NEDERLANDSE TRANSPLANTATIE VERENIGING

PROTOCOL
Indication and selection of patients with colorectal carcinoma liver metastases eligible for liver transplantation

(Version 8.0, 15-09-2026)

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This guideline contains recommendations of a general nature. These recommendations may not be applicable in every individual case. It is the responsibility of the treating physician to determine whether the guideline is applicable in practice. Circumstances may arise in which, in the interests of providing appropriate care to the patient, it is necessary to deviate from the guideline.

Colofon
PROTOCOL INDICATION AND SELECTION OF PATIENTS WITH COLORECTAL CARCINOMA LIVER METASTAES ELIGIBLE FOR LIVER TRANSPLANTATION
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NEDERLANDSE **TRANSPLANTATIE** VERENIGING

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Indication and selection of patients with colorectal carcinoma liver metastases eligible for liver transplantation

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1. INTRODUCTION AND RATIONALE

Colorectal carcinoma (CRC) is a frequent cancer in western societies. The annual incidence of CRC in the Netherlands is 15,000 per year and half of these patients will develop metastases [1,2]. Median survival for patients with untreated metastatic CRC is approximately 12 months [3,4]. Over the last decade, treatment of patients with colorectal liver metastases (CLM) has markedly improved with advances in patient selection related to improved radiologic imaging and more accurate staging, identification of molecular markers associated with poor outcome, as well as improved systemic therapy [3-6]. Local treatment of the liver metastases is the only potential curative treatment available for resectable CLM with low operative mortality (1-2%) and a 5-year survival of up to 60% [2-8]. Disease recurrence occurs, however, in 70% of patients most often during the first 3 years after surgery [4,5]. Patients with recurrence, as well as those without initial curative surgical treatment options, are routinely treated with palliative chemotherapy, while a subset undergo repeat liver resection, local tumor ablation, radio-embolization, or hepatic artery infusion therapy, with a median overall survival (OS) of 10-38 months [3,6-10]. Moreover, the median survival for patients treated with 5-fluorouracil (5-FU), -leucovorin, irinotecan, with or without oxaliplatin containing regimens (FOLFOXIRI and FOLFIRI, resp.) is approximately 20 months [11]. Antibodies against VEGF (bevacizumab) or EGFR (cetuximab or panitumumab) combined with 5-FU, irinotecan or oxaliplatin have shown an increased response rate, prolonged time to progression and improved survival up to 30 months (in left sided metastatic tumors), with a 5 yr overall survival of 15 to 20% [12-16].

Liver transplantation (LTx) for otherwise irresectable liver metastases has been considered and performed until the 1990s [17,18]. Largely due to high recurrence rates and poor outcomes, the indication for LTx became much more restrictive over time in this patient group. More recently, however, the indications for LTx have expanded to include patients with more advanced hepatic cellular carcinoma (HCC), as well as other primary (eg, hilar cholangiocarcinoma) and metastatic (eg, neuroendocrine metastasis) tumors [17-21]. The use of LTx for metastatic tumors to the liver has been particularly controversial [17,21,22]. Given the systemic nature of metastatic disease, there has been concern that LTx and the associated post-operative immunosuppressive therapy may contribute to unfavorable post-operative outcomes due to decreased native immuno-surveillance that may lead to increased recurrence and poor outcomes [23-27].

Interestingly, advances in CLM treatment and LTx immunosuppression have caused some investigators to call for the re-evaluation of LTx as a treatment option for selected patients with unresectable CLM [22]. However, due to the universal shortage of organs, especially from deceased donors, it is not feasible -or perhaps appropriate- that LTx be used for all patients with unresectable CLM. Rigorous patient selection, as well as a critical review of the outcomes of LTx for CLM is therefore needed to assess whether this therapy is warranted.

The landmark SECA-I study from Norway has attracted extreme attention [28]. In 21 patients who underwent LTx using sirolimus as primary immunosuppression from the first postoperative day, the 5-year overall survival was 60%. Four factors (tumor diameter >5,5 cm, time from primary surgery <2 years, CEA levels >80 µg/l and progressive disease at the time of LTx) were identified as negative predictors of survival [28-30]. Differences in outcome are undoubtedly related not only to LTx, but also strict patient selection. To this point, patients with poor prognostic risk factors for recurrence and survival after CLM resection were excluded from the SECA study. Although all patients suffered from recurrent disease, those with pulmonary metastases were relatively indolent compared with those who were found to have hepatic metastases to the transplanted liver [31].

They further showed that LTx achieved a significantly higher OS rate of 56% compared to 9% in a similar cohort of patients with liver only disease treated with first line chemotherapy [32]. Recently the SECA-II study demonstrated that more strict selection criteria can indeed be used to obtain an OS after LTx for CLM comparable to that observed in conventional indications for LTx [33]. At a median follow-up of 36 months the 1,3, and 5 yr overall survival in the SECA-II study was 100%, 83% and 83% respectively. The disease-free survival was 53%, 44% and 35% at 1, 2 and 3 years respectively [33]. Moreover, LTx has been shown to be cost-effective in highly selected patients with CLM compared to chemotherapy alone [34].
In conclusion, following strict selection, patients with irresectable CLM benefit from LTx and therefore we will introduce this indication in the Netherlands.

1.1 Staging

Patients, considered eligible for the protocol will be evaluated for LTx according to institutional protocols. The final decision for inclusion in the study is made at the multidisciplinary transplant conference of the transplant centers Groningen/Leiden/Rotterdam. Only patients with irresectable CLM without evidence of extrahepatic disease are considered for this protocol. In case the patient is eligible for transplantation, the patient has to sign informed consent.

Definition of irresectability:

- R0 Resection or ablation of lesions in the liver is not possible.
- The liver remnant after treatment is smaller than 25-30% in normal livers and smaller than 35-40% in compromised livers (fibrosis/steatosis/cirrhosis).
- Assessment of liver volume should be performed by CT scan, and mebrofenin scintigraphy is strongly advised to asses liver function since systemic therapy is virtually always part of treatment plan.
- There is no opportunity to increase the volume with PVE or other measures, or these techniques have failed.

2. PROTOCOL PROCEDURE

Prior to referral to one of the three liver transplant centers all imaging should be discussed in a local or (if no liver surgery is performed) a regional multi-disciplinary team (MDT) meeting (MDT meeting as standardized by SONCOS). Decision on resectability (see criteria 1.2) is taken by a center that performs liver resections. If the patient meets the inclusion criteria for the protocol, they should be referred to a LTx unit.

2.1 Inclusion/Exclusion criteria

Inclusion Criteria

- Age between 18 and 70 years at time of diagnosis of NRCLM
- Good performance status, ECOG 0 or 1.
- Histologically verified (history of) adenocarcinoma in colon/rectum. Liver metastases, not amenable to liver resection or ablation when assessed at the institutional multidisciplinary tumor board.
- No signs of extra hepatic metastatic disease or local recurrence according to PET scan and CT thorax/abdomen/pelvis within 4 weeks prior to the MDT meeting at the transplant center.

- In case of metachronous presentation:
  - No local recurrence according to MR-pelvis scan in patients with rectal cancer within 4 weeks prior to the MDT meeting at the transplant unit
  - No signs of local recurrence judged by colonoscopy / CT colography within 12 months prior to the MDT meeting at the transplant unit.
  - Minimum interval from diagnosis NRCLM resection to transplant 1 year (ref 41)
- In case of synchronous presentation:
  - Standard surgical procedure with adequate (R0) resection margins including circumferential resection margins (CRM) of at least ≥1mm for rectal cancer patients.
  - Minimum interval from CRC diagnosis to transplant 1 year, minimum interval from CRC resection to transplant 6 months (41).
  - No local recurrence according to MR-pelvis scan in patients with rectal cancer within 4 weeks prior to the MDT meeting at the transplant unit
- All patients should have received at least 8 weeks of chemotherapy before liver transplantation is considered.
- Patients should have response to chemotherapy (PR) according to RECIST 1.1.
- Patients with a RECIST response of SD might be candidate for liver transplant if
  - Tumor response of index lesions is at least 10% with no progressive lesions
  - Response to chemotherapy for lesions that do not respond in size can be judged by using Chun criteria. [41,42]
- This response to bridging chemotherapy should be observed for at least 6 months. With a minimal interval from primary CRC diagnosis to transplant of 1 year (41).
- Preferably PET metabolic tumor volume (PET-MTV) is measured on PET scan after a 4 week chemotherapy discontinuation. PET-MTV <70 cm3 shows good prognosis.
- Signed informed consent and expected cooperation of the patients for the treatment and follow up must be obtained and documented according to GCP, and national/local regulations.
- (modified) Oslo score up to 2 (see figure 1)
- Patients should qualify to the general criteria to undergo liver transplantation.

Figure 1: Modified Oslo score 0-2, each factor representing 1 point [33]

Oslo Score	
Maximal Tumor diameter > 5,5 cm	1
Pre transplant CEA > 80 µg/l	1
Time interval: diagnosis to tx < 2 yrs	1

Exclusion Criteria

- Patients will be excluded from the protocol if they meet any of the following criteria:
- Primary tumor histology of undifferentiated adenocarcinoma and signet ring cell carcinoma [ref 40,41]
- Radiological or biochemical evidence or both of progressive disease observed while receiving bridging chemotherapy is a contraindication to liver transplantation. The indication can be reconsidered if the patient is responding after a switch in chemotherapy or in case chemotherapy is not an option TACE can be considered.
- Previous diagnosed and treated extrahepatic metastatic disease
- Previous diagnosed other metastatic cancer (e.g. malignant melanoma, breast cancer)
- Molecular markers associated with poor outcome: BRAF pos [17,36]
- MSI high status, because these patients could profit from immunotherapy.
- Unintentional weight loss >10% during the last 6 months
- Women who are pregnant or breast feeding
- Any reason why, in the opinion of the MDT, the patient could not be included. With this sentence we mean that acceptance on the waiting list for liver transplantation is not only based on the above mentioned oncological criteria, but the patient should be generally fit for transplantation. General in- and exclusion criteria for liver transplantation also account for these patients.

Relative Exclusion Criteria:

- Right sided (ascending colon) primary CRC tumor have worse outcome compared to other primary locations.[43,44] Only if patients show a relatively favorable course, (for instance metachronous tumor, long interval between tumor and metastases, low Oslo score, low MTV (<70m3), no BRAF and no RAS mutations) they can be considered for transplantation
- Nodal status of the primary tumor: pN2 status is associated with increased recurrence (local and regional). Since there is no specific data on local recurrence it is not a strict exclusion criterium upfront. However it is important to have at least 9 month follow-up after resection of the primary to exclude local recurrence in case of pN2.

2.2. Allocation

Patients are listed for transplantation according to standard Eurotransplant protocol. Patients will get a non-standard exception (NSE) status: 28 MELD points (decision taken during Dutch Liver Transplantation Board (LOL) meeting LOL, 4th of December 2020). After the patient is listed repeat diagnostics is scheduled every 3 months (CT chest/abdomen + CEA) and performance is checked. If the patient no longer meets the criteria for inclusion, the patient will be taken off the waiting list. We aim for transplantation between 1-2 months from listing. Chemotherapy should be continued, preferentially with capecitabine of 5FU iv monotherapy. Bevacizumab is stopped. The patient condition and blood tests need to be sufficient to undergo a liver transplantation at time of donor offer. In the event of a graft failure, high-urgency application can be submitted.

2.3 Validation committee

The final decision for inclusion is made after consultation of the case by the 3 Dutch transplant centers (similar to hilar cholangiocarcinoma protocol). They will discuss the case in a local validation committee, including HPB surgeon experienced in liver resection for CLM, a medical oncologist, a radiologist, a hepatologist, and a liver transplant surgeon: This committee needs to validate the indication of LTx in view of the oncological history of the patient preferably within one week if work-up is complete.

Policy after inclusion:
Repeat CT chest/abdomen while on waiting list every 3 months. Chemotherapy is continued, but bevacizumab is stopped.

Drop-out after inclusion:
Any sign of extrahepatic disease or tumor progression on imaging while patient is receiving (adequate) chemotherapy and on the waiting list for transplantation If any exclusion criterium is met after inclusion.

Drop out at time of transplantation:
At transplant, first exploratory laparotomy; criteria for premature termination of the procedure: any evidence of extrahepatic disease. Intraoperatively, prior to explantation of the liver, a regional lymph node exam (hepatoduodenal ligament) with frozen section will be performed. Positive regional nodes are considered extrahepatic disease. Any other suspicious lesions should be examined with frozen section.

3. SURGERY

The LTx will be performed according to standard procedures by the institutional protocol (Rotterdam, Leiden or Groningen). The LTx can be performed with a deceased donor liver (full size of split) or a graft from a living donor (right or left lobe according to current local protocols). The RAPID technique (38) is still considered an experimental procedure and should only be performed in trial setting. In case of a deceased liver graft the recipient operation should start as soon as the donor surgeon considers the liver transplantable. This policy saves time to call in a 2nd recipient in case there is extrahepatic disease. To speed up this process a back-up patient is already available. In case of extrahepatic disease and allocation to a back-up patient, Eurotransplant should be informed as soon as possible. The transplant procedure starts with an exploration of the abdomen to exclude extrahepatic disease. Careful inspection of peritoneum, omentum and lymph nodes is performed. Intraoperatively, prior to explantation of the liver, a regional lymph node exam (hepatoduodenal ligament) with frozen section will be performed. Any other suspicious lesions should be examined with frozen section. Any extrahepatic disease found during explorative laparotomy is a contraindication for transplantation. The transplantation can be performed according to local protocol, as long as tumor free margins can be achieved.

3.1 Postoperative Regimen

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

3.2 Immunosuppression

The immunosuppression regimen consists of standard induction with basiliximab, corticosteroids and mycophenolic acid (MMF). Tacrolimus is started within the first 5 days post-operatively. MMF can be stopped after reaching adequate trough levels of tacrolimus at discretion of the treating physician. Steroids are tapered during the first 3-6 months After 4-6 weeks, an option is to switch to CNI (tacrolimus) and mTOR inhibitor (sirolimus) combination therapy and aim for a combined through level of Tacrolimus and Sirolimus of 5-7 ng/ml during the first 6 months, thereafter judged on individual basis. There is little evidence to recommend specific immunosuppression strategies in patients undergoing liver transplantation for non-resectable colorectal liver metastases, with data mostly extrapolated from literature on recurrent hepatocellular carcinoma after liver

transplantation. Because of that, there cannot (yet) be firmly advised against other immunosuppressive strategies, such as the commonly used regimen of CNI (tacrolimus) monotherapy.

3.3 Standard anti-rejection therapy

Rejection is diagnosed and treated according to standard procedures by the institutional protocol.

3.4 Further treatment

At time of relapse the patient will receive best available treatment at the discretion of the treating physician. This includes (preferably) surgery, radiofrequency ablation (RFA), Microwave ablation (MWA), chemotherapy, radiation therapy, and other available treatment options.

3.5 Follow up protocol

Patients will be treated according to standard routines at the local transplantation unit. Oncological follow-up is performed according to the schedule below: during the first year the visits are every month with a CT scan of chest/abdomen every 3 months (see Table 1). If a relapse is observed, then further follow-up and treatment will be at the discretion of the treating physician.

Table 1.

Follow-up	Visit 1st and 2nd year (every 3 months)	Visit 3rd-10th year (every 6 months)
Hb, Ht, leuco, plts, CRP, Na, K, Creat	X	X
Bilirubin, ASAT, ALAT, ALP, Alb	X	X
INR, cholesterol, glucose, HbA1c	X	X
CEA,	X	X
Weight	X	X
BP	X	X
CT chest/abdomen/pelvis	every 3 months	every 6 months
Colonoscopy (only in pts without relapse)	National protocol	National protocol

4. JUSTIFICATION

This clinical protocol was based on the SECA 2 protocol (Clinical trials.gov NCT01479608) and adjusted for the Netherlands, in cooperation with the team of the Oslo University, Norway, under guidance of Professor P.D. Line, Professor of Surgery, and Professor S. Dueland, Professor of Oncology. To optimize the protocol for the Netherlands we've performed mutual visits to Norwegian and Dutch centers, and we've organized seminars.
Based on the Norwegian experience and the excellent results they've published over the years, we believe that strictly selected patients can profit from liver transplantation in liver-only colorectal liver metastases. However, liver grafts are scarce, and the national waitlist mortality is nowadays between 15-20% in the Netherlands. [39] We've decided that for this reason, we should be more strict in our inclusion criteria than our Norwegian colleagues because they do not face a scarcity problem, their donation rate is much higher than in the Netherlands.
Furthermore, this protocol was discussed on a national level with several professionals involved in the care for patients with colorectal carcinoma and colorectal liver metastases, which is reflected by the above-mentioned participants. Contents of this protocol were discussed during national

meetings of the Dutch Liver Transplantation Board (LOL) (1st of April 2019, 4th of December 2019 and 11th of May 2020).

5. EVALUATION

Despite the scarcity of donor livers, we advocate that strictly selected patients with irresectable CLM can be candidate for LTx, who would otherwise be condemned to poor outcome.
Evaluation is warranted and planned annually during Dutch Liver Transplantation Board (LOL) meetings.
Evaluation will focus on:

- Overall survival after 3 years with the aim to reach ≥ 60%.
- Disease free survival
- 90-day morbidity and mortality after transplantation
- The incidence of recurrence and administered treatment.

Given the fact that the inclusion criteria are strict, we believe maximum 10 patients per year will be included for transplantation. If inclusion rates are much lower, we might need to adjust the inclusion criteria. After inclusion of 20 patients the results will be presented, and a decision should be taken whether or not to proceed with this protocol.

UPDATE:
Meeting May 2023 during ILTS:
Adjustment protocol necessary because of low accrual rate (version 6) and new insights based on international publications.
Major proposed adjustments May 24:

- Right sided tumors not a strict exclusion
- pN2 not a strict exclusion
- Maximum 70 years at time of diagnosis NRCLM
- Maximum diameter and number of lesions not a strict contra-indication
- Start with analysing metabolic tumor volume (MTV) and Tumor Lesional Glycolysis (TLG) on PET scan pre-tx. [45]

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