PROTOCOL

(Version 5.0, 28/05/2020)

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

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PROTOCOL TITLE

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Protocol ID	GE20-01
Short title	LTx in CRC Liver Metastases
Version	5.0
Date	28/05/2020
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This 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.

TABLE OF CONTENTS

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.

1.2. 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.

<u>Definition of irresectability:</u>

- 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).
- There is no opportunity to increase the volume with PVE or other measures, or these techniques have failed.
- Assessment of liver volume should be performed by CT scan, and may include mebrofenin scintigraphy.

2. PROTOCOL PROCEDURE

Prior to referral all imaging should be discussed in a local multi-disciplinary team (MDT) meeting attended by at least one medical oncologist, one radiologist, one hepatologist, one liver surgeon and one LTx surgeon (both in case the LTx surgeon does not perform liver resections). If no liver surgery or LTx is performed in primary center the case should be referred to a LTx unit if the patient meets the inclusion criteria for the protocol.

2.1 Inclusion/Exclusion criteria

Inclusion Criteria

- Age between 18 and 70 years
- Histologically verified adenocarcinoma in colon/rectum. Liver metastases, not amenable to liver resection or RFA when assessed at the institutional multidisciplinary tumor board
- No signs of extra hepatic metastatic disease or local recurrence according to PET/CT scan within 4 weeks prior to the MDT meeting at the transplant center
- No signs of extra hepatic metastatic disease on CT thorax/abdomen/pelvis within 4 weeks prior to the MDT meeting at the transplant unit
- 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
- Good performance status, ECOG 0 or 1
- Satisfactory blood tests Hb >6,0 mmol/l, neutrophils >1.0 x 10^9/l (incl. after any G-CSF), thrombocytes >75 x 10^9/l, Bilirubin<2 x upper normal level, ASAT and ALAT<5 x upper normal level, Creatinine <1.25 x upper normal level. Albumin above lower normal level
- Standard surgical procedure with adequate (R0) resection margins including circumferential resection margins (CRM) of at least ≥2mm for rectal cancer patients
- 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

- All patients should have received at least 8 weeks of chemotherapy without progressive disease according to RECIST-criteria
- At least 10% response (RECIST-criteria) on chemotherapy. Patients must be accepted for transplantation before progressive disease on chemotherapy
- Before start of chemotherapy, no lesion should be larger than 10 cm, if more than 30 lesions all should be less than 5 cm and the patients should have at least 30% response by RECIST-criteria
- Patients with less than 10% response on chemotherapy may be included if they obtain at least 20% response after TACE (DEB-IRI) or SIRT by 90Y-spheres (treatments considered experimental in the Netherlands)
- One year or more time span from the primary CRC diagnosis and date of being listed on the transplantation list
- **Oslo score 0-2**, each factor representing 1 point [33]
    - pre- transplant tumour maximal diameter >5.5 cm,
    - pre-transplant CEA >80 µg/L,
    - time interval from resection of the primary to transplantation <2 years
    - (progression of the metastases under neo-adjuvant chemotherapy, which is prerequisite as mentioned before, so this will score 0 points)

<u>Exclusion Criteria</u>

Patients will be excluded from the protocol if they meet any of the following criteria:

- Weight loss >10% during the last 6 months
- Previous diagnosed and treated extrahepatic metastatic disease
- Previous diagnosed other metastatic cancer (e.g. malignant melanoma, breast cancer)
- Patients who have not received standard pre-operative, per-operative or post-operative treatment for the primary CRC
- Right sighted primary CRC tumor
- Palliative resection of primary CRC tumor
- Molecular markers associated with poor outcome (BRAF pos [17,36]

- MSI high status, because these patients could profit from immunotherapy.
- Primary tumor pN2 status
- 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.

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. In the event of a graft failure, high-urgency application can be submitted. After the patient is listed repeat diagnostics is scheduled every 2 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 is continued from time of listing but bevacizumab (avastin) is stopped. The patient condition and blood tests need to be sufficient to undergo a liver transplantation at time of donor offer.

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 confirm the technical unresectability of metastases and to validate the indication of LTx in view of the oncological history of the patient preferably within one week if work-up is complete.

<u>Policy after inclusion:</u>

- Repeat CT chest/abdomen while on waiting list every 2 months. Chemotherapy is continued, but bevacizumab is stopped.

<u>Drop-out after inclusion:</u>

- Any sign of extrahepatic disease on imaging while patient is on the waiting list for transplantation

- If any exclusion criterium is met after inclusion

Drop out at time of transplantation:

- Exploratory laparotomy: extrahepatic tumor deposits are a contraindication for LTx.
- 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. 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. The transplantation can be performed according to local protocol, as long as tumor free margins can be achieved.

3.2 Postoperative Regimen

After surgery the patient is treated according to standard procedures by the institutional protocol. This means the patient Is transferred to the ICU, and transferred back to the surgical/medical ward when feasible.

3.3 Immunosuppression

The immunosuppression regimen consists of induction with basiliximab, tacrolimus the first 4 to 6 weeks (trough levels 4-6) , and then conversion to sirolimus (mTOR inhibitor). Target trough levels of sirolimus 5-10 ng/ml thereafter individually. Glucocorticoids and mycophenolate mofetil will be

administrated from week 1; steroids will be tapered to 0 during the first 3 to 6 months. Mycophenolate mofetil reduced to 2dd 500 mg after 6 months.

3.4 Standard anti-rejection therapy

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

3.5 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), chemotherapy, radiation therapy, and other available treatment options.

3.6 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 year (every month)	Visit 2nd year (every 3 months)	Visit 3rd-10th year (every 6 months)
Hb, Ht, leuco, plts CRP,Na, K, Creat	X	X	X
Bilirubin, ASAT, ALAT, ALP, Alb	X	X	X
INR, cholesterol, glucose, HbA1c	X	X	X
CEA,	every 3 months	X	X
Weight	X	X	X
BP	X	X	X
CT chest/abdomen/pelvis	every 3 months	every 3 months	every 12 months
Colonoscopy (only in pts without relapse)	At 12 months	National protocol	National protocol
PET scan (only in patients without lesions on CT scan)	At 12 months	At 24 months	On indication

4. EVALUATION

Despite the scarcity of donor livers, we advocate that patients with irresectable CLM can be candidate for LTx, who would otherwise be condemned to poor outcome. Therefore, we would like

to be strict in our inclusion criteria and evaluate the protocol annually during Dutch Transplantation Board (LOL) meetings, or if inclusion rates are low, following inclusion of 20 consecutive patients.

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.

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