng/mL | 3·6 (2·2–12·4) | 3·6 (2·0–22·1) |
| CA19–9, IU/mL | 11·4 (5·9–30·0) | 15·0 (6·5–28·7) |
| Fong's clinical risk score* | | |
| Low (0–2) | 20 (43%) | 13 (28%) |
| High (3–5) | 27 (57%) | 34 (72%) |
| Time between diagnosis and randomisation, months | 15·9 (11·8–25·7) | 13·5 (9·0–19·4) |
| Ongoing chemotherapy | | |
| Type of chemotherapy | | |
| Fluorouracil alone | 7 (15%) | 1 (2%) |
| Oxaliplatin based | 12 (26%) | 11 (23%) |
| Irinotecan based | 20 (43%) | 27 (57%) |
| Triplet | 8 (17%) | 8 (17%) |
| Targeted therapy agent | | |
| None | 2 (4%) | 4 (9%) |
| Anti-VEGF | 17 (36%) | 16 (34%) |
| Anti-EGFR | 28 (60%) | 27 (57%) |
| Number of chemotherapy cycles (last line) | 14·0 (8·0–20·0) | 11·0 (7·0–14·0) |
| Tumour response† | | |
| Partial response | 26 (55%) | 21 (45%) |
| Stable disease | 21 (45%) | 26 (55%) |
| (Continued from previous column) | | |
| Grade ≥3 toxicity (CTCAE) | | |
| Yes | 6 (13%) | 8 (17%) |
| No | 39 (83%) | 34 (72%) |
| Missing | 2 (4%) | 5 (11%) |
| Cumulative chemotherapy | | |
| Total number of chemotherapy lines | | |
| 1 | 18 (38%) | 23 (49%) |
| 2 | 21 (45%) | 17 (36%) |
| 3 | 8 (17%) | 7 (15%) |
| Cumulative number of chemotherapy cycles (total lines) | 21·0 (18·0–29·0) | 17·0 (12·0–24·0) |
| ≤12 | 3 (6%) | 14 (30%) |
| 13–23 | 25 (53%) | 21 (45%) |
| ≥24 | 19 (40%) | 12 (26%) |
| Previous curative intent surgery | | |
| None | 43 (91%) | 37 (79%) |
| Minor hepatectomy | 2 (4%) | 5 (11%) |
| Major hepatectomy | 2 (4%) | 5 (11%) |
| Delay between primary resection and randomisation >24 months | | |
| Yes | 5 (11%) | 7 (15%) |
| No | 42 (89%) | 40 (85%) |

CA19–9=carbohydrate antigen 19–9. CEA=carcinoembryonic antigen. CTCAE=Common Terminology Criteria for Adverse Events. ECOG=Eastern Cooperative Oncology Group. EGFR=epidermal growth factor receptor. IU=international units. VEGF=vascular endothelial growth factor. Data are n (%) or median (IQR). *Despite the decrease in size and tumour markers levels, patients remained with multiple metastases impossible to resect completely. †Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumors criteria, version 1.1.

***Table 2:*** **Baseline characteristics at randomisation in the intention-to-treat population**

transplantation plus chemotherapy group had no liver transplantation because of intercurrent hepatic or extrahepatic progression while waiting for liver transplantation (n=5), intraoperative discovery of extrahepatic disease (n=3), or identification of prostate cancer during pre-transplantation checks (n=1; appendix p 7). The median time to progression for patients who progressed while waiting for liver transplantation was 30·0 days (IQR 14·0–48·0). Waiting times for three patients excluded at laparotomy were 15 days, 26 days, and 168 days. Recipient data are presented in the appendix (p 13).

Severe morbidity (34%), retransplantation (8%), and mortality rates (3%) within 3 months have been previously reported.[11] Median length of stay was 6·0 days (IQR 5·0–8·0) in the intensive care unit and 16·0 days (14·0–24·0) in the hospital (appendix p 13). Early post-liver transplantation immunosuppressive regimens for the liver transplantation plus chemotherapy group are presented in the appendix (p 14). Post-transplantation chemotherapy was administered overall in 26 (68%) of 38 patients, with 15 (58%) receiving for more than six cycles (appendix p 15).

Of 46 patients in the chemotherapy alone group who continued chemotherapy for a median of 16 cycles (IQR 5–45), six patients (13%) had one line, three (7%) had two lines, and 37 (80%) had three lines of systemic treatment from randomisation. Three patients underwent local ablation and 11 had radioembolisation to increase local control. Characteristics and outcome of nine patients who unexpectedly underwent partial hepatectomy (n=7) or liver transplantation (n=2) during the study period after a median interval of 20·7 months (IQR 12·2–25·8) from randomisation are shown in the appendix (pp 8–9).

In the intention-to-treat population, after a median follow-up of 59·3 months (IQR 42·4–60·2) at database cutoff, 56 deaths had been reported. Median survival was not reached for the liver transplantation chemotherapy group and was 29·7 months (95% CI 20·8–39·4) in the chemotherapy group.

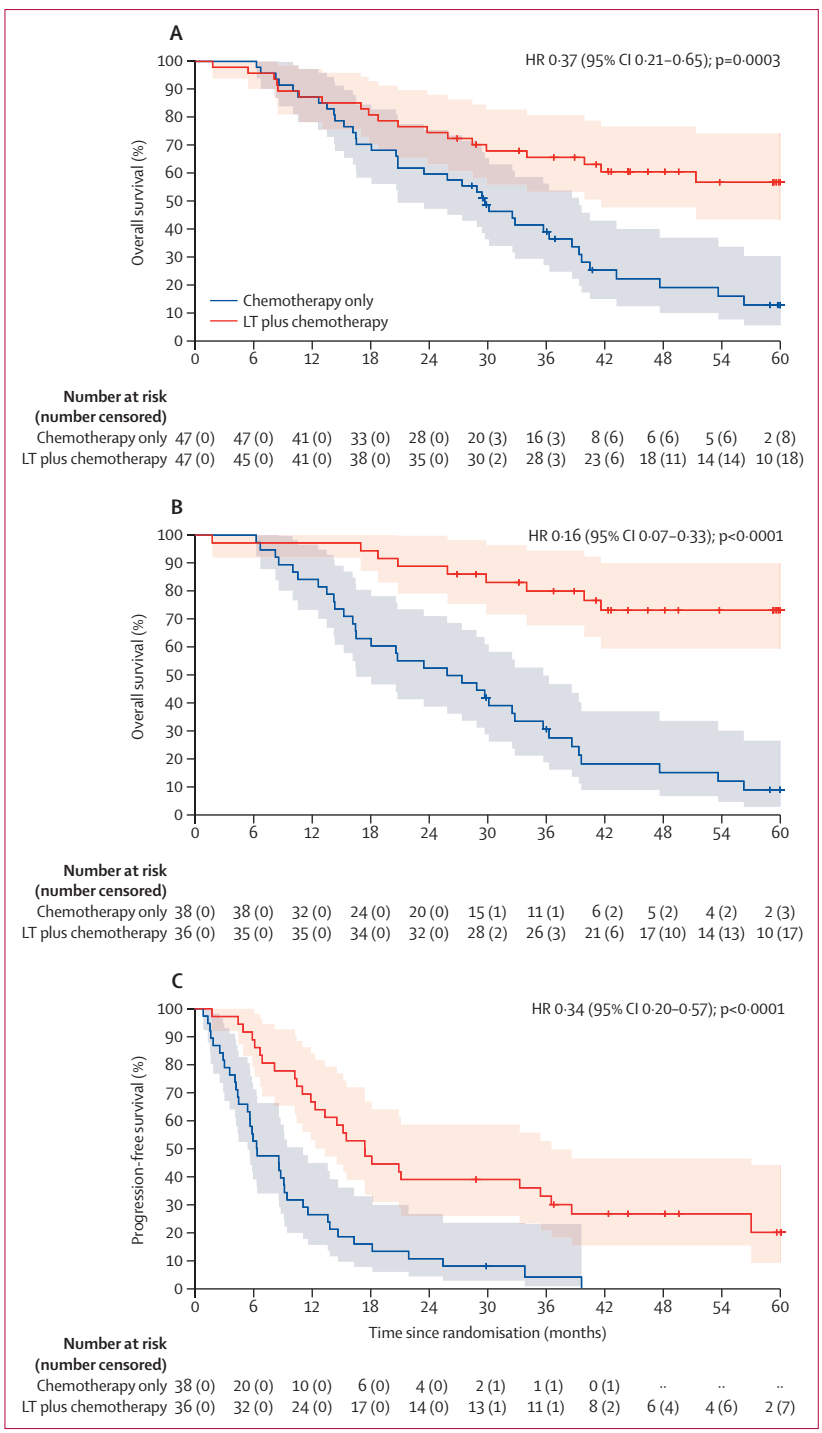


***Figure 2:*** **Survival outcomes in chemotherapy alone and chemotherapy plus liver transplantation**
Overall survival in the intention-to-treat population (A) and per-protocol population (B), and progression-free survival in the per-protocol population (C). Shaded areas represent 95% CIs. Tick marks represent censored patients. LT=liver transplantation. HR=hazard ratio.

5-year overall survival was 56·6% (95% CI 43·2–74·1) for liver transplantation plus chemotherapy and 12·6% (5·2–30·1) for chemotherapy alone (HR 0·37 [95% CI 0·21–0·65]; p=0·0003; figure 2A).

The estimated restricted mean survival time up to 60 months was 43·9 months (95% CI 38·0–49·9) for the liver transplantation plus chemotherapy group and 31·3 months (26·3–36·3) for the chemotherapy alone group, corresponding to a gain of 12·6 months (95% CI 4·9–20·4 months; p=0·0014). In the intention-to-treat analysis, 3-year overall survival was 65·5% (95% CI 53·2–80·8) for the liver transplantation plus chemotherapy group and 38·9% (26·9–56·2) for the chemotherapy alone group. In the per-protocol analysis, 5-year overall survival was 73·2% (95% CI 59·6–90·0; nine events) for the liver transplantation plus chemotherapy group and 9·3% (3·2–26·8; 33 events) the chemotherapy alone group. Median survival was not reached for the liver transplantation plus chemotherapy group and was 26·6 months (95% CI 16·5–35·7) for the chemotherapy alone group (HR 0·16 [95% CI 0·07–0·33]; p<0·0001; figure 2B).

The median progression-free survival was 17·4 months in the liver transplantation plus chemotherapy group versus 6·4 months in the chemotherapy alone group, with a 3-year progression-free survival rate of 32·9% (95% CI 20·6–52·7) versus 3·9% (0·7–23·0) and a 5-year progression-free survival rate of 19·9% (9·0–44·1) versus 0%, respectively (HR 0·34 [95% CI 0·20–0·57]; p<0·0001; figure 2C).

Among the 36 patients in the per-protocol analysis who underwent transplantation, 26 (72%) presented an isolated recurrence in the liver (one [4%]), the lungs (14 [54%]), the lymph nodes (three [12%]), in other sites (five [19%]), or in multiple sites (three [12%]). 19 (73%) of these 26 patients received chemotherapy. Surgery or local ablation with curative intent was performed in 12 (46%) patients (liver in one patient, lung in eight patients, colorectal in one patient, and other in two patients; appendix p 16). No patient in the liver transplantation plus chemotherapy group received best supportive care for first recurrence. The median secondary progression-free survival in the liver transplantation plus chemotherapy group was 35·4 months, with a 5-year secondary progression-free survival rate of 36·1% (95% CI 21·9–59·4; figure 3). At the last follow-up in the per-protocol population, 15 (42%) of 36 patients in the liver transplantation plus chemotherapy group were alive without disease compared with one (3%) in the chemotherapy alone group.

During the study period in the as-treated population, 110 serious adverse events were observed in 32 (80%) of 40 patients who underwent liver transplantation (from either group), and 69 serious adverse events were observed in 45 (83%) of 54 patients treated with chemotherapy alone. In the liver transplantation plus

chemotherapy group, three (8%) of 36 patients who received a transplant were retransplanted because of primary non-function, post-transplantation discovery of a gallbladder cancer in the graft, or caval obstruction related to a large-for-size liver graft. One patient died postoperatively of multi-organ failure.

The most frequent grade 3 or worse complications with liver transplantation plus chemotherapy were biliary complications (n=4), pulmonary complications (n=3), early allograft dysfunction (n=3), primary non-function (n=2), postoperative haemorrhage (n=2), and superficial site infection (n=2; table 3). In the liver transplantation plus chemotherapy group (per protocol), among patients who received post-liver transplantation chemotherapy, grade 3 or 4 toxicity was observed in eight (36%) of 22 evaluable patients (table 4). In the chemotherapy group (per protocol), chemotherapy-related grade 3 or 4 toxicity after randomisation occurred in 17 (47%) of 36 patients (table 4).[14,15]

Health-related quality-of-life data were available for 55 (74%) of 74 patients at inclusion. The median global health score from QLQ-C30 was 75 (IQR 58–83) in the liver transplantation plus chemotherapy group and 71 (58–83) in the chemotherapy alone group at baseline, with no significant difference between groups in QLQ-C30 scores (appendix pp 17–18). The global health scores did not vary substantially between the groups over time. However, we observed a trend towards physical functioning decline over time in the chemotherapy alone group. Similarly, there were declines in fatigue, pain, dyspnoea, and loss of appetite in the chemotherapy group (appendix p 22).

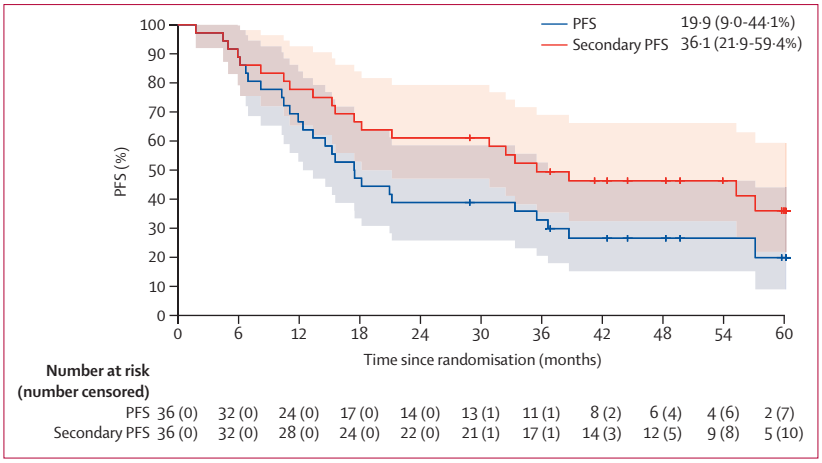


***Figure 3:*** **Secondary PFS in liver transplantation plus chemotherapy group who had a liver transplantation in the per-protocol population**

A significant proportion of the 28 patients who presented with recurrence after liver transplantation were considered eligible for potentially curative treatment of the recurrent disease. These patients were therefore censored from the PFS curve at the time of recurrence. As they become free from disease after resection or ablation of their recurrence, they were no longer considered to be censored in the corrected secondary PFS. Secondary PFS shows the effect of the treatment of recurrence when compared with primary PFS. Shaded areas represent 95% CIs. Tick marks represent censored patients. PFS is defined as the time to first recurrence after liver transplantation. Secondary PFS is the time to first recurrence without secondary remission occurring after liver transplantation. PFS=progression-free survival.

## Discussion

In the TransMet trial, liver transplantation plus chemotherapy in patients with permanently unresectable colorectal liver metastases was associated with significantly better 5-year survival than chemotherapy alone. These results were observed in the intention-to-treat population although 19% of patients allocated to liver transplantation plus chemotherapy dropped out and a similar proportion of patients allocated to chemotherapy alone subsequently underwent liver resection or transplantation. The per-protocol analysis yielded a greater 5-year survival benefit for liver transplantation plus chemotherapy versus chemotherapy alone, underlining the success of this approach.

Since liver transplantation was reconsidered as a potential treatment for patients whose only other option is palliative chemotherapy and who have a poor prognosis for long-term survival, several non-comparative studies have suggested that, with improved patient selection, liver transplantation combined with chemotherapy might have better outcomes than chemotherapy alone.[7,16]

Historically, however, confounding criteria might have resulted in patients with better prognoses undergoing liver transplantation than those selected for chemotherapy. This study is the first randomised controlled trial to show a clear benefit in overall survival for liver transplantation added to chemotherapy versus chemotherapy alone. This clear survival advantage could be related to three key factors. The first factor was strict patient selection by using more rigorous eligibility criteria than the initial Norwegian study,[8] as shown by the low Oslo score shared by all but one transplant recipients. Partial response or stable disease after chemotherapy was a prerequisite, as patients progressing on chemotherapy have poor outcomes after surgery or liver transplantation.[17,18] *BRAF* mutation was an exclusion criterion in light of reduced progression-free survival and overall survival in these patients after liver resection.[19,20] Also, no more than three lines of chemotherapy were permitted to avoid transplants in patients with no further active treatment options.

The second factor was the implementation of an independent expert committee, which excluded 40% of patients considered as potentially eligible by local tumour boards. Empathy for patients without curative options might lead local medical teams to propose liver transplantation as a compassionate indication, even with potentially worse outcomes.[21] In addition, the committee's expertise in radiological assessments and surgical assessment of unresectability of colorectal liver metastases was a key factor for accurate and homogeneous patient selection.

A third factor was prioritising patients for transplant. Rapid access to an organ ready for transplantation was essential to avoid long waiting times and risk of tumour progression in the context of multinodular bilobar

| | Any grade (n=36) | Grade ≥3b (n=36) |
|---|---|---|
| Hepatic | | |
| Biliary | 5/36 (14%) | 4/36 (11%) |
| Arterial | 6/36 (17%) | 1/36 (3%) |
| Early graft dysfunction* | 4/36 (11%) | 3/36 (8%) |
| Collection | 3/36 (8%) | 1/36 (3%) |
| Primary non-function† | 2/36 (6%) | 2/36 (6%) |
| Haemorrhage | 2/36 (6%) | 2/36 (6%) |
| Hepatic or caval | 1/36 (3%) | 1/36 (3%) |
| Ascites | 2/35 (6%) | 0 |
| Portal | 1/36 (3%) | 0 |
| Rejection | 3/35 (8%) | 0 |
| Digestive | | |
| Ileus | 3/36 (8%) | 1/36 (3%) |
| Malnutrition | 1/36 (3%) | 0 |
| Other | 7/33 (19%) | 1/35 (3%) |
| General condition | 2/34 (6%) | 0 |
| Haematological | | |
| Anaemia | 1/36 (3%) | 0 |
| Other or not defined | 3/34 (8%) | 0 |
| Pulmonary | | |
| Pleural effusion | 6/36 (17%) | 1/36 (3%) |
| Other | 4/36 (11%) | 3/36 (8%) |
| Cardiovascular | | |
| DVT | 2/35 (6%) | 0 |
| Other | 7/34 (19%) | 1/34 (3%) |
| Renal | 8/36 (22%) | 1/36 (3%) |
| Superficial site infection | 3/36 (8%) | 2/36 (6%) |
| Infection | | |
| CMV | 3/36 (8%) | 0 |
| Other | 7/33 (19%) | 1/35 (3%) |
| Diabetes | 6/36 (17%) | 0 |

Data are n/N (%). CMV=cytomegalovirus. DVT=deep vein thrombosis. *Early graft dysfunction was defined according to Olthoff and colleagues.[13] †PNF was defined according to Makowka and colleagues.[14]

***Table 3:*** **Postoperative complications in the liver transplantation plus chemotherapy group according to the per-protocol population**

| | Liver transplantation plus chemotherapy (n=24) | | Chemotherapy alone (n=38) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Any toxicity | 23/24 (96%) | 8/22 (36%) | 35/36 (97%) | 17/36 (47%) |
| Haematological disorders | 10/24 (42%) | 4/23 (17%) | 16/29 (55%) | 6/25 (24%) |
| Gastrointestinal disorders | 15/23 (65%) | 3/21 (14) | 26/29 (90%) | 3/27 (11%) |
| Nervous system disorders | 4/23 (17%) | 1/22 (5%) | 21/31 (68%) | 3/27 (11%) |
| General disorders | 15 (63%) | 0 | 29/34 (85%) | 2/24 (8%) |
| Renal disorders | 0 | 0 | 1/23 (4%) | 0 |
| Infectious disorders | 0 | 0 | 2/28 (7%) | 0 |
| Immune system disorders | 0 | 0 | 3/29 (10%) | 0 |
| Other disorders | 15/24 (63%) | 3/22 (14%) | 31/33 (94%) | 10/27 (37%) |

Data are n/N (%).

***Table 4:*** **Toxicity related to systemic chemotherapy after randomisation in the per-protocol population**

disease. The objective agreed with national organ-sharing organisations to do transplantations in these patients within 2 months of interruption of chemotherapy was achieved in 79% of patients, with only one patient waiting for more than 3 months after his last cycle of chemotherapy. Meeting this timeframe was especially important in countries with organ shortages. National organ-allocation policies, such as the sickest-first approach, are based on the model for end-stage liver disease (MELD) score.[22] However, patients with colorectal liver metastases have preserved liver function and a low MELD score, and are unlikely to be prioritised over patients with end-stage liver disease. Therefore, MELD exception points should be allocated to increase the priority for these patients, as in this study. An alternative approach to supplementing the limited donor pool is to use living donors[23–25] or technical refinements that enable the use of partial grafts (segments 2 and 3), such as in the RAPID concept (ie, resection and partial liver segment 2–3 transplantation with delayed total hepatectomy).[26,27]

Survival and toxicity data in the chemotherapy alone group were consistent with known regimens for metastatic colorectal cancer[28] and previously reported mortality and severe complication rates with liver transplantation plus chemotherapy were consistent with liver transplantation in common indications (eg, cirrhosis and other validated liver primary malignancies).[29] Although few data supported the combination, adjuvant chemotherapy was delivered with immunosuppression showing acceptable toxicity rates. However, no clinical benefit could be observed due to the limited number of patients.

From an oncological perspective, these results support liver transplantation as the best option for chemotherapy-controlled, liver-only, unresectable colorectal liver metastases. This finding might represent a major change in clinical practice and in perceiving the role that transplantation could play in prolonging survival and offering a cure for patients with metastatic dissemination. From a transplantation perspective, our findings support unresectable colorectal liver metastases as an indication for transplantation, with the 73% 5-year overall survival rate being in line with the survival rate seen in patients with common indications for liver transplantation.[30] A 19% dropout rate was observed during the wait for transplantation or at laparotomy, which is similar to that seen in liver transplantation for perihilar cholangiocarcinoma and, to a lesser extent, for hepatocellular carcinoma. Whenever contraindication was detected during surgical exploration, however, no graft loss was observed, and once transplanted, graft use was optimal.

From both perspectives, post-transplantation outcomes were notable for overall survival but less optimal for progression-free survival because of significant recurrence (74%). This was lower than the recurrence rate in the

SECA-I study,[8] but similar to that in the SECA-II study,[31] which was more rigorous in its patient selection. These results suggest that patient selection can be improved, by molecular biology and detection of microscopic residual disease by circulating tumour DNA. Recurrence was confined exclusively to the lungs in more than 50% of cases; 46% of recurrences were treated by surgery or local ablation. Both approaches led to secondary remission in 25% of patients, and a secondary 5-year progression-free survival rate after resection or ablation of recurrence of 36%. Altogether, 42% of transplanted patients were disease-free at the last follow-up, arguing for a real potential for cure with liver transplantation.

Some limitations of the study should be considered. Heterogeneity could have occurred in the chemotherapy regimens (as well as immunosuppressive therapies) depending on the different policies of local oncologists and hepatologists. Post-transplant chemotherapy was not possible for all patients, mainly because of complications or suboptimal recovery after liver transplantation. However, these variations reflect real-life practice, and the strength of the study relies on the homogeneous and rigorous patient selection, the reproducibility of which ensured strict adherence to the eligibility criteria and guaranteed prioritisation of patients for organ allocation. This approach could conceivably be generalised to transplant centres, thus expanding the indications for transplant oncology.

In summary, this study has shown that liver transplantation combined with chemotherapy significantly improves overall survival and offers potential for cure in selected patients with unresectable colorectal liver metastases versus chemotherapy alone. Patient survival after liver transplantation, when effectively performed, is similar to that observed in common indications for liver transplantation. These results support validating liver transplantation as a new standard option that might change current practice for liver-only, permanently unresectable, colorectal liver metastases.

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**Contributors**
RA designed the study. RA and MG coordinated the study and wrote the study protocol. RA, ML, MD, MG, FL, JL, and PM participated in the expert panel that conducted patient evaluations for eligibility. CP and LG oversaw the methodology and statistical analysis. RA, MG, and CP supervised the data analysis and wrote the manuscript. RA, EB, PB, DC, FC, LCh, LCo, UC, MD, KG, MG, VG, BH, JH, HJ, VL, FM, J-YM, DP, ES, OS, JPA, and CV participated in the recruitment of patients and verified the local raw data. RA, MG, and CP verified the raw data according to local investigators. All authors were involved in drafting the work or reviewing it critically for important intellectual content. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Declaration of interests**
We declare no competing interests.

**Data sharing**
Data are available on reasonable request. The Commission Nationale de l'Informatique et des Libertés (French data privacy authority) and the European Union's General Data Protection Regulation mean that the database and information and consent documents signed by the patients cannot be transmitted. De-identified individual participant data underlying the results might be considered by the editorial board for availability to interested researchers subject to terms and conditions of such consultation and compliance with the applicable regulations. For all enquiries, please contact: drc-secretariat-promotion@aphp.fr.

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