Review

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Transplantation for metastatic liver disease

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Summary

The liver is a common site of metastases from many cancers, particularly those originating in the gastrointestinal tract. Liver transplantation is an uncommonly used but promising and at times controversial treatment option for neuroendocrine and colorectal liver metastases. Transplantation with meticulous patient selection has been associated with excellent long-term outcomes in individuals with neuroendocrine liver metastases, but questions remain regarding the role of transplantation in those who could also be eligible for hepatectomy, the role of neoadjuvant/adjuvant treatments in minimising recurrence, and the optimal timing of the procedure. A prospective pilot study of liver transplantation for unresectable colorectal liver metastases that reported a 5-year overall survival rate of 60% reinvigorated interest in this area following initially dismal outcomes. This has been followed by larger studies, and prospective trials are ongoing to quantify the potential benefits of liver transplantation over palliative chemotherapy. This review provides a critical summary of currently available knowledge on liver transplantation for neuroendocrine and colorectal liver metastases, and highlights avenues for further study to address gaps in the evidence base.

Introduction

Gastrointestinal malignancies commonly metastasise to the liver, and the presence of hepatic metastases exerts a strong, negative effect on prognosis.[1,2] Whilst systemic palliative therapies are often used in patients with liver metastases,[1] surgical treatment with curative intent is an option for some highly selected individuals.[3–7] Liver transplant(ation) (LT) is a radical approach to unresectable liver metastases in which an R0 procedure is conceptually implicit. However, initial outcomes were very poor and it was not until the 1990s, following the introduction of stringent selection criteria reflecting those introduced by the Milan group for hepatocellular carcinoma (HCC),[8] that acceptable survival was achieved with this approach for hepatic metastases.

Since then, evidence of increasingly higher quality has been emerging regarding the risks, benefits and suitability of LT as a therapeutic strategy in individuals with neuroendocrine tumours and colorectal carcinomas that have metastasised to the liver. The available evidence is at times controversial and hotly debated, and includes consideration of organ waiting lists and optimal selection criteria.

In this review, we summarise the available evidence regarding LT for neuroendocrine and colorectal liver metastases, with a focus on the potential for cure and outcomes *vs.* liver resection (where appropriate), and we discuss avenues for future research to mitigate current evidence gaps.

Neuroendocrine liver metastases

Neuroendocrine tumours (NETs), more recently reclassified as neuroendocrine neoplasms (NENs) are an uncommon but increasingly prevalent collective of tumours which may arise in multiple organs from cells comprising the ubiquitously distributed neuroendocrine system.[9] They most commonly arise in the gastrointestinal tract, pancreas and bronchopulmonary system. They present several clinical challenges, most notably their propensity to metastasise (particularly to the liver), and the management of systemic symptoms due to supraphysiological hormone secretion from 'functional' tumours.[10]

Epidemiological data have demonstrated a 6-fold increase in incidence since the 1990s,[9,11] and experience at specialist centres shows that up to 90% of patients with small bowel NETs display evidence of nodal spread at diagnosis,[12] with up to 91% of patients with small bowel NETs and 77% with pancreatic NETs developing hepatic metastases.[13] These may develop synchronously or metachronously. Although patients with neuroendocrine liver metastases (NELM) may display protracted survival relative to similarly staged patients with adenocarcinomas from the same organs, NELM are a significant, negative prognostic factor and frequently, multimodal treatment is mandated to attain disease control.[2]

Three morphological categories of NELM have been described, which have relevance to prognosis and treatment

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Keypoints

- LT is a challenging and controversial but potentially highly effective approach for the management of individuals with neuroendocrine or colorectal liver metastases.
- Over time, improvements in patient selection, alongside technical advances, have led to improved long-term outcomes.
- For neuroendocrine liver metastases, outstanding issues include selecting the best surgical approach for patients who are eligible for transplant or resection, as well as determining the optimal timing of the procedure and the role of neoadjuvant/adjuvant therapies.
- With respect to colorectal liver metastases, we await trial data that should help to clarify the impact of LT *vs.* palliative chemotherapy and hence guide selection criteria.

selection: type I refers to a single metastatic lesion of any size, type II refers to isolated metastatic bulk accompanied by smaller deposits usually in both lobes, type III refers to disseminated metastatic spread throughout the liver.[14] These categories, in conjunction with tumour grade, can influence treatment strategy. Grading is based on the Ki67 index or number of mitoses per 10 high-powered fields (HPF). NENs may be classified as neuroendocrine tumours or neuroendocrine carcinomas. Grade 1 NETs have a Ki67 of <3%, or <2 mitoses per 10 HPF. Grade 2 NETs have a Ki67 index of between 3% and 20%, or between 2 and 20 mitoses per 10 HPF. Grade 3 NENs have a Ki67 index of >20%, or >20 mitoses per 10 HPF, and can be sub-classified into G3 NETs and G3 neuroendocrine carcinoma – this is on the basis of their differentiation (well-differentiated or poorly differentiated, respectively).[15]

Treatment strategies for NELM

Recent developments in the management of metastatic NETs have been informed by randomised clinical trial evidence for several medical therapies, including somatostatin analogues,[16] peptide receptor radionuclide therapy[17] and kinase inhibitors, such as sunitinib[18] and everolimus.[19] However, whilst showing evidence for improving progression-free survival (PFS), these agents have not been shown to improve overall survival (OS). Percutaneous ablative techniques and angiographic liver-directed therapies such as trans-arterial embolisation/chemoembolisation and, more recently, selective internal radiotherapy have shown promise for temporary disease control in the liver.[20–22]

Only radical surgical approaches offer the potential for cure in the metastatic setting.[2] This may be through resection of the liver metastases alongside extirpation of locoregional disease (if oncologically and technically appropriate). However, even if R0 status is attained, recurrence rates are high, with a reported rate of recurrence of 29% (range 6-66%) by 5 years;[5] recurrence typically occurs within the liver. LT presents another surgical option and may be performed orthotopically (*i.e.* a liver-only allograft) or, more rarely, as a component of a multivisceral transplantation procedure.

LT for NELM – outcomes

Traditionally, indications for LT in NELM have fallen into three broad categories: symptom control for hormonal symptoms that are refractory to medical therapy, to ameliorate the effects of hepatic tumour bulk, or for oncological control with the aim of improving long-term survival. Initial outcomes were poor,[23,24] but technical improvements and refined selection criteria have led to improved survival.[25]

Given the rarity of NELM, and the low proportion of hepatic transplant activity that it accounts for, there have been no randomised-controlled trials comparing LT with other modalities. Evidence pertaining to LT for NELM is concentrated in retrospective case series, with one notable prospective cohort of patients selected according to the framework of the Milan NET criteria (see below).

A systematic review by Moris *et al.* identified 64 studies comprising 1,120 patients undergoing LT for NELM between 1974 and 2016.[4] The majority of studies included were single-centre, with four registry studies (from the European Liver Transplant Registry [ELTR] and the United Network for Organ Sharing [UNOS] database), and three multicentre studies. There were variations between studies in the reporting of demographic factors (such as age), primary tumour site, indication for LT, pre-transplant treatment history, immunosuppression strategy and – most importantly – selection criteria. Recurrence after LT ranged from 31.3% to 56.8% based on aggregated multicentre data.[4] Table 1 summarises key results from a selection of recent reports.

The largest study to date is the multicentric ELTR report comprising 213 patients (mean age 46 years, standard deviation 11.1) transplanted between 1982 and 2009.[26] Over 80% of patients had undergone prior resection of the primary tumour and/or liver deposits, and 76% had received prior hormone therapy or chemotherapy. LT was indicated for oncological control in 54%, to treat the effects of tumoural bulk in 24%, and to control hormonal excess/functional syndrome in 17%. Overall survival at 5 years was 52%, approximately 60% experienced disease recurrence, and 90-day post-operative mortality was 10%. This study also demonstrated improved outcomes over time, with 5-year OS rates of 46% and 59% for those transplanted before and after 2000, respectively.

The most recent report from the UNOS/Organ Procurement and Transplantation Network database comprised 206 patients undergoing 'isolated' LT for NELM, out of a total of over 160,000 transplants between 1988 and 2018.[27] This study reported a 5-year OS rate of 64.9%, a 10-year OS rate of 46.1%, and observed that time on the waiting list and patient age were associated with both risk of tumour recurrence and survival. In those whose disease recurred after LT, 74.3% had waited for under 6 months, whereas 25.7% had been on the waiting list for longer than 6 months. The authors used propensity score matching based on MELD score and sex to match patients with

Table 1. Summary characteristics and outcomes reported from selected, large series on liver transplantation for neuroendocrine liver metastases.

First author	Year of publication	Inclusion period	Country/ies	Study design	Transplanted patients (n)	Median age	Sex (M:F)	Median follow-up	1 yr OS	3 yr OS	5 yr OS	10 yr OS	1 yr DFS	3 yr DFS	5 yr DFS	10 yr DFS
Gedaly* [35]	2011	1988-2008	United States	Retrospective registry	150	Mean 45.1 years ±12.5	84:66	Mean 36.8 months	81%	65%	49%					
Nguyen* [63]	2011	1988-2011	United States	Retrospective registry	184	Mean 44.9 years (range 11-69)	100:84	NR	79.5%	61.4%	49.2%					
Le Treut[26]	2013	1982-2005	Multiple in Europe	Multicentre, retrospective case series	213	Mean 46 years ± 11. Median 48 years (range 16-71)	114:99	Mean 56 ± 49 months (range 0-283)	81%	65%	52%		65%	40%	30%	
Nobel* [64]	2016	2002-2014	United States	Retrospective registry	230	NR for overall cohort	129:101	NR	87%	69%	63%					
Sher[65]	2015	1988-2012	United States, Canada, Europe	Multicentre, retrospective case series	85	Median 48 years (range 16-75)	51:34	2.7 years (range 0.05 to 21.4)	83%	60%	52%					
Mazzaferro[29]	2016	1995 onwards	Italy	Single-centre, retrospective case series	42	Median 40.5 (range 13-62)	26:16	NR			97.2%	88.8%			86.9%	86.9%
Valvi[27]	2021	1988-2018	United States	Multicentre, retrospective case series	206	Mean 48.2 years (SD 11.7, range 19-75)	117:89	NR	89%	75.3%	65%	46.1%	74.9%	55.7%	43.9%	
Maspero[31]	2022	1984-2019	Italy	Single-centre, retrospective case series	48	44 (range 15-60)	30:18	158 months		98%	95.5%	93%		84%	75%	52%
Eshmuminov[32]	2022	1988-2021	International	Multicentre, retrospective case series	225	47 (range 380-55	120:105	93 months			73%				64.2%	
Post-OLT recurrence																
Sposito[36]	2021	2004-2018	Italy	Single-centre, retrospective case series	32 with recurrent disease after transplantation	At recurrence, median 55 (range 48.5-60.3)	16, 15	Median 73.7 months after recurrence			76.3%	45.5%				

DFS, disease-free survival; OS, overall survival.
*Centres reporting iterative updates using same database (United Network for Organ Sharing), therefore there will be substantial overlap in their included patients.

NELM to those undergoing transplantation for HCC and cholangiocarcinoma. The disease recurrence rate was 34% in the NELM group, compared to 8% for HCC and 19.6% for cholangiocarcinoma, but there were no significant differences in 5-year OS rates between these three matched groups: 75.4%, 79.9% and 70.4%, respectively. However, propensity score matching has limitations including a dependence on the matching model, an inability to avoid unmeasured confounding and relative inefficiency due to reduced sample sizes, which mandate cautious consideration of these results.[28]

The only prospective study with explicitly defined selection criteria that compares transplanted and non-transplanted groups was performed by Mazzaferro *et al.*[29] These 'Milan NET criteria' are: confirmed histology of grade 1 or 2 NET, primary tumour drained by hepatic portal system and removed (as well as extrahepatic deposits in a separate curative resection prior to consideration for orthotopic liver transplant(ation) [OLT]), <50% total liver involvement, at least 6 months of stable disease/disease response prior to consideration of OLT, and age <60 years (relative criterion).[30] Of 88 patients, 42 underwent OLT and 46 did not (22 refused or were non-compliant, 24 due to non-availability of transplant organs). The transplanted group were on average younger than the non-transplanted group (median ages 40.5 years *vs.* 55 years) and underwent more locoregional therapy (40.5% *vs.* 21.7%). On adjusting propensity scores for the likelihood of receiving a transplant (based on clinicopathological characteristics), the 5-year and 10-year OS rates were 97.2% and 88.8%, respectively, in transplanted patients, compared to 50.9% and 22.4%, respectively, in non-transplanted patients. Interestingly, the survival benefits of OLT appeared to increase over time, with an adjusted survival benefit at 5 years of follow-up of 6.82 months (95% CI 1.10–12.54), increasing to 38.43 months (95% CI 21.41–55.45) at 10 years of follow-up. Disease-free survival (DFS) at 10 years was 86.9% for transplanted patients.

A subsequent analysis by the Milan group retrospectively compared outcomes in individuals undergoing OLT (n = 48) to non-transplanted patients who specifically underwent liver resection (n = 56).[31] Individuals undergoing resection were older than the transplanted group at diagnosis (median 48 years *vs*. 44 years) but not at the time of liver surgery, had shorter time between primary tumour resection and liver surgery (median 6.5 months *vs.* 38.5 months), and 79% of them had <25% liver involvement. Patients undergoing resection had poorer long-term outcomes compared to transplanted patients: 5-year and 10-year OS rates of 90% and 75%, *vs*. 95.5% and 93%, respectively; 5-year and 10-year DFS rates of 33% and 18%, *vs*. 75% and 52%, respectively.

These single-centre results were extended by a recent international, multicentre (n = 15) analysis pooling data for 455 patients with NELM who underwent LT (n = 295) or liver resection (n = 230) between 1988 and 2021.[32] Selection criteria for OLT and their stringency varied between centres. Analysing transplanted and R0 resected patients matched 1:1 by propensity scores (based on age, tumour grade, Ki67 and largest tumour lesion size) showed that the 5-year PFS rate for resected patients was 14.2% compared to 64.2% for transplanted patients. In terms of OS, at 5 years, this was 68.3% for resected patients compared to 75% for transplanted patients. These benefits were not observed if considering patients undergoing transplantation outside the Milan criteria. Whilst the authors concluded that these results support a superior survival benefit of OLT over liver resection, it is notable that there were missing data for grade (*e.g*. in 27% of transplanted patients) without a clear explanation for how this was handled in the modelling, and the study did not account for extrahepatic disease, time between diagnosis and surgery, or prior treatments, which typically differ between patient groups, have relevance to both prognosis and surgical approach selection, and would ideally be accounted for. These factors, in conjunction with weighting or matching methods being unable to mitigate bias from unmeasured confounding,[28] mean that the superiority of transplantation over resection should be cautiously considered. Rightly, the authors caution against uniform use of OLT due to ethical considerations, and state that transplanted patients have significantly higher post-operative mortality than those undergoing resection.

Selecting patients with NELM for transplantation

The current evidence base is typified by non-uniform, centre-specific (often poorly reported or *ad hoc*) selection criteria. Given their clear, objective definition and well-documented prospective implementation, the results associated with use of the Milan NET criteria may be a useful benchmark by which treatment with curative intent for NELM should be adjudged, but this should be considered in the context of their stringency, meaning that some patients who could derive substantial benefit from LT may be excluded.

Other registry studies have retrospectively explored alternative prognostic factor-based scoring systems. In the ELTR report by Le Treut *et al.*[26] using data from 106 patients transplanted after 2000, a points-based score was developed based on: presence of hepatomegaly, age over 45 years, and concomitant additional resection. Significantly divergent OS curves were observed between two score-defined groups: patients with 0-1 factors *vs.* 2-3 factors exhibited a 5-year OS rate of 79% *vs.* 38%, respectively, and 5-year DFS rate of 38% and 19%, respectively. However, whilst this prognostic score is attractive in its simplicity and apparent ability to stratify, it presents several methodological issues such as dichotomisation of continuous predictors, univariate screening of predictors and limited assessment of performance (*i.e.* crude separation of survival curves rather than an assessment of discrimination, calibration and clinical utility[33]). Indeed, dichotomisation of age may produce step artefacts and lead to situations where two patients with otherwise identical clinicopathological characteristics but a 1-year difference in age may have vastly different 'eligibility' and expected outcomes.

Other potential selection factors that have been explored in several studies are age and time from diagnosis to transplantation.[29,34] For example, Valvi *et al.*[27] showed that patients aged 45 years and under have significantly improved survival than older patients, but again, simplistic cut-offs ignore potential non-linearities and may lead to fringe effects that are over-restrictive. Whilst it is not advisable to use LT as an *ultima ratio* approach after several lines of failed treatment for metastatic NEN,[10,34] evidence from registries in the US suggests that outcomes may be superior in patients who spend longer on transplant waiting lists.[27,35] The causal relevance of this is not fully clear but could reflect a longer period of successful disease control, and/or tumour indolence.

Post-transplant recurrence

In a case series by Sposito *et al.*, comprising 32 patients with recurrence after transplantation according to Milan NET criteria,[36] recurrence most commonly occurred at a single site (81.2% of cases), particularly in the distant lymph nodes (40.6%) or locoregional lymph nodes (18.8%), but it also manifested as peritoneal or pulmonary lesions. The inadequacy of chromogranin A for post-transplant surveillance was suggested, as only 12 patients (37.5%) had elevated levels at the time recurrence was ascertained. Fourteen patients (43.8%) underwent treatment with radical intent, with 13/14 having no evidence of disease on follow-up radiology at 3 months. Other individuals who were not candidates for aggressive treatment due to non-resectability received chemotherapy, peptide receptor radionuclide therapy or somatostatin analogues. Within a median follow-up from recurrence of 73.7 months, 5- and 10-year post-recurrence OS rates were estimated to be 76.3% and 45.5%, respectively, suggesting that even in cases of post-LT recurrence, favourable long-term outcomes are attainable with further therapy.

Patients undergoing LT for NELM exhibit different recurrence patterns to those undergoing liver resection. In the Milan group analysis by Maspero *et al.*, of those that developed recurrent disease, transplanted patients experienced more multisite recurrences (48% *vs*. 12%), were less likely to recur in the liver (8% *vs*. 88%), and had longer median time-to-recurrence (6.5 years *vs*. 2 years) than those undergoing liver resection.[31] Post-recurrence survival was not statistically significantly different between the two groups, with 3-year and 5-year survival rates of 95% and 72% for transplantation, and 83% and 69% for liver resection, respectively.

Taken together, these observations could suggest that: post-resection recurrence is predominantly driven by residual micrometastases (likely undetected by current best available imaging) left *in situ*; post-transplant recurrence could be due to engraftment of tumour cells from undetected extrahepatic foci (early), or engraftment of low-level, less aggressive circulating tumour cells (late).

Median time from LT to recurrence for NELM is longer than that for HCC (median 18-20 months[37,38]), and also than that for colorectal liver metastases (median 10.2 months). Further, post-recurrence survival after LT for NELM is longer than that observed for HCC (median 10.6 months).[37,38] These findings underlie the importance of long-term follow-up and aggressive approaches to re-attaining disease control in cases where post-LT recurrence occurs in patients with NEN.

Multivisceral and living donor transplantation

Multivisceral transplantation in the setting of metastatic NET is less commonly performed. In their series of patients transplanted between 1997 and 2005, Olausson and colleagues included five patients with pancreatic NEN undergoing multivisceral transplantation with curative intent.[39] Within a mean observation time of 22.4 months, two of five died of transplantation-related issues, another died of recurrent disease 27 months after multivisceral transplantation, another was without evidence of disease at 12 months, and the final patient experienced disease recurrence 4 years after multivisceral transplantation.

As with other indications, living donor LT may be an option for NELM. Clearly in this scenario, risks to the donor need to be considered against the benefits to the recipient. Based on the available evidence, it is currently not possible to ascertain the comparative advantages of living donor LT over deceased donor LT for NELM.[34]

Future directions

LT can be associated with excellent outcomes in stringently selected patients with NELM. However, the risks of the procedure, the availability of donor organs, and the non-randomised nature of the available evidence call into question its optimal position within the surgical sphere of the NELM armamentarium.[40]

Patients with resectable (type I) NELM who are good surgical candidates are more likely to undergo liver resection with curative intent than LT. Identifying the best surgical approach in those patients who may be eligible for either LT or resection requires further study, ideally through randomised studies which, although historically unfeasible, could be supported by increasing centralisation of care within centres of excellence, and collaboration within international societies.[41] This should be supplemented by standardisation of follow-up strategies, consideration of aggressive approaches to manage recurrent disease,[36] identifying the optimal 'window' in which transplantation should occur,[34] and exploration of novel biomarkers which may be able to detect recurrence before it becomes apparent on radiology.[42,43] Advanced NEN may require multiple lines of therapy,[2] and NELM treated surgically appear to be no exception. Therefore, randomised studies should also consider implementation of neoadjuvant concepts and adjuvant therapies to reduce the risk of recurrence, such as peptide receptor radionuclide therapy. No active trials yet exist in this area.

Given the available evidence, the future direction of travel should be to consider how best to identify the right surgical option (and timing) for patients with NELM, and the appropriate neoadjuvant/adjuvant therapy for effective, long-term, disease control.

Colorectal liver metastases

Over 40% of individuals diagnosed with colorectal carcinoma develop liver metastases (CRLM) during the course of their disease.[44] Radical liver resection is the predominant treatment option for suitable patients, when technically feasible, and might confer benefits in terms of long-term OS.[7,45,46] Despite the possibility of parenchyma-sparing techniques, which have increased the proportion of patients for whom resection is feasible,[47,48] up to 50% of patients with CRLM have unresectable disease.[49–51] This is a major negative prognosticator, as the 5-year survival for patients with CRLM treated only with systemic (cytotoxic) therapy is under 20%.[52]

Post-liver resection recurrence typically occurs in the liver,[53,54] and despite the possibility (in some patients) for repeated resections to attain disease control, liver failure and death may occur due to subsequent progression. In this context, liver transplantation (LT) was initially proposed in the 1980s as a radical approach with curative intent for those with unresectable CRLM.

Results with LT for CRLM

Initial results with LT for CRLM were dismal, likely attributable to inadequate patient selection strategies, the low-effectiveness of

chemotherapy, and poorer immunosuppression; post-operative mortality was high, with 5-year post-transplant survival of 0-18%.[3,24,55]

As LT expertise has improved, alongside improvements in imaging and the efficacy of chemotherapy, the concept of LT for CRLM in a highly selected group of patients was revisited in the 2000s, and the preliminary results were promising.[66]

The SECA-I pilot study[56] reinvigorated interest in this approach. In this study, LTs were performed for unresectable CRLM (n = 23), the inclusion criteria were wide and the study population heterogeneous regarding extent of disease and previous lines of cancer treatment. With median follow-up of 27 months (range: 8-60 months), a 5-year OS of 60% after LT was reported. Cases of recurrence, primarily pulmonary, were universal but treated aggressively when possible. In a recently published long-term follow-up of the SECA-I study, actual 5- and 10-year OS rates were 43.5 and 26.5%, respectively.[57] A subgroup of five patients who were alive at 10 years post-LT had been without evidence of disease for a median of 86 months (31-133 months), with a median OS of 161 months (133-168 months). The Oslo score (Table 2; 0-4 points; based on largest lesion size, plasma carcinoembryonic antigen, time from primary surgery to LT of less than 2 years, progressive disease seen at the time of LT) were proposed based on the SECA-I study population. For patients with an Oslo score of 0 or 1, the 5- and 10 -year actual OS rates were 75% and 50% (n = 6), while all patients with Oslo scores of 3 or 4 had died by 86 months post-LT. The study demonstrated that LT for CRLM could confer long-term survival and potentially even cure with proper patient selection.

Since this study, the Norwegian group commenced SECA-II,[58] and there have been notable results from the RAPID study,[59] a study from the Compagnons Hépato-Biliaires group,[60] and preliminary data from trials of living donor LT in specialist centres in North America.[61] Table 3 summarises risk factors for poor prognosis after LT for CRLM.

Arguably, the best results with LT for CRLM were achieved in the prospective SECA-II trial.[58] This study increased the stringency of patient selection compared to its predecessor SECA-I and reported data for 15 patients. Inclusion criteria included: histologically confirmed colonic or rectal adenocarcinoma, no evidence of extrahepatic disease or local recurrence on PET/CT, no evidence of the same on CT or MRI (within 4 weeks before transplant faculty meeting), no signs of local recurrence as per colonoscopy/CT colonography within 12 months, ECOG performance status 0 or 1, routine biochemistry results within set limits (*e.g.* creatinine <1.25x the upper limit of normal), standard resection of primary tumour with adequate resection margins, undergone first-line treatment, no lesion larger than 10 cm prior to chemotherapy, at least 10% response as per RECIST on chemotherapy (at least 30% if more than 30 lesions, all <5 cm in size), at least 1 year of time elapsed since diagnosis of colorectal cancer and date of being listed for a transplant. Patients with a body mass index greater than 30 were excluded, as were those with >10% weight loss in the preceding 6 months, other malignancies, previous hepatic metastases or local relapse, or those who underwent palliative resection of the primary tumour. Candidates underwent risk stratification according to both the Fong clinical risk score and the Oslo score (Table 2). Median follow-up was 36 months (range 5 to 60 months), with 1-, 3-, and 5-year OS rates of 100%, 83% and 83%, respectively. Median DFS was 13.7 months, and DFS rates at 1-, 2, and 3-years were 53%, 44%, and 35%, respectively. Further, patients with a Fong score of 1 or 2 at the time of diagnosis had significantly longer DFS than patients with a score of 3 or 4 (median DFS not reached *vs.* 11.8 months, respectively). Seven of the fifteen patients had IIIa-IVa complications (as per Clavien-Dindo classification). Further follow-up of this study is required to provide more precise estimates of longer-term OS – in the context that 15 patients were studied over a median follow-up period of 36 months and only two were at risk by 5 years. While no confidence intervals were reported, they may be wide. Further, this study was not randomised, mandating careful

Table 3. Summary of factors associated with poor prognosis after liver transplantation for colorectal liver metastases.

Category	Factor associated with poorer outcomes after liver transplantation for colorectal liver metastases
Characteristics of the primary tumour	Primary tumour in right side of large intestine Lymph node positive primary tumour Time interval between primary resection to liver transplantation <2 years Signet ring cell carcinoma *BRAF* mutation
Characteristics of the liver metastases	Largest lesion >5 cm in size (Fong score) or 5.5 cm (Oslo score) More than one lesion Synchronous metastases Progression of metastases during chemotherapy Metabolic tumour volume >70 cm^3
Disease extent	Presence of extrahepatic disease
Molecular biomarkers	Carcinoembryonic antigen

Table 2. Description of the Oslo and Fong clinical risk scoring systems as used to select patients with colorectal liver metastases for liver transplantation.

Oslo score		Fong clinical risk score	
Criterion	**Score value**	**Criterion**	**Score value**
Largest lesion diameter >5.5 cm	1	Node positive primary	1
Pre-transplant CEA level >80 μg/ml	1	Interval from diagnosis of primary to liver metastasis <12 months	1
Progression on chemotherapy	1	>1 liver metastasis	1
Time from resection of primary tumour to transplant <24 months	1	Pre-resection CEA level >200 μg/ml	1
		Maximal lesion diameter >5.0 cm	1

For both, selection based on a score of 0 to 2 has been associated with 5-year survival outcomes comparable to other indications for liver transplantation.[67]
CEA, carcinoembryonic antigen.

Table 4. Summary of ongoing trials of liver transplantation for CRLM.

Trial	Country	Type of study	Population	Number of patients	Eligibility (oncological criteria)	Recruitment status	Experimental arm	Control group	Primary endpoint	Estimated results
TRANSMET (NCT02597348)	Europe	Multicentric phase III RCT	Definitively unresectable CRLM	80	• Primary tumour resection according to oncological principles • *BRAF* non-mutated • CRLM definitively unresectable according to multidisciplinary panel expert • ≤3 chemotherapy lines for metastatic disease • Stable disease (RECIST criteria) on chemotherapy >3 months • CEA level <80 μg/L or at least 50% decrease of maximal level • No extrahepatic disease confirmed by CT and PET/CT	Recruiting	LT and perioperative chemotherapy	Exclusive chemotherapy	Survival (5-year survival rate)	2024
SECA-II (NCT01479608)	Norway	Phase III RCT	Initially unresectable CRLM	25	• Six or more liver metastases technically resectable • Maximal size of CRLM <10 cm and total number < 20 • CEA <100 ng/ml at time of diagnosis • Standard surgical procedure with adequate resection • pN0 primary tumour as pN0 • No extra hepatic disease confirmed by CT and PET/CT • At least 3 cycles of chemotherapy (6 weeks of treatment) • At least 10% response according RECIST criteria • For metachronous CRLM more than 12 months interval	Recruiting	LT and perioperative chemotherapy	Surgical resection	Survival	2025
NCT02864485	Canada	Open label	Definitively unresectable CRLM	20	• Primary CRC tumour stage ≤T4a • *BRAF* non-mutated • Bilateral and non-resectable CRLM without major vascular invasion by LM • Time from primary CRC resection to transplant is ≥6 months • No extra hepatic disease • Preoperative systemic chemotherapy for ≥3 months • Stable disease on chemotherapy >3 months • CEA values are stable or decreasing at all timepoints	Recruiting	LDLT after systemic chemotherapy	—	Survival	2023

(*continued on next page*)

Table 4. (*continued*)

Trial	Country	Type of study	Population	Number of patients	Eligibility (oncological criteria)	Recruitment status	Experimental arm	Control group	Primary endpoint	Estimated results
RAPID (NCT02215889)	Norway	Phase I-II		20	• Unresectable liver metastases technically • Maximal size of CRLM <10 cm and total number <20 • CEA <100 ng/ml at time of diagnosis • Standard surgical procedure with adequate resection • pN0 primary tumour as pN0 • No extra hepatic disease confirmed by CT and PET/CT, except patients may have 1-3 resectable lung lesions all <15 mm • At least 8 weeks of chemotherapy	Recruiting	Liver resection and partial liver segment 2/3 transplantation followed by total hepatectomy	None	Completion rate, 2nd hepatectomy within 4 weeks	2019

CEA, carcinoembryonic antigen; CRLM, colorectal liver metastases; LDLT, living donor LT; LT, liver transplantation.

consideration of the extent to which the clinical outcomes observed reflects stringent selection compared to the intervention itself.

The study of Hernandez-Alejandro *et al.*[61] was the first to report data on a cohort of individuals who underwent living donor LT for unresectable CRLM. It comprised 10 patients (of 91 evaluated for possible transplantation at three centres in the US or Canada). Median follow-up was 1.5 years (range 0.4 to 2.9 years) and, based on the latest update, OS and recurrence-free survival were 100% and 62%, respectively.

Emerging techniques and ongoing trials of LT for CRLM

Other technically highly advanced approaches to LT for CRLM have been described. These include the 'RAPID' procedure[59] (which can be performed in a deceased donor or living donor transplantation framework, and comprises left hemihepatectomy followed by a left lateral liver graft and ligation of the right portal vein, followed by later right hemihepatectomy after enough time has elapsed for sufficient regeneration of the left-sided graft), and the RAVAS technique[62] (which involves a heterotopic transplant of a left lateral liver graft into the splenic fossa after splenectomy, followed by total hepatectomy of the native liver after sufficient regeneration of the graft). Results with these approaches are described in case reports and therefore further data is required to understand their potential ramifications for long-term outcomes.

Regarding ongoing trials (Table 4), TRANSMET (NCT02597348) is a multicentric, randomised trial comparing chemotherapy with LT against chemotherapy alone in individuals with unresectable, hepatic-only metastases. It has a primary endpoint of 5-year OS, secondary endpoints of DFS/PFS and quality of life, has enrolled 94 participants, and was finalised in July 2021 with provisional results expected by the end of 2023. COLT (NCT03803436) is a non-randomised, parallel study assessing outcomes with deceased donor LT – the primary endpoint is OS at 5 years, with secondary endpoints of PFS at the same time point. The estimated completion date is January 2024, and outcomes will be compared against results from the phase III TRIPLETE trial which assessed the effects of modified FOLFOXIRI + panitumumab *vs*. modified FOLFOX6 + panitumumab in RAS and BRAF wild-type metastatic colorectal cancer. Lastly, MELODIC (NCT04870879) is another prospective, non-randomised trial assessing outcomes of LT against a matched cohort of patients undergoing palliative chemotherapy. The primary endpoint is OS (at 3 and 5 years), with PFS as one of the secondary endpoints.

Collectively, in the next 2 to 3 years, results from these trials will significantly contribute to the evidence base regarding the role for LT in CRLM.

Discussion

LT is a challenging and controversial, but potentially highly effective, approach for the management of individuals with neuroendocrine or colorectal neoplasms that have metastasised to the liver. Over time, improvements in patient selection (both in terms of transparency and stringency) have manifested as improved long-term outcomes in these patients. This is in parallel with improved immunosuppression strategies.

Despite promising results with stringent selection in specialist centres, there is no randomised trial data that

quantifies the effects of LT or clearly demonstrates its optimal position in the treatment armamentarium. For NELM, major unresolved issues include identifying the best surgical approach in those patients that may be eligible for either LT or resection, and the roles of neoadjuvant/adjuvant therapies to reduce post-transplant recurrence. Inter-centre collaboration and specialist networks supported by international societies could play a role in supporting a randomised trial in this space. For CRLM, the outputs of a number of ongoing prospective trials over the next 2-3 years will undoubtedly help clarify the impact of LT *vs.* palliative chemotherapy, and the appropriateness of selection criteria.

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Abbreviations

CRLM, colorectal liver metastases; DFS, disease-free survival; ELTR, European Liver Transplant Registry; HCC, hepatocellular carcinoma; HPF, high-powered fields; LT, liver transplant(ation); NELM, neuroendocrine liver metastases; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; OLT, orthotopic liver transplant(ation); OS, overall survival; PFS, progression-free survival; UNOS, United Network for Organ Sharing.

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Conflict of interests

The authors declare no conflicts of interest that pertain to this work.

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Supplementary data

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