Expert Opinion

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Liver transplantation for secondary liver tumours: The difficult balance between survival and recurrence

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Summary

Assessing the balance between survival and recurrence after transplantation for secondary liver tumours should be based on the type of cancer in question. For neuroendocrine liver metastases, high recurrence rates are clearly related to reduced long-term survival. For colorectal liver metastases, experience to date indicates that pulmonary recurrence alone has a modest impact on survival outcomes. Further studies focusing on this group of patients will be important for the development of this field of transplant oncology. Liver transplantation for secondary liver tumours should be implemented in accordance with stringent transplant criteria and preferably in the context of prospective trials. Expansion of the donor pool by utilising extended criteria donors and partial liver transplantation could be considered for this indication.

Keywords: Colorectal cancer; Neuroendocrine cancer; Liver metastasis; Secondary liver tumours; Disease free survival; Liver transplantation; Overall survival; Recurrence; Transplant benefit.

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Introduction

The concept of liver transplantation for patients with secondary malignant liver tumours was explored at different points in the liver transplant era but was hampered by inferior outcomes and high recurrence rates, and therefore abandoned.[1,2] Similar results were observed for hepatocellular carcinoma (HCC) until robust clinical selection criteria were introduced.[3]

Colorectal cancer is the most prevalent metastatic cancer type in the liver.[4] Neuroendocrine tumours (NETs) are relatively rare, slow growing cancers that most often arise in the gastrointestinal tract or the respiratory system; their mode of presentation is heterogeneous, ranging from asymptomatic to the carcinoid syndrome. NET liver metastases (NETLMs) are the most frequent metastatic manifestation of NETs, occurring in about 50% of cases.[5] The standard of care for colorectal cancer liver metastases (CRLMs) and NETLMs is usually liver resection, frequently preceded by neoadjuvant therapy, but this is only possible in a small proportion of patients. Palliative therapy aimed at slowing tumour progression is the main treatment option in most cases. Liver transplantation is an alternative for non-resectable metastases, but this is controversial. Patients with metastatic cancer have, by definition, disseminated malignant disease and are thus at increased risk of aggressive recurrence. Chronic immunosuppression increases the incidence of *de novo* malignancy and could theoretically increase the risk of relapse after transplantation. Furthermore, transplanted patients who develop malignant disease have a dismal prognosis compared to the general population.[6] Finally, because of the scarcity of available liver grafts, caution is warranted before introducing new 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 favourable tumour biology, which is an ill-defined term linked to an array of clinicopathological features and molecular properties with high variability among patient groups and tumour types. A schematic overview of common principles for patient selection is presented in Fig. 1.

Patients with CRLMs

Pre-transplant imaging

The purpose of pre-transplant imaging is to exclude patients with signs of extrahepatic manifestations and to quantify hepatic tumour load, given as total number and size of the largest lesion. Maximal tumour size above 5.5 cm has been shown to be a negative prognostic factor. CT, MRI and PET with the tracer ^{18}F-fluorodeoxyglucose (^{18}F-FDG) are usually combined. The metabolic tumour 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 standardised uptake volume. Some tumours are PET negative, so regardless of negative preoperative imaging, systematic lymph node sampling is mandatory at the outset of the

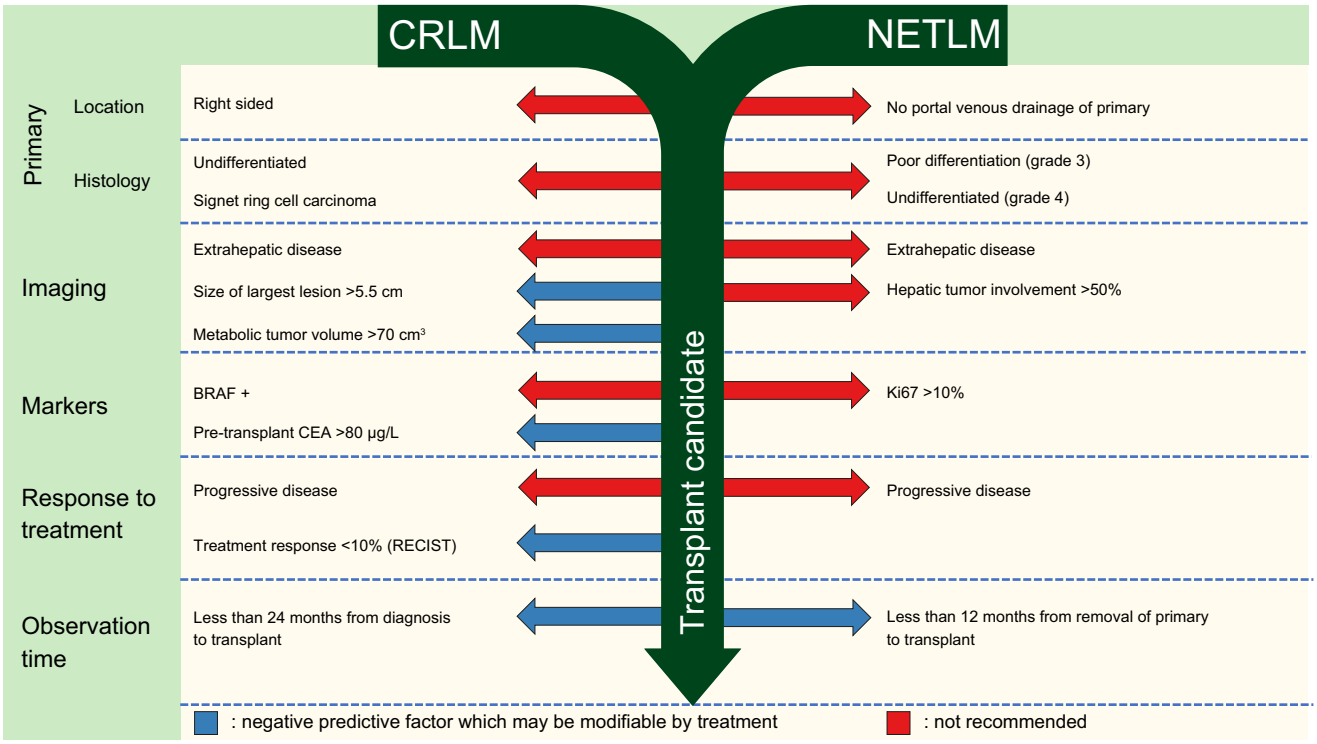

Fig. 1. Schematic overview over main steps in the selection process for liver transplantation in patients with CRLMs and NETLMs. CEA, carcinoembryonic antigen; CRLMs, colorectal cancer liver metastases; MTV, metabolic tumour volume on 18F-FDG PET-CT; NETLMs, neuroendocrine tumour liver metastases.

transplant procedure. A proportion of patients with CRLMs and node positive disease will only be identifiable in this manner.[9]

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 are a negative prognostic factor.[10] Undifferentiated adenocarcinomas/signet ring cell carcinomas and BRAF mutations are linked to inferior survival after liver transplantation.[11] To date, KRAS mutations have not been proven to be a significant negative predictive factor like in liver resection, but this might be due to a lack of statistical power linked to small sample sizes. Nevertheless, KRAS mutations alone are not a reason to exclude patients. Survival rates after resection seem to be better in patients with no lymph node involvement (N0 stage primary) than in patients with more extensive lymph node involvement (N2 stage primary), but node status is not an independent prognostic factor.

Tumour location

Right-sided primary tumours are generally associated with worse prognosis due to a higher frequency of aggressive histological phenotypes and BRAF mutations,[12] and seem to represent an independent risk factor for recurrence and short overall survival following liver transplantation for CRLM.[11]

Response to treatment and observation time

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

Patients with NETLMs

Pre-transplant imaging

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

Histological grading and molecular parameters

Tumours should be classified as low grade (G1-G2) to warrant consideration for transplantation. Poorly differentiated (G3) and undifferentiated tumours (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]

Tumour location

The liver is the first microvascular bed exposed to circulating malignant cells from the portal system. Non-gastrointestinal NETs are a relative contraindication for transplant because of the increased risk of extrahepatic metastatic sites and consequently systemic recurrence. Pancreatic NETs are associated with lower overall survival compared to gastro-enteric NETs, possibly due to higher Ki67 indices and greater 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]

Response to treatment and observation time

Treatment response is also an important selection criterion for metastatic NETs. Patients will usually receive somatostatin analogues as first-line therapy. Locoregional therapy with transarterial chemoembolisation or transarterial radioembolisation are other options, particularly for symptom control. In somatostatin receptor-positive progressive disease, peptide receptor radionuclide therapy may be used with either Y90- or Lu122-labelled somatostatin analogues. 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 NETLMs or CRLMs. In general, 5-year overall survival of about 75% is required for liver transplantation to be considered 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 patients with CRLMs who have a high probability of obtaining a 5-year overall survival of 75% or more.[5,8] The benefit of transplantation must also be weighed against alternative treatment options. Five-year overall survival in patients with CRLMs starting first-line chemotherapy is about 10%.[18]

Patients with CRLMs

There are essentially only 2 prospective controlled studies, both from Oslo University Hospital, on liver transplantation for non-resectable CRLMs. 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 depend on 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 >5.5 cm, 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 FCRS of 0 had a 5-year overall survival of 60% from time of liver resection compared to just 14% in patients with FCRS of 5.

Pre-transplant Oslo Score 0–2, an MTV value below 70 cm^3 and an FCRS of 0–2 yield 5-year overall survival rates of 70%, 78% and 100%, respectively.[8] All 3 of these selection criteria are intercorrelated, meaning that most patients with low MTV have a low Oslo score and all patients with FCRS of 0–2 had low MTV, thus, a staged approach to patient selection can be used based on these criteria, as demonstrated in Table 1. The caveat with strict criteria is, however, that some patients who would benefit substantially from transplantation will inevitably be excluded.

Since, as a rule of thumb, patients with CRLMs have normal liver function and no portal hypertension, they can probably tolerate a lower graft quality than the typical patient with chronic liver failure. Hence, the donor pool could be expanded through increased utilisation of extended criteria donor grafts[21] and utilisation of split livers. The RAPID concept is a novel technique of 2-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 taken as surplus from a deceased donor graft, as long as no paediatric 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 or time to

Table 1. Transplant criteria for liver only colorectal liver metastasis with 3 staged levels of selectivity.

Level of selectivity	Criterion	Item	Value	Interpretation
I	Oslo score	Largest lesion diameter >5.5 cm	1	
		Pre-transplant CEA level >80 μg/ml	1	
		Progression on chemotherapy	1	Oslo score ≤2
		Time from resection of primary tumour to transplant <24 months	1	
II	Metabolic tumour volume (MTV)	Volume of all lesions >40% of SUVmax	<70 cm^3	MTV <70 cm^3 and Oslo score ≤2
III	Fong Clinical Risk Score (FCRS)	Node positive primary	1	
		Interval from diagnosis of primary to liver metastasis <12 months	1	FCRS score ≤2
		>1 liver metastasis	1	
		Pre-resection CEA level >200 μg/ml	1	
		Maximal lesion diameter >5.0 cm	1	

CEA, carcinoembryonic antigen, SUVmax, maximal standardised uptake value on ^{18}F-FDG PET scan.

progression given that there is a strong correlation between disease-free survival and overall survival. If, however, this is not the case, a more nuanced view on recurrence with a 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 experienced 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 CRLMs 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 3 years, and 4-year survival after recurrence was 73%.[19] Multisite recurrence occurs in a minority, and liver recurrence is rare, occurring at a rate of about 5%.[25] This pattern is distinctly different to that seen after liver resection for CRLM: about 70% relapse within 3 years, with about 30–50% of these patients displaying new liver lesions. A retrospective examination of chest CT scans in transplanted patients reported that about 40% of these lesions were most likely present at the time of transplantation.[24] Thus, it is unclear 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 CRLMs. Interestingly, lung metastases in transplanted patients display similar growth rates as in patients that are not immunosuppressed.[26] After liver transplantation, small pulmonary lesions can be observed without specific treatment until the diameter is about 10–15 mm, at which point they should be resected. The clinical impact of recurrence is diverse. For example, in HCC, recurrence severely impairs long-term survival, whereas the effect on survival is much more moderate in well-selected patients with CRLMs.[27]

Patients with NETLMs

The available literature on liver transplantation for NETs 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 *vs.* non-transplant treatment.[5]

A recent meta-analysis of NETLM studies including heterogenous patient populations and large variations in inclusion criteria reported recurrence rates ranging from 31–57%, with corresponding 5-year survival rates 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 were not registered.[5] NETs do, however, often display an indolent, slow growing nature. Therefore, it is advisable to monitor patients transplanted for NETLMs regularly over a long period for evidence of disease recurrence. The Milan criteria for liver transplantation in patients with NETLMs are listed in Box 1.

Transplant programme considerations

The scarcity of liver grafts forces most centres to consider a separate waitlist with extended criteria donor grafts for patients with secondary liver tumours, and few centres offer living donor liver transplantation for this indication. It is advisable to only consider patients with a 70–75% chance of survival at 5 years. Based on the Norwegian experience in CRLM, this would only increase the annual liver transplant volume by 1–2%.[8]

To coordinate pre-transplant treatment, ensure correct staging and maintain close follow-up schedules, a multidisciplinary transplant oncology board with dedicated oncologists and radiologists is essential. The work-up of patients with secondary liver tumours and the associated costs are otherwise relatively similar to those in patients with HCC. Importantly, we have shown that liver transplant is cost-effective compared to modern oncological treatment in patients with low-risk CRLMs.[29] However, we acknowledge that

implementation of liver transplantation for secondary tumours is challenging for most programmes, particularly during the present COVID-19 pandemic.

Abbreviations

CEA, carcinoembryonic antigen; CRLM, colorectal cancer liver metastases; FCRS, Fong Clinical Risk Score; HCC, hepatocellular carcinoma; MTV, metabolic tumour volume; NET, neuroendocrine tumour; NETLM, NET liver metastases.

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Conflicts of interest

Dr. Line and Dr. Dueland declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Both authors contributed equally to conceptualization, drafting revision and approval of the manuscript.

Box 1. 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)

Data availability statement

All data presented are based on published, referenced studies.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.08.015.

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