ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2018 May 28; 24(20): 2137-2210

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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Weekly Volume 24 Number 20 May 28, 2018

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World Journal of Gastroenterology
Volume 24 Number 20 May 28, 2018

ABOUT COVER

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORIAL OFFICE
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PUBLICATION DATE
May 28, 2018

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World Journal of Gastroenterology

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World J Gastroenterol 2018 May 28; 24(20): 2152-2162

DOI: 10.3748/wjg.v24.i20.2152

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Liver transplantation and multivisceral transplantation in the management of patients with advanced neuroendocrine tumours

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Author contributions: Both authors contributed equally to this work and approved the final version.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Manuscript source: Invited manuscript

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Received: April 3, 2018
Peer-review started: April 4, 2018
First decision: April 19, 2018
Revised: May 3, 2018
Accepted: May 18, 2018
Article in press: May 18, 2018
Published online: May 28, 2018

Abstract

Orthotopic liver transplantation (OLT) represents a generally accepted albeit somewhat controversially discussed therapeutic strategy in highly selected patients with non-resectable hepatic metastases from neuroendocrine tumours (NET). Whilst there are some exclusion criteria, these are not universally followed, and the optimal set of inclusion parameters for deeming patients eligible has not yet been elucidated. This is due to heterogeneity in the study populations, as well differing approaches employed and also divergences in selection criteria between centres. Recent data have suggested that OLT may represent the most efficacious approach in terms of overall and disease-free survival to the management of NET metastatic to the liver when conducted in accordance with the modified Milan criteria. Therefore, a consensus set of selection criteria requires definition to facilitate stringent and fair allocation of deceased-donor organs, as well as consideration for living-donor organs. In the context of classically non-resectable metastatic tumour bulk, multivisceral transplantation with or without the liver may also be indicated, yet experience is very limited. In this review, we discuss the diagnostic work-up of patients in whom the aforementioned transplantation approaches are being considered, critically analyse the published experience and also anticipate future developments in this field, including a discussion of immediate and longer-term research priorities.

Key words: Neuroendocrine; Transplantation; Metastases; Liver; Multivisceral

Core tip: Liver transplantation is a generally accepted option in selected patients with advanced neuroendocrine tumours metastatic to the liver. Outcomes may be favourable in exquisitely selected patients, yet the optimal selection criteria have not yet been elucidated. Multivisceral transplantation is valid but rarely utilised, for example, in cases of metastatic bulk threatening gut

vascular supply.

Clift AK, Frilling A. Liver transplantation and multivisceral transplantation in the management of patients with advanced neuroendocrine tumours. *World J Gastroenterol* 2018; 24(20): 2152-2162 Available from: URL: http://www.wjgnet.com/1007-9327/full/v24/i20/2152.htm DOI: http://dx.doi.org/10.3748/wjg.v24.i20.2152

INTRODUCTION

Representing an increasingly prevalent class of neoplasms, neuroendocrine tumours (NET) display protean clinical manifestations, and those arising from the lung, pancreas and bowel possess a particular proclivity for metastasis to the liver. Up to 90% of small bowel NET display evidence of at least nodal metastasis at initial diagnosis[1], and the incidences of liver metastases (LM) in small bowel and pancreatic NET treated at specialist centres range between 67%-91% and 28.3%-77%, respectively[2,3]. The liver is the sole location of distant oligo-metastatic disease in approximately half of all NET[4] and their presence has markedly detrimental impact on the long-term survival of NET patients, thus conferring great significance on the management of neuroendocrine liver metastases (NELM)[5-7].

Therapeutic strategies for NELM may incorporate surgical approaches, *i.e.,* resection with curative or palliative intention, peptide receptor radionuclide therapy, liver-directed trans-arterial or percutaneous treatments and medical therapies[8]. Hepatic surgery is the only approach offering potential cure, and resection of liver deposits if attainable has classically been held as the first-line modality conferring the best survival outcomes[8]. However, cure is rarely realised even with complete elimination of the hepatic tumour burden as patients almost invariably develop recurrent disease, and resection should be regarded in most to be a palliative endeavour. Under the premises of complete resection of the primary tumour and loco-regional lymph node metastases , the radical approach of total extirpation of the liver with unresectable NELM in the context of orthotopic liver transplantation (OLT) has re-gained attention as outcomes continue to improve. In fact, stringently selected patients undergoing OLT may actually attain the most favourable survival outcomes, based on recent data from Mazzaferro and his group following the modified Milan ('Milan NET') criteria[9]. However, there is great divergence in the selection criteria followed at different centres, and a recent systematic review of retrospective case series calculated a median overall survival at 1-, 3-, and 5-years of 89%, 69% and 63%, respectively[10].

Multivisceral transplantation (MVT) with or without the liver (*i.e.*, modified [M]MVT)[11] is a seldom utilised approach for highly selected patients with extensive metastatic burden, either in those with pancreatic head tumours and LM[12], or potentially some patients with no LM but extensive mesenteric lymph node metastases threatening vascular supply to the gut by encasement of mesenteric vessels[13,14]. Again, recent data suggest improving outcomes over time with such approaches involving intestinal allografts[15] and therefore these could be more widely utilised in the near future.

In this review, we provide an overview of the diagnostic work-up of patients with NELM being considered for transplantation, specifically the power of both functional and morphological imaging in patient selection. Thereafter, we provide a critical analysis of the reported outcomes from OLT and MVT/MMVT and conclude with discussion of future perspectives in this burgeoning field.

PRE-TRANSPLANT EVALUATION – PATIENT SELECTION

Liver transplantation may be offered to patients with metastases of low- or intermediate grade (G1/2) NET (Ki67 of < 20%[16]) confined to the liver without extra-hepatic metastases, unless these are themselves resectable[8]. Up to 80% of NELM display diffuse multifocal and bilobar spread, and are therefore not amenable for standard resections with curative attempt[17]. In patients with non-miliary metastases but nevertheless conventionally non-resectable hepatic disease, advanced surgical procedures such as ALPPS may be considered to offer chance of resection *via* a two-stage approach[18,19]. Accordingly, meticulous selection of patients with advanced NET for transplantation approaches relies on the use of high quality imaging strategies to accurately depict disease burden, with emphasis both on the distribution of disease within the liver, but especially also possible extra-hepatic deposits as these could render a patient ineligible for transplantation (Figure 1A-C). Morphological and functional imaging modalities have important roles in the evaluation of NET and their metastases.

As most NELM are hypervascular, computed tomography (CT) imaging must include hepatic arterial phases[20]. Furthermore, diffusion-weighted magnetic resonance imaging (DW-MRI) should be systematically performed in any evaluation of NELM as it possesses the highest specificity of all MRI phases, even in tumours < 1 cm in size[21].

Functional imaging with positron emission tomography (PET) using 68-gallium radiolabelled DOTA peptides combined with CT (*e.g.*, ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC PET/CT) represents the gold standard approach in G1/G2 NET as it may detect lesions that morphological imaging modalities cannot, as well as those not identified by somatostatin-receptor scintigraphy with ^{111}In-conjugated radiopharmaceuticals[21-23]. Imaging with ^{68}Ga-DOTA PET/CT detects NELM with a sensitivity between 82%-100%, a specificity of

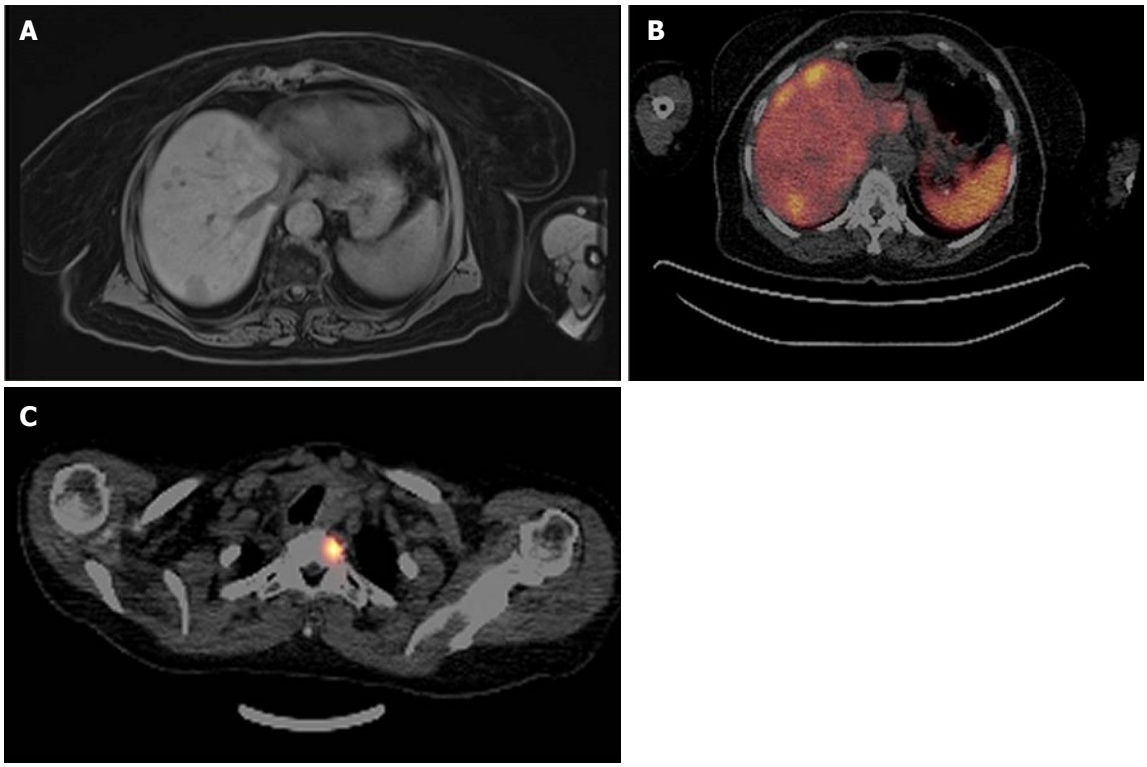

Figure 1 Multimodality imaging in a patient with neuroendocrine liver metastases considered for transplantation. A: Magnetic resonance imaging of the liver in a patient with hepatic metastases from a small bowel neuroendocrine tumour. This patient underwent resection of the primary tumour, and then a left hepatectomy. Following post-hepatectomy lanreotide, peptide receptor radiotherapy and also selective internal radiotherapy for recurrent hepatic metastases, this patient was considered for orthotopic liver transplantation. There was no extra-hepatic disease on conventional cross-sectional imaging. B: ^{68}Ga-DOTATATE PET/CT in the same patient. Multiple foci of increased avidity are demonstrated within the liver that were not appreciated on magnetic resonance imaging. C: Radiotracer uptake corresponding to one of multiple bone metastases. According to standard criteria, these would exclude this patient from orthotopic liver transplantation.

67%-100%, and also detects extra-hepatic disease with a sensitivity of 85%-100% and a specificity of 67%-90%[23]. In fact, a major proportion of the power of ^{68}Ga-DOTA PET/CT in terms of surgical selection is in its ability to identify extra-hepatic disease that is capable of altering clinical strategies[24,25], which is especially relevant when considering visceral transplantation.

Novel radiotracers for PET/CT, such as those using 64-copper have shown promising results comparable to ^{68}Ga-DOTA , although they are not in wide circulation as of yet[26]. The archetypal oncological radiotracer ^{18}F-FDG is widely used in the imaging of adenocarcinomas, and there is increasing evidence to support its implementation in the radiological work-up of NET patients alongside ^{68}Ga-DOTA PET to assess the metabolic activity of tumours which correlates with disease aggressiveness and prognosis[27]. However, one may argue that there is limited (if any) role of ^{18}F-FDG PET/CT in NET patients as part of pre-transplant work-up as lower-grade disease is the *sine qua non* for consideration of this approach. Additional radiotracers have also been assessed in cohorts of NET patients, especially in European centres, specifically ^{18}F-DOPA and ^{11}C-5-hydroxytryptophan[28,29]. However, experience with these tracers is limited, and can at present only be recommended as part of investigative studies, or as an adjunct to lessen radiological uncertainty when there are inconclusive findings with 'standard' functional imaging.

Alongside detailed radiological depiction of disease status, patient functional status and relevant co-morbidities must also be evaluated in the overall assessment of patients being considered for transplantation. Carcinoid heart disease (CHD) manifests as fibrous endocardial thickening involving cardiac valves and sub-valvular apparatus, particularly in the right heart. It has an incompletely elucidated aetiology but is presumed to be linked to excessive circulating vasoactive substances secreted by NET, and exerts considerable morbidity and mortality in NET patients. Transthoracic echocardiography is the gold-standard modality for assessment of cardiac function in patients suspected of having/at risk of CHD[30]. Furthermore, untreated CHD is an accepted contraindication for OLT, and should be treated before OLT, or even any hepatic surgery is planned[30].

Patients with advanced NET considered for transplantation require extensive evaluation. This includes assessment of their anaesthetic risk and co-morbidity profile, including specific emphasis on the presence (and if applicable, treatment of) carcinoid heart disease, which is a contraindication to transplantation. Radiological evaluation of disease should include CT (hepatic arterial phase), MRI (especially DW-MRI) and if available, ^{68}Ga-DOTA PET/CT. The latter is essential in

Table 1 Results from liver transplantation in selected registry reports, multicentre series and recent single centre series

Ref.	Year	Study type/setting	Total patients		Overall survival (%)						Disease-free survival (%)					
					1 yr	2 yr	3 yr	4 yr	5 yr	10 yr	1 yr	2 yr	3 yr	4 yr	5 yr	10 yr
Nobel *et al*[58]	2015	Registry (UNOS)	120		87		69		63							
Le Treut *et al*[38]	2013	Registry (ELTR)	213 (6 MVT)	*Overall*	81	73	65	55	52		65	49	40	33	30	
				ELTR score 0-1					79						57	
				ELTR score 2-3					38						19	
Nguyen *et al*[40]	2011	Registry (UNOS)	184	*Overall*	79.5		61.4		49.2							
				Post-MELD	84.7		65		57.8							
Gedaly *et al*[37]	2011	Registry (UNOS)	150 (13 MVT)		80		64		48		77[1]		50[1]		32[1]	
Sher *et al*[51]	2015	Multicentre series (United States)	85		83		60		52							
Mazzaferro *et al*[9]	2016	Single centre series (Italy)	42						97.2	88.8					86.9	86.9
Bonaccorsi-Riani *et al*[59]	2010	Single centre series (Belgium)	9		88		77		33		67		33		11	
Olausson *et al*[50]	2007	Single centre series (Sweden)	15 (5 MVT)						90				70		20	
Van Vilsteren *et al*[60]	2006	Single centre series (United States)	19		88						80					
Frilling *et al*[61]	2006	Single centre series (Germany)	15 (1 MVT)		78.3				67.2		69.4				48.3	

[1]Calculated from 83 patients. UNOS: United Network for Organ Sharing (United States); ELTR: European Liver Transplant Registry; MELD: Modified end-stage liver disease score; MVT: Multivisceral transplantation.

patients considered for liver transplantation as it enables the best opportunity for the depiction of extrahepatic disease which could invalidate this form of approach. As it represents the gold-standard imaging modality in NET, ^{68}Ga-DOTA PET/CT is also most useful in patients considered for intestinal/multivisceral transplantation.

ORTHOTOPIC LIVER TRANSPLANTATION

Curative (R0) resection of NELM may be associated with the most favourable survival outcomes in reported retrospective series however is subject to significant limitations[8,31-33]. First, approximately 80% of patients with NELM will not be eligible for this approach due to the anatomical distribution of hepatic disease burden abrogating the feasibility of radical surgical tumour elimination[17]. Second, to what extent R0 resection is actually associated with favourable outcomes cannot be confidently assessed given that studies are retrospective and thus outside the auspices of randomised trials, and that whilst patients are highly selected, the selection criteria themselves are often very poorly defined, if at all[34]. Essentially, the effects of favourable tumour biology and favourable patient characteristics, such as co-morbidity profiles are impossible to disentangle from the reported outcomes due to this selection bias. Third, even in patients undergoing hepatectomy/other hepatic resection with curative intent, vertiginous rates of recurrence are clearly recognised[8,33], to the extent that disease recurrence should not only be considered, but actively expected. The juxtaposition of favourable overall-survival against starkly poor disease/recurrence-free survival in hepatic resection is attributable to most likely the presence of undetected micro-metastases that given the relative indolence of NET, clinically manifest over a protracted period of time. Current gold-standard imaging modalities understage disease burden by 50% when compared with meticulous pathological examination[35], thus explaining the clinical reality that resection with curative intent is almost always a palliative endeavour, albeit an excellent one in terms of significant improvement in the duration of patient overall survival.

Therefore, OLT represents an attractive paradigm for radical therapy of NELM, insofar as total hepatectomy with subsequent transplantation theoretically offers complete resection of both macro- and micro-metastatic disease burden at a single time-point. This approach is heavily debated and rarely utilised (just over 700 patients)[36], and represents only 0.2%-0.3% of all liver transplants recorded in US/European liver transplant registries[37,38]. Table 1 summarises recent published experience from selected series.

There is growing evidence to support consideration of wider implementation of OLT in NET. However, major obstacles include the already heavy demands on deceased-donor livers for non-malignant conditions and also HCC, as well as the limited use of living-donor liver transplantation (LDLT) outside of Asia, where LDLT accounts for up to 60%-90% of all liver transplant activities in some countries[39]. The use of LDLT of course introduces complex ethical considerations, such as risks of morbidity and perhaps even mortality to the healthy donors.

Results with orthotopic liver transplantation

A recent comprehensive systematic review of Moris *et al*[10] identified 64 studies for inclusion, 4 of which represented registry reports (which were described narratively), and 57 were single-centre reports. Registry

reports did not uniformly document the primary tumour site in transplanted patients, but cumulative analysis of single-centre studies identified the pancreas as the primary tumour derivation in the majority of patients (53.4%) with the ileum the second most common (23%). However, only 3 studies described the histologic type of these primary tumours. The majority of patients presented with synchronous hepatic disease, and most received pre-transplant therapy with medical modalities (hormone-based or chemotherapy), resection of primary tumour or NELM resection. Only approximately 5.6% of patients did not undergo any pre-OLT treatment. Given the large number of heterogeneous studies, rates of concomitant primary tumour resection and OLT were not reported, nor were the comparative survivals between patients receiving pre-OLT treatment or not. Regarding immunosuppression therapy utilised, no large cohort studies discussed this. With regards to the long-term outcomes with OLT, 1-, 3-, and 5-year OS was 89%, 69% and 63%, respectively. Recurrence after LT ranged between 31.3-56.8%. There was no clear information regarding the radiological modalities used in pre-transplant assessment, nor in follow-up; therefore one could speculate that recurrence may in truth be higher if ^{68}Ga-DOTA PET/CT was not used during follow-up.

The review of the United Network for Organ Sharing (UNOS) database by Gedaly *et al.* reported 150 liver transplants performed for metastatic NET (of a total of 87280) between October 1988 and January 2008[37]. Thirteen of these patients received more than one organ (see later), and the overwhelming majority (91.3%) underwent LT using organs from deceased donors. The tumour histology/functional status was not uniformly reported, with 46.7% of cases documenting 'unspecified NET'. Gedaly and colleagues calculated 1-, 3-, and 5-year OS rates of 81%, 65% and 49%, respectively for patient undergoing OLT. Recurrence information was available for 83 patients, and 1-, 3-, and 5-year DFS rates were 77%, 50% and 32%, respectively. There was no significant difference observed in survival in patients older or younger than 55years, however there was a significant improvement in 5-year survival in patients undergoing transplantation after the 67day median wait-time versus those transplanted earlier (63% *vs* 36%). Lastly, an interesting comparison was drawn between OS of patients undergoing OLT for NET and HCC (n = 4693) which failed to identify any significant difference.

Another study from the UNOS database encompassing a wider time-frame (1988 to March 2011) and 184 patients with metastatic NET focussed on the effect of the introduction of the model for end-stage liver disease score/paediatric model for end-stage liver disease (MELD/PELD) scores in 2000 on OLT outcomes[40]. Overall survival rates for the entire NET cohort at 1-, 3-, and 5-years were 79.5%, 61.4% and 49.2%, respectively. In contrast to the aforementioned UNOS database study[37], these rates were significantly lower than those observed in patients with HCC, or those undergoing LT for non-malignant indications in the same time period (85.8%, 71.1% and 60.6%; 85.2%, 78.3% and 73%). Seventy-four OLT for NET occurred prior to MELD/PELD introduction, and these patients had significantly worse survival outcomes compared to those transplanted following MELD/PELD implementation. Pursuant to this, when only the LT for NET occurring after 2002 were considered, there were no significant differences between overall survival when compared to HCC (84.7% *vs* 88%; 65% *vs* 74.3%; and 57.8% *vs* 64.4%), although patients transplanted for non-malignant indications fared significantly better (87.1%, 79.5% and 73.7%).

The largest series yet reported is the analysis of the European Liver Transplant Registry by Le Treut *et al*[38]. Their retrospective analysis over a 27-year period identified 213 patients receiving LT for one of 3 classes of indication: hormonal syndrome/symptoms (17%), tumour bulk (24%), or 'oncological' (54%). The LM were synchronous in 119/213 cases, and the median interval between diagnosis of LM and LT was 25 months (1-149). Prior to LT, 83% of patients underwent surgical therapy targeting the primary tumour (n = 158) or LM (58); these included 23 cases of major hepatic resection (10.8%). In terms of non-surgical treatment, there were 161 instances of 'chemotherapy' (76%) including somatostatin analogues in 63 patients, and trans-arterial chemoembolisation in 76. The 3-mo post-operative mortality was 10%, with early re-transplantation, upper abdominal exenteration, splenectomy, operative duration > 10 h, R1/R2 resection margin, hepatomegaly and surgery in addition to LT identified as significant arbiters of this. Regarding survival, the median OS post-LT was 67months, with 1-, 3-, and 5-year overall survival rates of 81%, 65% and 52%, respectively. Disease-free survival rates at the same intervals were 65%, 40% and 30%, respectively. There were no associations between long-term survival and three age cut-offs, nor time between diagnosis and LT. However, poor prognosis generally was associated with major resection in addition to LT, poorer tumour differentiation and hepatomegaly. Furthermore, as the authors identified improved outcomes in those transplanted after 2000 (n = 106, 59% OS *vs* 46% prior to this), multivariate analyses were utilised to develop a 4-point prognostic scale in which the presence/absence of hepatomegaly, age > 45, or their undergoing major resection with LT were considered/'scored'. Patients with 0/1 of these factors demonstrated 5-year OS and DFS of 79% and 57%, respectively, whereas patients with 2/3 of these predictors had 5-year OS and DFS of 38% and 19%, respectively.

Clearly, these larger studies are limited by the heterogeneity of included patients. This has effects on the divergent adverse prognosticators identified[41]. Furthermore, the selection criteria utilised are usually very poorly documented. An exception to this is the

Table 2 Comparison of published selection criteria for liver transplantation in neuroendocrine liver metastases, and cirrhosis with hepatocellular carcinoma

Criteria and context	Parameters
Milan NET criteria[42]	Age < 60
Neuroendocrine liver metastases	G1/G2 tumour grade
	Primary tumour drained by the portal venous system
	Metastatic involvement limited to the liver
	Hepatic tumour burden not > 50%
	Six months of no tumour progression
Milan criteria[62]	Single tumour ⩽ 5 cm
HCC and cirrhosis	Or, ⩽ 3 tumours each ⩽ 3 cm in size
	No macrovascular invasion
UCSF criteria[63]	Single lesion ⩽ 6.5 cm
HCC and cirrhosis	Or, 2-3 lesions ⩽ 4.5 cm each, with total tumour diameter ⩽ 8 cm
	No macrovascular invasion
Navarro criteria[64]	Single lesion ⩽ 6 cm
HCC and cirrhosis	Or, 2-3 lesions ⩽ 5 cm each
	No macrovascular invasion
Valencia criteria[65]	1-3 lesions ⩽ 5 cm each, total tumour dimeter ⩽ 10 cm
HCC and cirrhosis	No macrovascular invasion
'Up-to-7' criteria[66]	Number of tumours + size of tumours (in cm) ⩽ 7
HCC	No microvascular invasion

HCC: Hepatocellular carcinoma; G: Grade.

recent data from Milan, which have detailed impressive outcomes from patient selection using their 'Milan NET' criteria[42]. Table 2 compares the Milan NET criteria for NELM and also documented transplantation criteria for HCC, including the original Milan criteria applicable only to HCC.

In their most recent report of a prospective series, Mazzaferro, *et al*[9]. reviewed 88 patients referred for consideration of OLT, of which 42 were offered transplant. Forty-six patients either had waiting-list conditions that precluded transplant consideration, or refused transplantation. In those undergoing OLT, the median OS was not attained, whilst 5-year and 10-year OS rates were 97.2% and 88.8%, respectively. Rates of disease progression in those receiving OLT were 13.1% at 5- and 10-years, *i.e.,* all recurrence/progression occurred within the first 5 years of follow-up. Contrastingly, 5-, and 10-year OS rates in those not undergoing OLT were 50.9% and 22.4%, respectively. Follow-up comprised CT or MRI every 3-4 mo, with Octreoscan, ^{68}Ga-DOTA PET/CT or ^{18}F-FDG PET/CT only used when morphological imaging/chromogranin assays were suspicious for recurrence. There was no clear documentation on how many patients underwent each of these tumour-targeted imaging modalities, nor what their specificities were for recurrent disease.

Although these survival outcomes certainly appear to be the most favourable encountered in the literature pertaining to therapy of NELM, these results must be considered with due diligence as by their nature, such studies possess important inherent bias, similar to those expressed by series of hepatic resection. Whilst tumour burden did not differ between the transplanted and non-transplanted groups, patients not undergoing transplant were significantly older than those that did (median 55.5 years *vs* 40.5 years), had higher T stages of the primary tumour (69.5% T3/4 *vs* 54.8% T3/T4), had higher WHO grade, and underwent less locoregional therapy including liver resection, transarterial chemoembolisation (TACE) or peptide receptor radionuclide therapy (PRRT) (73.9% of the non-transplant group received none *vs* 57.1% of the transplanted group). Lastly, the earlier discussed prognostic score as developed by Le Treut *et al*. was 0 or 1 in 52.4% and 35.7% of transplanted patients, respectively. Evidently, patients undergoing OLT are incredibly highly selected and thus the extent to which positive outcomes can be attributed to appropriate OLT 'itself' rather than favourable patient/tumour biology is unclear. It may be possible that a considerable proportion of transplanted patients would be candidates for hepatic resection. Nevertheless, at face value, these results with the Milan NET criteria appear favourable in the context of an 86.9% 10-year DFS.

Neoadjuvant and adjuvant therapy

There are no significant differences between post-transplant immunosuppression therapy for NELM and HCC. Consideration of neoadjuvant and adjuvant concepts should be incorporated into the multidisciplinary discussion of patients evaluated for possible transplantation. Recurrence rates post-OLT in general range between 31.3%-56.8%[10]. A consensus is yet to be established regarding such approaches, however one may speculate that pre-OLT PRRT, or the use of post-transplant somatostatin analogues could be useful given their anti-proliferative effects as documented in randomised clinical trials[43,44]. These methods could theoretically downstage/control disease prior to transplantation, or retard the development of recurrent

micro-metastases. An additional consideration could be the use of mammalian target of rapamycin (mTOR) inhibitors such as everolimus, which has documented anti-proliferative effects on NET in clinical trials[45] , and also serve immunosuppressive functions with the advantage of exerting no nephrotoxic effects[46,47]. Pre-transplant cytotoxic chemotherapy does not have an established role – indeed, NET in general exhibit a low response rate to such treatment, and the effects of cytotoxic agents appear limited to advanced pancreatic NET[8].

Recent data suggest that OLT is a promising therapeutic option in metastatic NET and may be associated with favourable long-term survival outcomes. It should be used when hepatic disease is controlled, after the resection of the primary tumour, and not as a 'last resort' intervention. In addition, concomitant major resection should be avoided if possible at the time of transplant. Carcinoid heart disease is an accepted contraindication. However, OLT patients present a highly selected cohort, especially those transplanted in accordance with the Milan NET stipulations. The optimal selection criteria require definition, and reports of OLT should adhere to a number of reporting standards (see discussion). The role of neoadjuvant and adjuvant concepts in liver transplantation for NELM needs to be defined to reduce disease recurrence. Outcomes from OLT were initially poor, but have considerably improved as a result of refined immunosuppression regimens, surgical technique and patient selection. In the modern era, outcomes with OLT for metastatic NET are not statistically dissimilar to those encountered in HCC.

INTESTINAL AND MULTIVISCERAL TRANSPLANTATION

Intestinal transplantation (IT) has gained acceptance as a standard therapeutic strategy in patients with intestinal failure failing rehabilitation, diffuse portal thrombosis or other intra-abdominal catastrophe, but has also been performed in patients with non-resectable, slow-growing tumours encasing the mesenteric root as this threatens the vascular supply to the gut[15,48,49]. Transplantation of the intestines may be within the context of simultaneous transplantation of the stomach, duodenum, pancreas and small bowel with (multivisceral transplantation, MVT) or without the liver (modified MVT, MMVT)[11]. Experience with this radical approach in neuroendocrine tumours is incredibly limited to either case reports or to small numbers within cohorts composed predominantly of patients undergoing OLT[13,37,38,50]. In this setting, patients either have pancreatic head tumours, and/or bulky metastatic load within the small bowel mesentery.

Less than 20% of all NET patients undergoing liver transplantation also receive additional organs – in the aforementioned systematic review of Moris *et al*[10] only 5.7% of transplants (16/279) outside the largest registry reports/multicentric series receive a multi-organ allograft. The multicentre series of Sher *et al*[51] included 17 patients (total 85, 20%) undergoing a multivisceral transplantation and reported overall survival rates at 1-, 3- and 5-years of 81%, 40% and 40%, respectively. These were lower than those undergoing OLT, however not significantly so. Thirteen of the 150 patients reported by Gedaly *et al*[37] (8.7%) received additional organs alongside the liver, however the survival data specifically for this sub-set of patients was not clearly detailed as the authors merely stated that on inclusion of MVT cases, the cohort OS data did not change significantly. Lastly, the published data from Nordic centres have described a 2-year overall survival of 67% in 6 patients with pancreatic head NET that underwent intestinal transplantation within a multivisceral graft, which was not inferior to the outcomes from those transplanted for intestinal failure[12].

Clearly, reports of IT/MVT/MMVT in NET are limited by: (1) The small numbers of patients transplanted; (2) the inconsistent quality of outcome reporting and selection criteria in publications; and (3) the inclusion of multiple indications in single publications (often including non-malignant indications).

Nevertheless, as outcomes continue to improve for IT/MVT/MMVT, one may anticipate a cautiously managed expansion of the number of patients with advanced NET being considered for and undergoing such procedures. As with OLT, emergent concepts will include the optimisation of patient selection criteria, as well as innovative neoadjuvant/adjuvant concepts to abrogate disease recurrence and monitor for allograft dysfunction. For example, recent case reports have detailed the use of everolimus post-MVT in 2 NET patients in attempts to suppress recurrence whilst avoiding the nephrotoxicity of calcineurin inhibitors[52], as well as the use of PRRT to stabilise disease prior to MMVT which also included simultaneous transplantation of a sentinel skin flap from the organ donor to aid monitoring of rejection and tailoring of immunosuppression regimens[13].

Intestinal/multivisceral/modified multivisceral transplantation has been utilised in a very small number of patients with advanced NET worldwide. Case series tend to be small yet highly heterogeneous in terms of patient inclusion, and outcome reporting is of varying quality. Nevertheless, innovative approaches continue to be described in the setting of such advanced surgical procedures.

CONCLUSION

For patients with well-controlled, G1/G2 neuroendocrine tumours, transplantation approaches may be valid therapeutic strategies in those with classically non-resectable metastases confined to the liver (OLT) and/or bulky mesenteric tumour load threatening the vascular supply to the gut (IT/MVT/MMVT). It is generally advised that the primary tumour and any attendant locoregional lymph node metastases be resected prior to undergoing OLT, and there is a suggestion that longer

wait times/observance period prior to transplant to monitor for disease stability, although this is not based on high-quality evidence[9,36]. It is debatable if small volume bone metastases are necessarily a contra-indication to transplantation given that they may be well-controlled with PRRT.

Patients are stringently selected in accordance with a mixture of criteria that are either well defined, or barely documented. As with the NET clinical arena in general, the majority of data available to inform modern clinical practice is derived from retrospective case series of varying quality in their reporting. Prospective studies and randomised clinical trials of surgical treatment for NET are logistically challenging given their relative rarity and relative indolence requiring prolonged follow-up, even before considering the difficulties in randomisation of surgical therapy. Transplantation approaches in NET are subject to the same difficulties. Decision making such as expanding the criteria/exceptions of transplant co-ordinating institutions to include NELM will rely on sound identification of patients most suitable for receiving donated organs which in turn can expect the best outcomes. This is mandated in the context of limited yet heavily demanded availability of deceased donor organs and also limited use of LDLT outside of Asia. Therefore, at least in the short-to-medium terms, such decision making must be based on analyses of the currently available data which is mostly of a retrospective nature. Collaborations such as registries and inter-institutional initiatives will enable statistical analysis of ever-larger pooled patient cohorts. Going forward, the non-mutually exclusive NET and surgical communities must recognise the shortcomings thus far experienced in data reporting in order to improve current and future data collection for use in novel informative projects.

In order to counteract the previously discussed deficiencies in data reporting and also facilitate inter-centre collaboration in the analysis of larger cohorts, we propose that each of the following be documented at an individual patient level within institutional databases, and be available to collaborators, notwithstanding ethical approval for the secure sharing of such data:

(1) Indication for transplantation and timing – time between diagnosis and transplantation, duration of disease stability prior to OLT/MVT.

There is a need to clearly distinguish at which point during the patient journey that the best outcomes may be attained. Patients undergoing OLT when disease is controlled with therapy are posited to derive true benefit with excellent survival. Whilst it is suspected that patients undergoing OLT/MVT as an ultima ratio approach will have poorer outcomes, *i.e.* marginal life gains, this needs to be categorically confirmed and also judiciously analysed as a possibly legitimate 'salvage' option.

Reports suggest that the observation of tumour behaviour for 6 months to ensure disease control is associated with preferable outcomes in OLT. This needs to be clearly documented in larger numbers. Such data also add to the temporal treatment trajectory of individual patients, which may be complex as transplant patients are often heavily 'pre-treated'. Clear comparisons will only be valid when results are interpreted in the context of the 'patient journey'.

(2) Clinicopathological characteristics – especially age at transplantation, Ki67 index, hepatic tumour burden (if applicable), clinical syndromes, grade and differentiation of primary tumour and metastases, disease stage (including other metastatic sites and treatment for these), surgical histopathology results (margin and lympho/vascular invasion) and patient co-morbidities.

Optimised selection criteria in the short-to-medium term will likely be developed by multivariable analyses of individual-level data accrued from disparate centres, and clinicopathological characteristics are often reliable arbiters of tumour behaviour and thus patient outcomes. Therefore, clear documentation of parameters that are potentially predictive/prognostic in nature is essential.

(3) Selection criteria – *e.g.* compliance with Milan NET criteria, or other institutional protocols; imaging modalities and patient-specific parameters for disease assessment.

As aforementioned, selection criteria for surgical intervention are typically very poorly documented, confounding the collation and interpretation of multi-centric data. Whilst the Milan-NET criteria are clearly followed in its respective centre, whether or not alternative protocols are used versus collective multidisciplinary decision making should be documented.

(4) Use of neoadjuvant/adjuvant concepts: Despite excellent results from one centre that does not appear to have utilised post-operative prophylaxis against disease recurrence, whether or not such strategies have been/should be employed in other centres has not been documented clearly. As previously discussed, medical therapies with anti-proliferative/anti-tumour effects could theoretically be useful in disease stabilisation prior to transplant, or to reduce the risks of post-transplant recurrence. This must be clearly delineated from pre-transplant treatment and treatment for post-transplant recurrence. The use of such concepts may be included in multivariable analyses to examine for associations between their utilisation and outcomes (or lack thereof/thereon).

Lastly, it is becoming increasingly clear that multifactorial assessment of neuroendocrine tumour characteristics have tangible benefits in not only prognostication[53], but also detection of recurrence[54,55] and prediction of response to treatment[56]. Novel markers developed from 'omics'-based technologies, such as the multi-analyte NETest are able to

predict outcomes from PRRT and also disease recurrence, and therefore possibly offer improved selection and impact follow-up decisions[56,57]. Precise molecular definition of patient-specific neuroendocrine tumour biology may also have ramifications on patient selection for surgery or transplantation, as well as monitoring for detection of recurrence possibly before lesions are detectable on imaging. Such techniques should also be investigated within the remit of transplantation for advanced NET.

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P- Reviewer: Akbulut S, Hilmi I, Sugawara Y, Tsoulfas G, Topaloglu S
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ISSN 1007-9327