

Belgian protocol for indication and selection of patients with unresectable colorectal cancer liver metastases eligible for liver transplantation

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Abstract

Background and study aims: Colorectal cancer (CRC) is common in Western countries, about 50% of patients develop liver metastases (CLM). While local CLM therapies can achieve 5-year survival up to 60%, most patients eventually become unresectable (uCLM) and have poor outcomes with systemic treatment alone. Prospective studies, including SECA I and II and the TransMet trial, showed that in carefully selected patients, liver transplantation (LTx) can achieve survival outcomes comparable to standard LTx indications. The aim of this work was to develop a harmonized national consensus protocol for the indication and selection of uCLM patients eligible for LTx.

Patients and methods: Under the coordination of the Belgian Liver & Intestine Advisory Committee (Be-LIAC), all six Belgian transplant centers delegated a transplant surgeon, an oncologist and an hepatologist to a working group that performed a literature review and drafted preliminary criteria. Three successive national meetings and a structured voting refined these criteria in the current protocol.

Results: Consensus was reached on inclusion and exclusion criteria for LTx in uCLM. Two key conditions are liver-only disease and technically uCLM. Strict requirements include a six months disease stability or response on systemic therapy and an obligatory eight-week treatment holiday. Absolute CEA levels and specific somatic mutations are not excluded. A national Be-LIAC governance model was established, combining local prospective decision-making with central auditing and registry-based evaluation.

Conclusions: A harmonized national protocol for LTx in uCLM has been established, ensuring consistent patient selection across all Belgian centers. Stricter criteria and a national governance model aim to optimize outcomes while maintaining ethical allocation of donor organs. (*Acta gastroenterol belg.*, 2026, 89, 483-492).

Keywords: LTx, uCLM, national consensus, selection.

Introduction and rationale

Colorectal carcinoma (CRC) is common in western countries, with around 8,000 annual cases in Belgium. Approximately 50% will develop metastases (1,2). Untreated metastatic CRC has a median survival of 12 months (3,4). Advances in imaging, staging,

molecular markers, and therapy, both systemic and local, have improved outcomes for colorectal liver metastases (CLM) (3-6). Local treatment remains the only curative option for resectable CLM, with a 5-year survival of up to 60% (7-8), though 70% of patients face recurrence within 3 years (4,5). In this setting palliative chemotherapy, repeat liver resection, or other local treatments offer median survival of 10-38 months (6-10). Systemic treatment regimens (FOLFOX, FOLFIRI, FOLFOXIRI) extend median survival to 20 months (11), and combining VEGF/EGFR antibodies with chemotherapy improves survival up to 30 months, with 5-year survival rates of 15-20% in some cases (12-16).

Liver transplantation (LTx) for unresectable CLM (uCLM) was explored and performed until the 1990s (17,18). However, a high recurrence rate in addition to the inferior results of LTx for all indications in this early period, led to progressive abandonment of this indication. Since then the results of LTx have improved and hepatocellular carcinoma (HCC) (fulfilling the Milan criteria) has become a leading indication. In more recent years, the scope of LTx for oncological indications has broadened to include selected patients with more advanced HCC as well as other primary tumors (e.g., hilar cholangiocarcinoma) and even metastatic tumors (e.g., neuroendocrine metastases and hemangioendothelioma) (17-21). However, the application of LTx for metastatic liver tumors remains

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Submission date: 07/10/2025
Acceptance date: 09/06/2026

controversial (17, 21, 22). Concerns stem from the systemic nature of metastatic disease and the effect of post-operative immunosuppressive therapy in reducing immuno-surveillance, and potentially leading to increased recurrence and poorer outcomes (23-27).

Advances in CLM treatment and LTx immunosuppression have prompted some researchers to reconsider LTx as a potential option for selected patients with uCLM (22). However, the global shortage of donor organs, particularly from deceased donors, makes it impractical—and potentially inappropriate—to offer LTx to all patients with uCLM. Careful patient selection and thorough evaluation of LTx outcomes for CLM are essential to determine the viability of this approach.

The landmark SECA-I study from Norway received significant attention (28). Among 21 patients who underwent LTx with sirolimus as primary immunosuppression starting on the first postoperative day, the 5-year overall survival (OS) rate was 60%. Four factors were identified as negative predictors of survival: tumor diameter >5.5 cm; time from primary surgery <2 years; CEA levels >80 µg/L; and progressive disease at the time of LTx (28-30). Importantly, the SECA study excluded patients with poor prognostic factors for recurrence and survival after CLM resection. While all patients experienced recurrent disease, those with pulmonary metastases showed relatively indolent behavior compared to those with hepatic metastases in the transplanted liver (31). The study also demonstrated that LTx resulted in significantly improved OS rates, with 56% for LTx patients compared to 9% for a similar cohort treated with first-line chemotherapy (32). The subsequent SECA-II study confirmed that stricter selection criteria could achieve OS rates after LTx for CLM comparable to standard LTx indications (33). At a median follow-up of 36 months, the SECA-II study reported 1-, 3-, and 5-year OS rates of 100%, 83%, and 83%, respectively, with disease-free survival rates of 53%, 44%, and 35% at 1, 2, and 3 years, respectively (33). Additionally, LTx has been shown to be cost-effective for carefully selected CLM patients compared to chemotherapy alone (34).

The latest addition to this body of knowledge comes from the recent TransMet trial. This was a prospective multicenter randomized study, evaluating the efficacy of combining chemotherapy with LTx versus chemotherapy alone in patients with uCLM. The trial that included French, Belgian, and Italian centers, reported a 5-year overall survival rate in the per protocol group was 73% (while 57% in the intention to treat analysis) for the LTx plus chemotherapy group, compared to 12.6% for the chemotherapy only group. Oncological relapse was observed in 72% (26/36) of the transplanted population. Localization of recurrence was mainly pulmonary (54% or 14/26). Only one patient had hepatic recurrence in the graft. Surgery or ablation was performed in 46% (12/26) recurrences. With a median

follow-up of 50 months, no evidence of disease (NED) was disclosed in 42% (15/36) of the transplanted group versus 3% (1/38) in the standard of care group. These findings suggest that, with appropriate patient selection, LTx with chemotherapy can offer a durable approach for patients with liver-limited metastatic colorectal cancer. Importantly, the study highlighted the critical role of an independent multidisciplinary validation committee to make sure the patients fulfilled the strict inclusion criteria. The study also highlighted the importance of rapid transplantation after listing to avoid drop off, as 19% of patients allocated to the LTx arm failed to undergo transplantation due to too long waiting time and disease progression (35).

In conclusion, with rigorous selection criteria, LTx offers to patients with uCLM, a 5 year survival benefit similar to other standard indications. As a result, Belgium (similar to other national LTx programs worldwide), wishes to introduce this indication in its armamentarium. Because the 6 LTx centers share the same pool of organ donors, it is important that patient selection be identical at all centers. For this reason, the BeLIAC proposes a national protocol.

LTx for uCLM is an “unfinished” product. Despite excellent survival data, progression-free survival remains inferior to 50%. Development of a prospective database is essential to analyze the results particularly in the long-term. Studies are necessary to better understand the biology of recurrence and design selection tools and intervention strategies to reduce it.

Methods

Following the publication of the TransMet trial, renewed enthusiasm grew regarding LTx in the context of uCLM. In the following months, a substantial increase in referrals was observed, both from colleagues and from patients who presented spontaneously. To streamline this growing demand, the idea of developing a national protocol for selection of patients was proposed. Given that grafts originate from an international pool with strict allocation rules, and that they remain in competition with other LTx indications, the need for a nationally agreed selection framework was considered imperative.

Be-LIAC (Belgian Liver Intestinal Advisory Committee) was identified as the appropriate forum to coordinate this effort. Each of the six Belgian LTx centers was requested to delegate a transplant surgeon, an oncologist, and a hepatologist to the working group. An initial review of the literature was performed, upon which a preliminary draft was developed.

This proposal was presented during the national Be-LIAC meeting of February 13, 2025. This first discussion highlighted two key areas of consensus. First, it was agreed that the TransMet selection protocol would not be adopted uncritically. The working group was convinced that refinements were needed, aiming for stricter selection criteria in order to achieve improved outcomes.

This was considered all the more relevant given that the original TransMet protocol had been conceived years earlier, and that substantial national expertise had since become available. The Belgian protocol should therefore be regarded as a national expert consensus framework informed by TransMet and the Oslo experience, but adapted to Belgian clinical practice and designed for prospective evaluation rather than as a direct reproduction of any single previous protocol. Second, there was unanimous agreement on the need for national oversight and auditing through Be-LIAC. While a prospective independent validation committee, as used in TransMet, was initially considered an important strength and served as a conceptual starting point, its implementation within a national real-world program was further refined during subsequent discussions.

A second national Be-LIAC meeting was convened on April 28, 2025, to present the revised draft. Key issues that emerged from this discussion were reformulated into concise statements, which were circulated afterwards to all centers for a structured vote (approve/disapprove).

After collection of responses, a third national meeting was held on September 2, 2025, in which final deliberation took place with the explicit aim of achieving unanimous consensus on the selection criteria.

During a subsequent Be-LIAC meeting on February 12, 2026, the governance model was further refined. While a prospective independent validation committee had initially been considered in analogy with the TransMet trial, the working group agreed on a more pragmatic framework combining local prospective decision-making within each accredited transplant center with mandatory central post-hoc review of all transplanted cases through Be-LIAC. Pre-transplant central review was retained for cases with borderline or ambiguous eligibility, or whenever deviation from the protocol is considered.

The outcome of this multi-step process is the present national protocol, to which all six accredited Belgian transplant centers have formally committed.

Protocol procedure

Prior to referral to one of the six liver transplant centers the patient file should be discussed at the local oncology multi-disciplinary team (MDT) meeting (also known as 'MOC' or 'COM'). Next, patient is seen at the outpatient clinic of the transplant center by the multidisciplinary team (including oncologist, hepatologist and transplant surgeon). The file is then discussed at the oncology MDT and the transplant MDT of the local transplant center, after eventual completion

of the required diagnostic procedures (MRI whole body and/or FDG-PET-CT).

Patients considered eligible for the protocol will be evaluated for LTx according to standard institutional work up. The final decision for inclusion is made by the local multidisciplinary oncology and transplant teams of one of the six accredited Belgian liver transplant centers, according to the nationally agreed criteria. All transplanted cases will undergo mandatory post-hoc central review through Be-LIAC and will be entered into the prospective national registry. Pre-transplant central Be-LIAC review is required in cases of borderline or ambiguous eligibility, or whenever deviation from the protocol is considered. When the patient meets the inclusion criteria, a Non Standard Exception (NSE) will be audited via Eurotransplant by Be-LIAC. In case the patient is eligible for transplantation, the patient has to sign an informed consent.

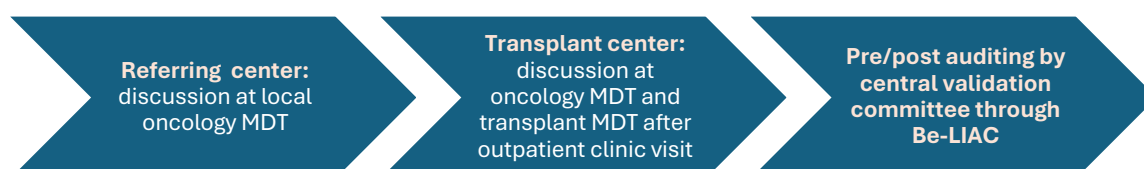
Core eligibility criteria

The following represent the two key eligibility criteria; they are further detailed below alongside additional inclusion and exclusion criteria

- No (history of) metastatic disease beyond the liver
- Unresectable CLM status

Inclusion criteria

Histology	• Adenocarcinoma colon or rectum
Surgery primary	• R0 oncological resection of primary tumor
Staging	• Liver only disease according to MRI whole body and/or FDG-PET-CT within 4 weeks prior to MDT at transplant center
uCLM	• R0 resection or ablation of CLM is not possible. • The liver remnant after treatment is <25-30% in normal livers and <35-40% in compromised livers (fibrosis/steatosis/cirrhosis). • There is no opportunity to increase the volume with portal vein embolization (PVE) or other measures, or these techniques have failed.



No local recurrence	• No local recurrence on colonoscopy within 12 months prior to MDT at transplant center, when resection of primary tumor was done >12 months before • For rectal cancer also according to MR pelvis within 4 weeks prior to MDT at transplant center
Systemic treatment	• Partial response (PR) and/or stable disease (SD) per RECIST 1.1 should be observed for at least 6 months on the same treatment regimen. • Stability or liver-only progression after a minimum therapeutic pause of 8 weeks*. This pause is intended as an additional biological stress test and does not replace the requirement for prior disease control. • In synchronous CLM presentation the chemotherapy-free window for primary resection (pre- and postoperative) counts as this mandatory pause**.

*The mandatory treatment pause is not intended to replace the requirement for prior disease control on systemic therapy, but rather to serve as an additional biological and staging stress test before transplantation. After a minimum therapeutic pause of 8 weeks, patients must show no evidence of extrahepatic disease. Limited intrahepatic progression may be observed during this interval and does not automatically preclude transplantation, provided the disease remains confined to the liver, technically transplantable, and without features of aggressive or uncontrolled tumor biology. Any progression should be carefully evaluated in terms of pace, extent, and overall disease behavior, and must be reviewed by the central validation committee. Since early extrahepatic relapse after LTx may reflect occult disease suppressed by ongoing chemotherapy, a chemotherapy-free interval may help unmask clinically relevant extrahepatic disease before committing a scarce graft. This approach must be combined with repeat high-quality staging, including MRI whole body and/or FDG-PET-CT, and central committee reassessment.

**In unresectable synchronous disease, the asymptomatic primary tumor remains in place due to the inability to stop chemotherapy. The necessity to invert the 'Liver First' paradigm (36) in transplantation

imposes a prior colorectal surgery that can be synchronized with this therapeutic pause.

Exclusion criteria

Histology	• Incomplete pTNM • Hepatic pedicle nodal involvement in right-sided CRC is considered M1a disease and therefore an exclusion
Biology Staging	• dMMR/MSI • (History of) metastatic disease beyond the liver
Disease control	• Radiological and/or biochemical evidence of progressive disease observed while receiving bridging systemic treatment. The indication can be reconsidered if the patient is responding after a switch in chemotherapy or in case chemotherapy is not an option other local therapies (TACE, TARE, RT) can be considered.
Pregnancy	• Women who are pregnant or breastfeeding
Other	• General in- and exclusion criteria for liver transplantation beyond the oncological setting also account for these patients.

Considerations

Age Patients are explicitly not excluded exclusively on the number of their age.

ECOG

Performance is not a unique exclusion criterium. For other LTx indications patients are often transplanted beyond an ECOG PS of 1 when the underlying disease is the origin and main contributor of this score. However specifically in the oncology setting, ECOG-PS hold certain prognostic value, as such a score of 0-1 is favorable. Case by case assessment seems appropriate in this setting.

CEA

Although CEA has been incorporated in previous selection models, including the Oslo score, this protocol does not use an absolute CEA threshold as an independent exclusion criterion. This decision reflects the fact that CEA is not informative in non-secreting tumors and that a single absolute cut-off may insufficiently capture individual tumor biology.

However, CEA dynamics are considered clinically relevant. In patients with CEA-secreting tumors, a rising CEA level during adequate systemic therapy or

during pre-transplant surveillance should be regarded as biochemical evidence suggestive of disease progression and should prompt re-evaluation. In this context, rising CEA may constitute a contraindication to proceeding with transplantation, particularly when concordant with radiological findings or other indicators of uncontrolled disease.

Histology

One could discuss whether undifferentiated tumors should be excluded. It is believed the inclusion criteria are strict enough to spontaneously rule out cases with unfavorable prognosis.

Discussion exist for mucinous tumors and signet ring cell differentiation. Again, it is believed the inclusion criteria are strict enough to spontaneously rule out those cases. In these specific histology subtypes we do recommend MRI whole body additionally to, or instead of FDG-PET-CT evaluation.

Tumor biology

BRAF mutant types are excluded from other protocols. While other less common, albeit well known aggressive drivers like SMAD4 or FBXW7, only to name a few, are not mentioned. However it is believed our criteria for inclusion are strict enough to on the one hand halt classic aggressive (BRAF and other) biological behavior spontaneously (37). On the other hand, clinical observational experience warrants for a small subset of BRAF patients with less aggressive behavior. Moreover in our retrospective Belgian cohort two BRAF-mutated patients were transplanted with follow-ups of 36 and 110 months (per analysis in September 2025), and are alive without relapse. This suggests BRAF status alone (among other mutations) should not exclude patients from LTx; disease control and behavior might be more relevant.

Rectal tumors with complete clinical response after neoadjuvant treatment

For rectal tumors managed with a watch-and-wait strategy after achieving a clinical complete response (cCR) following neoadjuvant therapy, a minimum of two years of structured active surveillance is required before consideration within the LTx for uCLM protocol. This requirement reflects the fact that cCR does not equate to pathological complete response or definitive oncological clearance, and that the risk of both local regrowth and metastatic progression remains non-negligible compared to patients undergoing total mesorectal excision.

The two-year interval represents a pragmatic, evidence-informed threshold, acknowledging that the risk of regrowth and distant relapse is highest within the first years of follow-up, and that sustained disease-free surveillance over time is associated with an increasing

likelihood of durable remission. Although distant relapse in this subgroup frequently involves the lungs, hepatic metastatic evolution cannot be excluded, warranting a cautious and standardized surveillance interval prior to transplantation (38-39).

Perihepatic lymph nodes

Systematic perihepatic lymph node sampling should be performed pre- or per transplant surgery procedure.

If performed before the day of transplant surgery, sampling can be done endoscopically or surgically. If during the transplant procedure, frozen section examination is performed.

Ideally this preliminary step is done beforehand, in order to minimize the risk of encountering extra-hepatic disease extension on the day of transplantation. The goal is to maximally avoid having to resort to an urgent back-up, which is burdensome and ethically questionable if foreseeable in advance.

Interval primary surgery

Unlike previous protocols we do not include a minimum of 12 months between surgery of the primary tumor and LTx provided that there is a complete and lege artis pTNM staging.

Treatment line

Previous protocols seem to respect an arbitrary ≤ 3 treatment lines rule. Given the anticipated ever growing landscape of systemic treatment options, and in light of an unclear consensus definition of 'a treatment line', we explicitly do not exclude patients uniquely on this number. Also taking into consideration the semantic discussion of the definition of 'one treatment line'.

Immunotherapy

Although dMMR/MSI tumors are excluded, immunotherapy is increasingly being investigated in pMMR/MSS colorectal cancer, currently predominantly within clinical trials, with potential future implementation in routine clinical practice. In the absence of disease-specific data, a pragmatic approach is adopted by extrapolation from hepatocellular carcinoma, recommending a minimum interval of 3 months between the last dose of immunotherapy and liver transplantation. This interval is intended to reduce the risk of acute graft rejection potentially associated with residual immune activation and the prolonged pharmacodynamic effects of immune checkpoint inhibitors (40).

Synchronous presentation

Patients with liver-only metastases at diagnosis of CRC should be discussed early in the disease course at

the MDT of one of the 6 centers in order to anticipate an optimal strategy for local therapy and/or eventual indication of LTx.

Other trials

Prior to liver transplantation, the treating oncologist should explicitly inform the patient that LTx generally constitutes an exclusion criterion for most clinical trials, and ensure that the potential implications of this are understood and documented within the informed consent process.

ctDNA

The use of circulating tumor DNA (ctDNA) is encouraged within the context of prospective clinical studies, given its potential role as a biomarker for minimal residual disease and early relapse detection. However, in the absence of strong evidence supporting its use for clinical decision-making in the context of LTx, ctDNA should not be used as a standalone criterion for patient selection or exclusion outside of a study setting.

In particular, the clinical interpretation of ctDNA remains uncertain in patients with known in situ tumor burden, such as unresected CLM, where ctDNA positivity may reflect ongoing tumor shedding rather than unfavorable tumor biology. Conversely, longitudinal dynamics (e.g., rising or declining ctDNA levels) may prove more informative, but their clinical relevance in this setting has not yet been established.

Furthermore, multiple heterogeneous testing platforms are currently in use, without a universally accepted standard or validated assay for this indication. In light of these limitations, and considering principles of equity and access, ctDNA testing should not be recommended outside a research setting, particularly when associated with out-of-pocket costs for patients. This remains a rapidly evolving field that warrants further prospective research.

National Be-LIAC auditing and governance

National governance of this protocol is organized through Be-LIAC. In contrast to the TransMet trial, where an independent committee prospectively validated every case, this Belgian protocol relies primarily on prospective decision-making by the local multidisciplinary oncology and transplant teams of the six accredited Belgian liver transplant centers. This choice reflects the fact that all six centers participated in the development of the protocol, formally endorsed the selection criteria, and share responsibility for their consistent application.

To ensure transparency, quality control, and equity across centers, all transplanted cases must be submitted for mandatory post-hoc central review through Be-LIAC and entered into a prospective national registry.

This post-hoc review evaluates adherence to the protocol, patient selection, imaging, disease course, allocation pathway, perioperative findings, recurrence patterns, and outcomes. Deviations from the protocol must be explicitly reported and justified.

The central Be-LIAC auditing body is composed of two hepatobiliary surgeons experienced in liver resection for colorectal liver metastases, two medical oncologists with expertise in colorectal cancer, one expert MRI radiologist, and one nuclear medicine physician. A rotating system is implemented to ensure balanced representation across centers. In case of institutional overlap, members directly involved in the case under review are excluded from the evaluation.

Pre-transplant central Be-LIAC review remains mandatory for cases with borderline or ambiguous eligibility, or whenever deviation from the protocol is considered. This includes, in particular, cases with uncertain tumor biology or disease dynamics (e.g. limited intrahepatic progression during the treatment pause or rising CEA in secreting tumors), equivocal findings suggestive of possible extrahepatic disease, uncertainty regarding technical unresectability, suspicious lymph node involvement, atypical or high-risk tumor characteristics requiring individualized interpretation, or complex treatment histories. More generally, any situation in which eligibility cannot be considered unequivocal, or where the proportionality of transplantation is uncertain, should prompt mandatory central review prior to proceeding.

This governance model aims to balance feasibility in real-world national practice with the need for harmonization, accountability, transparency, and fairness in the allocation of scarce donor organs.

Situation requiring mandatory central review

Tumor dynamics	- Limited intrahepatic progression during the therapeutic pause - Rising CEA in CEA-secreting tumors
Extrahepatic disease assessment	- Equivocal findings on MRI whole body or FDG-PET-CT suggestive of possible extrahepatic disease - Uncertain or borderline lymph node involvement beyond strictly perihepatic regions
Technical assessment	Uncertainty regarding unresectable CLM status
Adherence / ethics	- Any intended deviation from protocol criteria - Any situation in which proportionality of

transplantation or benefit-risk balance is uncertain.

Work up

Before listing a standard work up for liver transplantation beyond the oncological setting is performed per center protocol.

Allocation

Patients are registered on the Eurotransplant waitlist according to standard national procedures. Given the risk of dropout due to disease progression during prolonged waiting time, the aim is to proceed to transplantation within 1–2 months after listing, in line with the time frame achieved in TransMet, where transplanted patients underwent LTx after a median delay of 51 days and 19% of patients dropped out because of progression while awaiting transplantation (35).

At the Belgian national level, timely access is operationally supported by two complementary pathways:

1. Allocation through an agreed non-standard exception status, corresponding to at least 28 MELD points.
2. Transplantation through center offers, particularly using suitable DCD grafts. The latter is increasingly feasible given improvements in donor organ preservation, including machine perfusion strategies, which have improved the assessment and utilization of extended-criteria and DCD liver grafts (41).

Based on the most recent Belgian experience in the past year 2025, all 11 patients received a graft within the intended 1–2 month time frame. However, this operational feasibility is dependent on the national donor pool, allocation system, transplant-center organization, and access to suitable DCD grafts, and should therefore not be assumed to be directly generalizable to other countries or allocation systems.

Management on the waiting list

Policy after inclusion	• FDG-PET-CT or MRI whole body q3m • CEA q3m if secreting tumor • Clinical examination q3m at outpatient clinic of both GI oncology and transplant surgery • Systemic treatment is continued, bevacizumab is stopped
Drop-out after inclusion	• Extrahepatic disease • Tumor progression on adequate chemotherapy

Drop-out at time of LTx

- If any exclusion criterium is met after inclusion
- An exploratory laparotomy is done first at transplant
- Any suspicious lesions should be examined with frozen section
- Any evidence of extrahepatic disease is a criterium for premature termination of the procedure. If an R0 resection is anticipated in the event of local growth towards the diaphragm this can be deemed an exception

Surgery

LTx will be performed following standard procedures as outlined in the institutional specific protocols of Centre Hospitalier Universitaire de Liège, Cliniques Universitaires Saint-Luc, Hôpital Universitaire Bruxelles, Universitair Ziekenhuis Antwerpen, Universitair Ziekenhuis Gent en Universitair Ziekenhuis Leuven. The protocol only considers recipients of full size (of reduced/split) grafts from deceased donors. The RAPID technique (42) remains experimental and should only be performed within a trial setting.

The recipient operation commences immediately after the transplantability of the liver graft has been confirmed. The transplant procedure begins with an abdominal exploration to rule out extrahepatic disease. A thorough inspection of the peritoneum, omentum, and lymph nodes is conducted. Systematic perihepatic lymph node sampling should be performed if not yet carried out surgically or endoscopically before the day of the transplant surgery. Before any irreversible step is undertaken, a frozen section examination of any suspicious lesion (and if done, of the systematic perihepatic lymph node sampling) is performed.

Discovery of extrahepatic disease leads to abortion of the transplant procedure and the graft is immediately reallocated via Eurotransplant to a pre-selected back up recipient (Local if center offer, national if NSE allocation).

The transplantation itself follows local protocols, provided tumor-free margins are achieved.

Postoperative Regimen

After surgery the patient is treated according to standard procedures by the institutional protocol.

Immunosuppression

Immunosuppression should be considered according to center-specific protocols. There is limited evidence

to support a specific immunosuppressive regimen for patients undergoing LTx for uCLM, as most data are extrapolated from studies on recurrent hepatocellular carcinoma after liver transplantation.

A strategy of minimal immunosuppression is generally favored. The impact of calcineurin inhibitors does not appear to increase the incidence of colorectal cancer, although their role in established metastatic disease remains to be defined. At present, there is no clear evidence supporting the routine use of mTOR inhibitors in this specific setting.

It should be acknowledged, however, that alternative immunosuppressive strategies have been explored in transplant oncology programs, including in the context of TransMet, where mTOR-based regimens have been considered given their potential antiproliferative properties (35). Nonetheless, robust data demonstrating a clear oncological benefit of such approaches in colorectal liver metastases are lacking.

As a general rule, a tailored, restrictive immunosuppressive regimen should be pursued, aiming to allow host-versus-tumor response while preserving graft function and avoiding rejection. A steroid-free immunosuppressive regimen may be considered, aiming to minimize overall immunosuppressive exposure by maintaining drug levels within the lowest effective therapeutic range, while ensuring adequate graft protection.

Graft failure

An issue compromising the functionality of the graft will be addressed in the same way as it would be for a transplant for any other indication (primary non-function, arterial thrombosis, rejection, or other). Rejection is diagnosed and treated according to standard institutional procedures. In the event of a graft failure, high-urgency application can be submitted.

Further treatment

Currently, there is no validated consensus regarding the role of adjuvant treatment after transplantation for metastases. The TransMet protocol recommended restarting systemic treatment one month after LTx (35). Transplantation, viewed as total hepatectomy, should be integrated in the same way as conventional hepatic resection in the oncological management algorithm (43).

The oncologist should discuss with the patient before LTx the implications in terms of potential exclusion from further clinical trial options in a post LTx setting.

Follow up protocol

Patients will receive treatment and follow-up in accordance with standard protocols at their local transplantation center. An eventual index MRI whole

body 12 weeks after LTx can be considered. Regular oncological follow-up will be conducted by the oncologist with a CT thorax-abdomen every three months. In the event of an oncological relapse, further treatment will be determined by the treating oncologist. Preferred options include surgery, radiofrequency ablation (RFA), microwave ablation (MWA), chemotherapy, radiation therapy, and other available treatments.

Justification

This clinical protocol is based on the SECA 2 protocol (Clinical trials.gov NCT01479608) and on the TransMet protocol (Clinical trials.gov NCT02597348) and adjusted for Belgium.

Despite the ongoing debate of optimal patient selection for this indication, the accumulated experience and in particular, the Norwegian and more recently French data seem to justify application of LTx to strictly selected patients with liver-only uCLM, since they benefit from a survival advantage (at 5 years) similar to other standard indications. The current waitlist mortality in Belgium is 10,5-12% (44)) and therefore strict adherence to the aforementioned criteria should be mandatory.

This protocol was discussed on a national level with several professionals involved in the care for patients with CRC and CLM, which is reflected by the above-mentioned participants. Contents of this protocol were discussed during national Be-LIAC meetings (13/02/2025, 28/04/2025 and 02/09/2025).

Evaluation

Despite the demonstrated survival benefit of transplantation compared to standard treatment, prolonged remission remains highly questionable: less than 40% of secondary progression-free survival (PFS) at 5 years after resection or ablation of recurrence in the French randomized study and 40% relapse-free survival (RFS) at 3 years in the Rochester protocol (45). In the context of organ scarcity, different transplantation centers are requested to report post-operative results both short and long-term in a transparent and centralized manner.

Evaluation is warranted and planned annually during the Be-LIAC meetings. Evaluation will focus on:

- Overall graft and patient survival after 3 months, 1,3, 5, and 10 years
- Disease free survival after 1, 3, 5, and 10 years
- Incidence and patterns of recurrence and subsequent administered treatment.

This protocol is intended as a dynamic framework and may be refined over time based on accumulating clinical experience and observed outcomes, ensuring an adaptive and responsible approach.

The estimated number of eligible patients is limited and is not expected to exceed approximately 15 per year. This figure represents a pragmatic planning estimate based on stepwise epidemiological approximation and extrapolation from larger European cohorts, reflecting the highly selective nature of the eligibility criteria. This represents around 10% of the overall wait list. If inclusion rates are substantially lower or higher, and in function of the results, inclusion criteria might need to be adjusted. After inclusion of 30 patients, the results will be presented.

Research

Next to a standardized flow and agreement on this protocol across liver transplant centers in Belgium in order to guarantee quality and parity, high level research opportunities at different levels should be made available to all LTx centers

- Registry for prospective and retrospective data analysis
- Standardized biobanking of explants
- Cellular analysis
- Serial liquid biopsies pre and post transplant
- Academic vaccination trials post transplant
- Others

Be-LIAC can serve as a structure for implementation of these research collaborations.

Conclusion

A harmonized, national consensus protocol for liver transplantation in unresectable colorectal liver metastases has been established, ensuring consistent and rigorous patient selection across all six Belgian liver transplant centers. The protocol incorporates stricter inclusion criteria than TransMet, including a mandatory 6 months period of disease stability/response on systemic therapy, alongside an obligatory 8-weeks treatment holiday. These strict measures aim to optimize clinical outcomes. In light of these stricter selection criteria, absolute CEA levels and specific somatic mutations are not excluded.

While informed by the TransMet and Oslo experiences, this protocol has been adapted to the Belgian clinical context and is intended as a prospectively evaluated national framework rather than a direct replication of previous protocols.

National Be-LIAC auditing was established to safeguard uniformity, transparency, and ethical allocation of donor organs, combining local prospective responsibility with mandatory post-hoc central review and pre-transplant review for borderline or protocol-deviating cases. A negative decision rendered by the central auditing committee constitutes a formal contraindication to liver transplantation for the patient under any modality. This protocol facilitates prospective

data collection, providing a robust framework for evaluating long-term survival and recurrence patterns in this high-risk patient population. National research collaborations across all LTx centers are encouraged and facilitated through this protocol. This protocol is designed as an adaptive framework and may be refined over time based on emerging evidence and observed outcomes, ensuring a responsible and evidence-informed approach.

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