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Liver transplantation for secondary liver tumors: the difficult balance between survival and recurrence

Pål-Dag Line$^{1,2,3}$, Svein Dueland$^2$

$^1$Department of Transplantation Medicine, $^2$Experimental Transplantation and Malignancy Research Group, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital and $^3$Institute of Clinical Medicine, University of Oslo, Oslo, Norway

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Corresponding author: Pål-Dag Line
Email: p.d.line@medisin.uio.no
Address: Department of Transplantation Medicine, Oslo University Hospital, Postboks 4950 Nydalen, 0424 Oslo, Norway

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Introduction
The concept of liver transplantation in patients with secondary malignant liver tumors was explored at different points of the liver transplant era but was hampered by inferior outcomes and high recurrence rates, and therefore abandoned [1,2]. Similar results were evident in transplantation for hepatocellular carcinoma (HCC) until robust clinical selection criteria was introduced [3]. Colorectal cancer (CRC) is the most prevalent metastatic cancer type in the liver [4]. Neuroendocrine tumors (NET) are relatively rare, slow growing cancers most often in the gastrointestinal tract or the respiratory system and the mode of presentation may be heterogeneous ranging from asymptomatic to the carcinoid syndrome. Liver metastases (MNET) is the most frequent metastatic manifestation in NET with a rate of about 50% [5]. The standard of care for liver metastases from colorectal cancer (CRLM) and MNET is usually liver resection, frequently preceded by neoadjuvant therapy, but is only possible in a smaller proportion of the patients. Palliative therapy aimed at slowing tumor progression is the main treatment option in the majority of cases. Liver transplantation could be an alternative in non-resectable metastases, but this is controversial. Patients with metastatic cancer have by definition disseminated malignant disease and increased risk of aggressive recurrence from dormant disease is conceivable. Chronic immunosuppression increases the incidence of de-novo malignancy and could theoretically increase the risk of relapse after transplantation. Furthermore, dismal prognosis has been reported in transplanted patients developing malignant disease compared to the general population [6]. Finally, the scarcity of liver grafts for transplantation urges caution in introducing new, controversial transplant indications.

Principles of patient selection
A prerequisite for transplant work-up is that the primary lesion has been radically resected according to standards of care. The selection process is essentially aimed at identifying patients with a favorable tumor biology, which is an ill-defined term linked to an array of clinicopathological features and molecular properties with high variability among patient groups and tumor types. A schematic overview on common principles for patient selection is presented in Figure 1.
1. Patients with CRLM

A: Pre-transplant imaging

The purpose of pre-transplant imaging is to exclude patients with signs of extra-hepatic manifestations as well as quantifying hepatic tumor load given as total number and size of the largest lesion. Maximal tumor size above 5.5 cm has been shown to be a negative prognostic factor. Computed tomography (CT), Magnetic resonance imaging (MRI) and positron emission tomography (PET) with the tracer $^{18}$F-FDG, is usually combined. The metabolic tumor volume (MTV) on pre-transplant PET-CT is an independent prognostic factor for survival after transplant [7,8]. MTV is calculated as the total enhancement volume in the lesions with an uptake exceeding 40% of standardized uptake volume. Some tumors are PET negative and regardless of negative pre-operative imaging, a systematic lymph node sampling for frozen section is mandatory at the outset of the transplant procedure. A proportion of patients with node positive disease in CRLM will only be identifiable in this manner [9].

B: Histological grading and molecular parameters

The level of carcinoembryonic antigen (CEA) is closely related to disease activity and aggressiveness of disease, and pre-transplant CEA levels above 80 µg/L is a negative prognostic factor [10]. Undifferentiated adenocarcinomas/signet ring cell carcinomas and BRAF mutation is linked to inferior survival after liver transplantation [11]. KRAS mutation has so far not been proven to be a significant negative predictive factor like in liver resection, but this might be due to lack of statistical power linked to small sample size. Nevertheless, KRAS mutation, alone is not a reason to exclude patients. Patients with N0 status of the primary tumor resection seems to have better survival than patients with N2 primary, but node status is not an independent prognostic factor.

C: Tumor location

Right sided primary tumors are generally associated with worse prognosis due to a higher frequency of aggressive histological phenotypes and BRAF mutation [12], and seem to represent an independent risk factor for recurrence and short overall survival in liver transplantation for CRLM [11].
D: Response to treatment and observation time

Failure to respond to tumor directed therapy usually signals an aggressive tumor biology or advanced stage of disease. A mandatory observation time with sustained treatment response is therefore essential to rule out further extra-hepatic metastases. Time from resection of the primary tumor to transplant > 2 years has been shown to be a prognostic factor in liver transplantation for CRLM [10,13].

2. Patients with MNET

A: Pre-transplant imaging

Patients with total hepatic tumor involvement exceeding 50% on CT or MRI have inferior post-transplant survival in MNET [5]. Octreotide or $^{68}$Ga/$^{64}$Cu-DOTATATE-PET for MNET examination is important to exclude extra-hepatic manifestations. If extrahepatic foci are detected, these should be dealt with separately, before transplant consideration, since concomitant extra-hepatic tumor resection and liver transplantation is clearly associated with poor outcome [14].

B: Histological grading and molecular parameters

Tumors should be classified as low grade (G1-G2) to warrant consideration for transplantation. Poorly differentiated (G3) and undifferentiated tumors (G4) have a high rate of synchronous metastatic disease and are associated with high risk of recurrence and poor survival. The cellular proliferation marker Ki67 should be lower than 10% [15].

C: Tumor location

The liver is the first microvascular bed exposed to circulating malignant cells from the portal system. Non-gastrointestinal NET cancers are a relative contraindication for transplant since they might have a higher propensity for extra-hepatic metastatic sites and risk of systemic recurrence. Pancreatic NET display a lower overall survival compared to gastro-enteric NET, possibly due to higher Ki67 indices and higher surgical morbidity and mortality following surgery for the primary [15]. Liver transplantation in patients with non-identifiable primary is controversial, although relatively good outcomes have been reported in a small cohort [16].
D: Response to treatment and observation time

Treatment response is also an important selection criterion in MNET. Patients will usually receive somatostatin analogs as first line therapy. Locoregional therapy with trans arterial chemoembolization or trans arterial radioembolization are other options particularly to gain symptom control. In somatostatin receptor positive progressive disease, Peptide Receptor Radionuclide Therapy may be used with either Y90 or Lu122 labelled somatostatin analogs. Patients considered for transplantation should display response or stable disease for at least 6 months after removal of the primary before being listed for transplantation.

Transplant criteria, survival and recurrence

There are no universally established transplant criteria for either MNET or CRLM. In general, 5-year OS of about 75% is required for liver transplantation to be considered as standard of care. Liver re-transplantation often yields survival figures well below this benchmark but is still generally offered [17]. From an ethical viewpoint one might argue that patients with similar expected overall survival should have the same access, regardless of primary diagnosis. With stringent selection criteria, it is possible to identify CRLM patients with high probability of obtaining a 5-year overall survival of 75% or more [5,8]. The benefit of transplantation bearing in mind the alternative treatment options is another relevant aspect to consider. The 5-year overall survival in CRLM patients starting first line chemotherapy is about 10% [18].

Patients with CRLM

There are essentially only two controlled prospective studies, both from Oslo University Hospital, on liver transplantation for non-resectable CRLM. More trials are, however, ongoing in Europe and Canada, both with deceased and living donors (Transmet NCT02597348, Colt NCT03803436, LiverT(w)oHeal NCT03488953 and Toronto Living Donor study NCT02864485). At present, no data are available.
In the pilot SECA-I trial, with a heterogeneous study population and wide inclusion criteria, the estimated survival at 5 years was 60% [10]. The sequel SECA-II study had more stringent criteria and the estimated 5-year survival in this cohort was 83% [19].

The overall survival will be dependent by the transplant criteria used. The Oslo Score summarizes 4 negative predictive factors for overall survival after liver transplantation for CRLM where each factor is assigned 1 point; maximal diameter of the largest lesion >5.5cm, pre-transplant CEA level >80 µg/L, progressive disease on chemotherapy and interval from diagnosis to transplant < 2 years [10]. The Fong Clinical Risk Score (FCRS) was developed to predict overall survival after liver resection for CRLM by assigning 1 point to each of the following factors [20]: node positive primary, interval from primary to diagnosis of CRLM < 12 months, > 1 liver metastasis, preoperative CEA level > 200 ng/ml, size of the largest lesion > 5.0 cm. Patients with F CRS of 0 had 60% 5-year overall survival from time of liver resection compared to just 14% in patients with F CRS of 5.

Pre transplant Oslo Score 0-2, a MTV value below 70 cm³ and a F CRS of 0-2 yield overall 5-year survival rates of 70%, 78% and 100% respectively [8]. All these three selection criteria are intercorrelated, meaning that most patients with low MTV have a low Oslo score and all patients with F CRS of 0-2 had low MTV, thus a staged approach to patient selection can be used based on these criteria, like given in Table 1. The caveat with strict criteria is, however, that some patients with substantial benefit from transplantation will inevitably be excluded.

Since patients with CRLM as a rule of thumb have normal liver function and no portal hypertension, their demands towards optimal graft quality is lower than the typical chronic liver failure patient. Hence, the donor pool could be expanded through increased utilization of extended criteria donor grafts [21] and utilization of split livers. The RAPID concept is a novel technique of two stage hepatectomy and split liver transplant. During the first stage, liver resection is done to provide space for an auxiliary segment 2+3 graft. After completion of the partial transplant, portal flow is diverted from the native remnant to the graft under guidance of portal venous pressure to facilitate fast liver regeneration [22]. Graft volume is monitored weekly, and a second stage hepatectomy is performed when the graft size is about 35-40% of standard liver volume. A segment 2+3 graft can be a surplus deceased donor graft as long as no pediatric recipient is available or it can be harvested from living donors, with less donor risk than left or right lobe donation [23].
The efficacy of any cancer treatment may be assessed by disease free survival (DFS) or time to progression (TTP) given that there is a strong correlation between DFS and overall survival. If, however, this is not the case, a more nuanced view on recurrence with focus on the actual impact of recurrent disease is needed to assess the efficacy of liver transplantation as treatment.

In the SECA-I trial, almost all patients had recurrence within 2 years, whereas in the SECA II trial, 35% were without recurrence after 3 years [19]. Similar outcomes have been reported in retrospectively collected clinical case series [13]. Importantly about 70% of all recurrences after liver transplantation for CRLM are small and slow growing lung metastases [24], and about 60% of the lung metastases can be resected with curative intent [19]. Consequently 76% of the patients in SECA II had no evidence of disease at three years, and 4-year survival after recurrence was 73% [19]. Multi-site recurrence occurs in a minority, and liver recurrence is rare with a rate of about 5% [25].

This pattern is distinctly different to that seen after liver resection for CRLM with about 70% relapse within 3 years, and about 30-50% of these patients display new liver lesions. By retrospective examination of chest CT scans in transplanted patients, about 40% of these lesions were most likely present at the time of transplantation [24]. Thus, one might speculate what proportion of the lung metastases are true recurrences and how many represent staging failures. Unfortunately, there is a lack of sensitive and specific methods to detect and reliably diagnose small lung metastases from CRLM. Interestingly lung metastases in transplanted CRLM patients display similar growth rate as in patients that are not immunosuppressed [26]. Small pulmonary lesions after transplant can be observed without specific treatment until the diameter is about 10-15 mm and then resected. The diversity in impact of recurrence can be illustrated if comparing transplant for HCC with CRLM. In HCC, the consequence of recurrence for long term survival is detrimental, whereas the effect on survival is much more moderate in well selected CRLM patients [27].

Patients with MNET

The available literature on liver transplantation for NET tumors is heterogeneous. The best reported outcomes in the literature are from the Milan group, with 5 and 10-year overall
survival rates of 97 and 89% respectively demonstrating a compelling transplant benefit versus non-transplant treatment [5].

A recent meta-analysis of MNET studies including heterogenous patient populations and large variations in inclusion criteria found recurrence rates ranging from 31-57%, with corresponding 5-years survival rate of 63% [28]. The recurrence rate when following the stringent Milan criteria was only 13%, which is comparable to liver transplantation for HCC within established transplant criteria. New recurrences beyond 5 years of observation was not registered [5]. NET tumors do, however, often display an indolent, slow growing nature. Therefore, it is advisable to follow up patients transplanted for MNET regularly over long time with respect to recurrence of disease. The Milan criteria for liver transplantation of MNET are listed in Table 2.

Transplant program considerations
The scarcity of liver grafts forces most centers to consider a separate waitlist with extended criteria donor grafts for patients with secondary liver tumors, and some few centers offer living donor liver transplantation also on this indication. It is advisable to only consider patients with expected 5-year overall survival of 70-75%. Based on the Norwegian experience in CRLM, this would add only about 1-2% to the annual liver transplant volume [8].

To coordinate pre-transplant treatment, ensure correct staging and maintain close follow-up schedules, a multi-disciplinary transplant oncology board with dedicated oncologists and radiologists is essential. The work-up of patients with secondary liver tumors and the associated costs are otherwise relative similar to HCC patients. Importantly, we have shown that liver transplant is cost-effective compared to modern oncological treatment in low risk CRLM patients [29]. However, we acknowledge that implementation of liver transplantation for secondary tumors is challenging for most programs, particularly in the present Covid-19 pandemic situation.

Summary
Assessing the balance between survival and recurrence after transplantation for secondary liver tumors should be done specific to the type of cancer in question. For MNET, high
recurrence rates are clearly related to reduced long-term survival. In CRLM, the experience so far indicate that pulmonary recurrence alone has a modest impact on survival outcomes. Further studies highlighting this group of patients will be important to bring this field of transplant oncology further. Implementation of liver transplantation for secondary liver tumors should be done with stringent transplant criteria and preferably in the context of prospective trials. Expansion of the donor pool by utilizing extended criteria donors and partial liver transplantation may be considered.
References


Legends to figures

Figure 1

Schematic overview over main steps in the selection process for liver transplantation in patients with colorectal liver metastases (CRLM) and liver metastases from neuroendocrine tumors (MNET). (MTV: Metabolic tumor volume on \textsuperscript{18}F-FDG PET-CT, RECIST: Response Criteria in Solid Tumors, CEA: Carcinoembryonic antigen)
Table 1: Transplant criteria for liver only colorectal liver metastasis with three staged levels of selectivity

<table>
<thead>
<tr>
<th>Level of selectivity</th>
<th>Criterion</th>
<th>Item</th>
<th>Value</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Oslo Score</td>
<td>Largest lesion diameter &gt; 5.5cm</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre transplant CEA level &gt; 80 µg/ml</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Progression on chemotherapy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time from resection of primary tumor to transplant &lt; 24 months</td>
<td>1</td>
<td>Oslo score ≤ 2</td>
</tr>
<tr>
<td>II</td>
<td>Metabolic Tumor volume (MTV)</td>
<td>Volume of all lesions &gt; 40% of SUVmax</td>
<td>&lt; 70 cm³</td>
<td>MTV &lt; 70 cm³ and Oslo score ≤ 2</td>
</tr>
<tr>
<td>III</td>
<td>Fong Clinical Risk Score (FCRS)</td>
<td>Node positive primary</td>
<td>1</td>
<td>FCRS score ≤ 2</td>
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<tr>
<td></td>
<td></td>
<td>Interval from diagnosis of primary to liver metastasis &lt; 12 months</td>
<td>1</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>&gt; 1 liver metastasis</td>
<td>1</td>
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<td></td>
<td></td>
<td>Pre resection CEA level &gt; 200 µg/ml</td>
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<tr>
<td></td>
<td></td>
<td>Maximal lesion diameter &gt; 5.0 cm</td>
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</table>

(CEA: Carcinoembryonic antigen, SUVmax: maximal standardized uptake value on ¹⁸F-FDG PET scan)
Table 2

Milan selection criteria for liver transplantation of patients with non-resectable liver metastases from neuroendocrine tumours [5]

- Low grade NET (G1-G2) confirmed on histology
- Primary tumor drained by portal system
- Primary tumor and all deposits radically removed in a separate operation before consideration for transplant
- Metastatic liver involvement < 50% of liver volume
- Stable disease or response to treatment for at least 6 months prior to listing
- Age < 60 years (relative criteria)
CRLM vs MNET

**Primary Location**
- Right sided

**Histology**
- Undifferentiated
- Signet ring cell carcinoma

**Imaging**
- Extrahepatic disease
- Size of largest lesion > 5.5 cm
- Metabolic tumor Volume > 70cm³

**Markers**
- BRAF +
- Pre transplant CEA > 80 µg/L

**Response to treatment**
- Progressive disease
- Treatment response < 10% (RECIST)

**Observation time**
- Less than 24 months from diagnosis to transplant

**Transplant candidate**
- Ki67 > 10%

**MNET**
- No portal venous drainage of primary
- Poor differentiation (grade 3)
- Undifferentiated (grade 4)
- Extrahepatic disease
- Hepatic tumor involvement > 50%

**Progressive disease**
- Progressive disease: negative predictive factor which may be modifiable by treatment

**Transplant candidate**
- Less than 12 months from removal of primary to transplant

**Notes:**
- Blue arrows: negative predictive factor which may be modifiable by treatment
- Red arrows: not recommended