Delivering Liver Transplantation for Grade 1 and 2 Well Differentiated Unresectable Liver Metastatic Neuroendocrine Tumours of Gastroenteric and Pancreatic Origin

Tahir Shah, Joanna Moore, Hema Venkataraman, Martyn Caplin, John Crookenden, Stacey Smith, Dermot O'Toole, Emir Hoti, Bobby Dasari, Samuel Ford, Vincenzo Mazzaferro, Paul Gibbs, Derek Mannas, John Isaac, Douglas Thorburn,

EXECUTIVE SUMMARY:

Following acceptance by the Liver Advisory Group of the Fixed Term Work Unit's [FTWU] advise in support of a pilot scheme to determine the benefits of liver transplantation for unresectable neuroendocrine tumour liver metastases [NET LM], we have now set up a national delivery framework. A National Board shall provide oversight and guidance on taking patients through the pathway.
Patients only meeting the Milan criteria are to be included initially, with expansion of criteria during second phase [Table 1A].

- ***The service evaluation will aim to transplant 50 patients with a NET diagnosis.***
- ***Method for timely allocation has been determined by the LAG committee.***
- ***Initial evaluation of safety and effectiveness shall be performed after 10 transplants [phase I], without a break in the programme.***
- ***National Advisory Board for NET Liver Transplantation has been created to manage the programme.***
- ***Patients are to follow the existing referral pathways to Transplant Centres.***
- ***Guidance on resection of primary and other areas of extra-hepatic disease is included***
- ***Guidance on safe removal of livers containing functional cancers may be provided in later versions of this document.***
- ***Immunosuppression will include mTORi.***
- ***Guidance on post-transplant follow-up is included [appendix III].***
- ***NHSBT to support a robust plan for prospective data collection.***
- ***Programme will be deemed successful if 1 year survival >60% (equating to a >50% 5 year survival) and if the observed outcomes are better than those predicted for this subset of patients with NET managed with standard treatments.***

The recommendations of liver transplantation for unresectable NET LM of gastro-enteric and pancreatic [GEP] origin are based on the accumulating evidence of transplant benefit in highly selected patients [table1, figure 3 and 4].

Liver transplantation in well selected patients with a G1/2 WD GEP NET diagnosis provides transplant benefit through:

- Prolongation of overall survival [Adjusted transplant-related survival benefit of 6.82 months and 38.43 months at 5 and 10 years, respectively; 88.8% 10-year overall survival and 13.1% disease progression compared to 22.4% and 89% respectively in the non-transplant group[1]]
- High recurrence-free survival rates.

- Additionally, survival even in the presence of recurrence is acceptably long and can likely be improved through increasing immunosuppression and cancer therapy options.

The improving outcomes with liver transplantation for NETs over the decades are due to development of strict selection criteria with a move away from ad-hoc and salvage transplantation.[2] Furthermore, a thoroughly planned and executed pathway culminating in liver transplantation, where all extra-hepatic disease is removed prior to listing for liver transplantation, also improves outcomes by minimising peri-operative mortality[1]

Best outcomes in liver transplantation for NET LM have been achieved using the Milan criteria [Table 1], where primary was of gastro-entero-pancreatic origin***, and*** all extra-hepatic disease was identified and removed prior to listing for liver transplantation.
The Milan criteria for liver transplantation for NET LM have been adopted by United Network for Organ Sharing [UNOS] and European Neuroendocrine Tumour Society [ENETS] but are not being routinely applied to patients who would qualify. They nevertheless provide the best basis for a programme in UK, Ireland and rest of Europe. The criteria can also be cautiously expanded whilst maintaining transplant benefit. This approach will provide prospective data to validate the Milan experience together with additional evidence for useful modifications of Milan Criteria.

Given the complexity of the pathway to transplantation, limited experience and expertise, and the lack of infrastructure for this indication, we have set up a National Board, consisting of the representatives of NET Centres of Excellence and Liver Transplant Centres as well as a limited number of additional relevant experts, to facilitate the programme and ensure consistency. There is a need for specialist commissioning of the service in order to build the infrastructure for delivering excellent outcomes and to document the programme in detail. LAG can support this call for extra funding from NHS and the Delivery Group shall mobilise support from patient groups, UKINETS and Transplant societies.

The programme will spur international collaborations in the field of liver transplantation for NETs and accelerate research in this ***increasingly prevalent*** cancer.

BACKGROUND:
The incidence of neuroendocrine tumours has increased more than six-fold over the past four decades to almost 9 per 100,000 probably due to improved diagnostic methods[3]. These tumours can originate at various sites in the body and generally behave better than high grade cancers [figure 1 and figure 2].

A large proportion of NET primaries are early and benign; incidentally found in the stomach, duodenum, appendix or rectum at an early stage and easily managed with curative local resections. About 40-50% of newly diagnosed cases present with distant metastases, commonly to the liver [4].

Liver metastases are most common in patients with small bowel or pancreatic NETs[5]. The presence of liver metastases has a negative effect on survival, with 5-year overall

survival rates reducing dramatically from 75-99% in localised disease to 13-54% in the presence of liver metastases [6].

Surgical Management of NET Liver Metastases

A number of treatment options are available for the management of NET liver metastases including liver surgery and loco-regional or systemic therapies, depending on the number, pattern and pathology of metastatic deposits[4]. Of these options, surgical resection with clear margins is the only means to potentially achieving a cure. In reality, only 10-20% of patients with liver metastases are eligible for resection with curative intent. Moreover, cure is seldom realised due to the high incidence of recurrence [5]. Indeed, based on a systematic review in 2012, median 5-year overall and disease-free survival rates were 70.5% and 29% respectively following liver resection with curative intent with a median R0 resection rate of 63% [7].

Distant NET spread is often confined to the liver. Given that R0 resection confers a better prognosis and that liver resection alone is rarely curative as detailed histological examination frequently reveals more microscopic lesions [8], it follows logically that clinicians would turn their attention to liver transplantation as a potential alternative therapeutic option in selected unresectable cases.

Non-Surgical Management of metastatic NETs

The last two decades have seen significant progress in treatments and expertise available for managing well differentiated, grade 1/2 [G1/2] NETs. A number of treatments are available that improve progression free survival. These include: octreotide[9], lanreotide[10], everolimus[11,12], sunitinib[13] and peptide receptor targeted radionuclide therapy (PRRT). Everolimus and PRRT has also shown improved overall survival.

Everolimus is particularly relevant since, as well as having anti-proliferative activity against NETs, it is an excellent immunosuppressant with proven efficacy in maintaining liver transplants [14, 15].

The Milan team have already shown excellent outcomes in carefully selected patients with achievement of very long periods of overall survival and disease free survival. The anti-cancer therapy advances listed above should help us to improve even further on transplant outcomes, provided transplantation is performed in a controlled manner [16]making good use of finite but high level expertise available in UK, Ireland and the rest of Europe.

Liver Transplantation in NETs

A recent systematic review summarises the published evidence on the role of transplantation in NET liver metastases reporting 5-year survival rates that ranged from 47-70.7% and recurrence rates between 31.3-56.8% [8]. Earlier evidence on this subject was limited to small sample studies in single centres to which the wide variation in outcomes is likely attributed (Table 2). Cumulative results from data registries in recent years have shown an improvement in survival outcomes over time [2]. The poor results from earlier studies were likely due to suboptimal patient selection and their preparation.

In 2007, the Milan group proposed a set of criteria for liver transplantation in patients with NET liver metastases based on experience from previous studies[17]. The Milan NET criteria include a confirmed histological diagnosis of low grade NETs (Ki67 index of less than 10%) regardless of function, a primary tumour (with venous drainage via the portal system) which has been completely resected prior to

transplantation, no more than 50% involvement of hepatic parenchyma, responsive or stable disease for at least 6 months prior to transplantation and a recipient age of 55 years or younger (limit later increased to 60 years). Although the evidence underpinning the proposed Milan NET criteria was based largely on non-controlled studies with significant heterogeneity, the group validated the selection criteria through a propensity score-matched prospective study published in 2016 which demonstrated superior survival and disease control in the group transplanted within the set criteria (88.8% 10-year overall survival and 13.1% disease progression compared to 22.4% and 89% respectively in the non-transplant group) [1]. Other reports have also underscored the prognostic value of various components of the Milan NET LT criteria such as tumour differentiation [18-21], need/extent of extra-hepatic resection at the time of transplantation [19,22] and patient age [23], although the significance of some of these factors has been challenged in other reports, though without good evidence [24]. Additional factors such as serum bilirubin level [25 26] and vascular or nodal involvement [2,18] have been suggested as negative prognostic indicators worthy of further validation in future studies.
Notably, a retrospective European Liver Transplant Registry ELTR-based multicentre study that included 213 metastatic NET transplant recipients from 35 European transplant centres also showed that poor tumour differentiation and concomitant resection of primary tumour were risk factors associated with reduced survival as was hepatomegaly – a surrogate of parenchymal involvement. Interestingly, the study showed that transplants after 2000 were associated with a significant improvement in 5-year survival (59% compared to 46% before 2000), an observation likely related to progress in patient selection[2].

Consequent to the inclusion of patients with fewer risk factors in the later years, recipient age over 45 (rather than tumour differentiation) emerged as a significant poor prognostic factor in the cohort of patients transplanted after 2000. Although survival rates in this study were much lower than those recently reported by the Milan group (59% 5-year overall survival after 2000 compared to 97.2%), the authors advocated a more liberal approach to patient selection wherein isolated risk factors are tolerated arguing that the more strict approach would have denied transplantation to more than one third of their low-risk cohort with no tangible improvement to survival rates. The 5-year overall and disease-free survival rates for recipients with no more than one risk factor were remarkably 79% and 57% respectively. Future prospective studies will be necessary to shed further light on the optimal patient selection criteria for transplantation.

The role of neoadjuvant and/or adjuvant therapy with liver transplantation for NET metastases remains unclear. No controlled studies addressing this issue have been published to date. A German trial investigating neoadjuvant 177Lutetium-labelled peptide receptor radiotherapy prior to transplantation is currently registered under the ClinicalTrials.gov identifier NCT01201096 but no results from this trial are thus far available.

At this current stage, the role of liver transplantation in NET LM remains limited in UK and Ireland. This is mainly due to a lack of understanding of the role of liver transplantation for NET LM and a lack of expertise to advocate for these patients. The most recent ENETS guidelines state that liver transplantation "is an option in highly selected patients, preferably in young patients with functional syndromes

demonstrating early resistance to medical therapy" [4]. This is echoed in NANETS guidelines, describing transplantation as "controversial, but possible option for some patients if the Milan and ENETS criteria are met" [27]. In the US, applications for non-standardised UNOS/OPTN MELD exception points are considered on a case-by-case basis with guidance largely based on the Milan NET criteria.

The restricted role for transplantation is unsurprising given the perceived indolent nature of this disease and some evidence suggesting that current standard multimodal therapy for metastatic NETs is superior to transplantation in younger patients [28]. With the emergence of new and effective therapies, a prospective trial may eventually become necessary for defining the role of transplantation for this indication.
There is accumulating evidence for liver transplantation leading to significant improvement in objective measurable outcomes such as significantly higher survival benefit. However, evidence of significant improvement in quality of life and symptom free survival in patients with severe or uncontrollable hormone secretion-related symptoms is needed.

A pilot study in UK and Ireland shall provide further evidence for determining the role of liver transplantation in NETs, using the combined expertise in NETs and liver transplantation that exists in UK and Ireland [Table 3]. It will lead to development of required infrastructure in order to deliver a successful service. It shall also put UK and Ireland at the forefront for developing an international clinical trial of liver transplantation as well as other trials and research in this field.

In summary, there is a need for validating the Milan Group's results and expanding on their criteria for liver transplantation in selected patients with NET LM. In the long-run, a clinical trial may be considered depending on the success of this pilot project in building infrastructure and collaborations, and the possible need for further evidence to determine the role of liver transplantation in NET LM.

PATIENT SELECTION AND PREPARATION

Investigations to Aid Patient Selection

Baseline Investigations, Grading and Staging of NETs

Patients being considered for liver transplantation will by definition have stage 4 disease with a primary outside of the liver. It is therefore imperative to be as certain as possible regarding the extent of disease.

Baseline biochemical investigations: are performed to determine the hormone secreting nature of the cancer, with carcinoid being the commonest syndrome. Chromogranin A is measured in all patients. 5Hydroxy-indole acetic acid [5HIAA] is measured in patients with gastrointestinal NETs or those suspected of carcinoid syndrome and Fasting Gut Hormones in patients with pancreatic NETs displaying specific clinical symptoms of functional NETs. ProBNP will also be assessed at baseline in patient with carcinoid syndrome.
Histology: Patients should always undergo a tumour biopsy to confirm a diagnosis of well differentiated neuroendocrine tumour [WD NET] of low grade. Often the biopsy is taken from the liver. Great emphasis is placed on accurate assessment of biopsy histology, by a histopathologist with expertise in NETs, prior to decisions on

treatment. Patients for liver transplantation will also have histology specimens from resection of primaries. All histology is to be assessed at the referring ENETS Centre of Excellence and documented centrally.

In Grade 1 and 2 NETs the percentage of cells undergoing division is low. This is measured using special stains of tumour histology slides and is given as a proliferative index in terms of a percentage [29]. Potential candidates for liver transplantation shall have proliferative index (Ki67) of 10% or less.

ENETS 2006/2007 grading proposal later endorsed by the WHO 2019 classification[30]
G1: Grade 1; G2: Grade 2; G3: Grade 3; HPF: High power fields.

Classification and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract and hepatobiliary organs, World Health Organization (WHO), 2019

Terminology	Differentiation	Grade	Mitotic rate* (mitoses/2 mm^2)	Ki-67 index* (percent)
NET, G1	Well differentiated	Low	<2	<3
NET, G2	Well differentiated	Intermediate	2 to 20	3 to 20
NET, G3	Well differentiated	High	>20	>20
NEC, small cell type (SCNEC)	Poorly differentiated	High$^{\Delta}$	>20	>20
NEC, large cell type (LCNEC)	Poorly differentiated	High$^{\Delta}$	>20	>20
MiNEN	Well or poorly differentiated¶	Variable¶	Variable¶	Variable¶

NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma; SCNEC: small cell neuroendocrine carcinoma; LCNEC: large cell neuroendocrine carcinoma; MiNEN: mixed neuroendocrine-nonneuroendocrine neoplasm.
* Mitotic rates are to be expressed as the number of mitoses/2 mm^2 (equalling 10 high-power fields at 40× magnification and an ocular field diameter of 0.5 mm) as determined by counting in 50 fields of 0.2 mm^2 (ie, in a total area of 10 mm^2); the Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hot-spots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher grade category.
¶ In most MiNENs, both the neuroendocrine and nonneuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indexes in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well differentiated; when feasible, each component should therefore be graded separately.
Δ Poorly differentiated NECs are not formally graded but are considered high grade by definition.

Imaging: The initial cross sectional imaging normally consists of a contrast enhanced CT scan of thorax, abdomen and pelvis. This provides an excellent overall picture and is particularly helpful in planning surgery for primary lesions and local lymphadenopathy.
MRI of liver is the most sensitive imaging modality for discovering liver lesions of any variety, whether benign or malignant.

Gallium-68 DOTA somatostatin analogue (SSTA)* PET (*most frequently either DOTATATE or DOTATOC) imaging is the most sensitive imaging modality for NET lesions and hence for staging.
Endoscopic ultrasound is the best modality for assessing the pancreas and associated lymphadenopathy.
CT TAP, MRI liver, Ga-68 DOTA PET +/- EUS pancreas are needed for assessing NETs of pancreatic origin.
CT TAP, MRI liver, Ga-68 DOTA PET are needed for NETs of any other origin.

Echocardiography & cardiac specialist evaluation (where pertinent)
In patients with carcinoid syndrome (elevated 5HIAA) and raised NTproBNP levels baseline echocardiography is required to look for early features of carcinoid heart disease.

Pre-transplant surgical preparation of patients; resection of primaries and other extra-hepatic disease
Patients shall require careful counselling and education on the risks and benefits of surgery.

Assessment of resectability of GI primary tumour with associated nodal disease, and role of diagnostic laparoscopy
Assessment of the potential for complete surgical resection of the primary tumour and associated mesenteric nodal disease can be challenging. Contrasted CT of the abdomen and pelvis (≤2mm slices) is essential for operative planning and viewed in conjunction with a surgeon with expertise and experience of managing GI-NETs. The majority of GI-NETs occur in the distal ileum and therefore the nodal disease often occupies the relatively avascular triangle between the terminal branches of the superior mesenteric artery (SMA) and the ileocolic vessels. The jejunal arcades are often spared unless the primary NET has arisen in the mid-small bowel. In general, if the nodal disease is more distal or involves the confluence of the ileocolic vein into the superior mesenteric vein (SMV) then the nodal disease can be resected with at least an R1 margin. More proximal to this, and especially if the nodal disease involves the confluence of the middle colic vein into the SMV, then a more circumspect view should be taken as to the merits of attempting resection in order to satisfy eligibility for liver transplantation. The risk of duodenal cicatrisation into the nodal mass needs to be considered if the nodal disease reaches the level of the border of the duodenum. If less than four proximal jejunal branches of the SMA are free of disease, attention must be given to the risk of short small bowel syndrome as a consequence of obtaining clear margins. Further risk of short small bowel syndrome can occur if the nodal disease is particularly complex with involvement of small bowel loops out with the immediate mesenteric drainage of the nodal mass.

Small volume transcoelomic metastases can be present on the visceral and parietal peritoneum that are too small to be characterised on Ga-68 DOTA PET and CT imaging. Diagnostic laparoscopy may be useful in planning treatment in some cases, prior to embarking on extensive GI or pancreatic surgery in order to qualify for liver transplant assessment.

The presence of multiple primary NETs in the small bowel is a relatively common phenomenon and as many of the primary lesions should be incorporated into the resection as practically possible.

The presence of para-aortic or pelvic nodal disease should be assessed for resectability by a surgeon experienced in the surgical exploration of the retroperitoneum and pelvis. The potential for retroperitoneal or pelvic nodal clearance needs to be balanced with risk of surgical morbidity and significant peri-operative complications.

Selection of patients with pancreatic NET LM for liver transplantation

Patients with the primary pancreatic disease previously resected: This situation may arise where removal of the primary and any associated lymphadenopathy has taken place previously and the patient has developed recurrence only within the liver.

Surgical resection of pNETs can be carried out in the form of radical surgery such as pancreaticoduodenectomy for lesions in the head of the pancreas, and distal pancreatectomy, with splenectomy for lesions in the body or tail of the pancreas. Non-radical surgical options include enucleation, central pancreatectomy and spleen preserving distal pancreatectomy. Non-radical resection options do not include lymphadenectomy, likely increasing the risk of recurrent disease compared to lymphadenectomy having been performed at first surgery[31]. Involvement of superior mesenteric vein/ portal vein/ splenic vein requiring venous resection and reconstruction as well as positive resection margins are considered poor prognostic indicators of long-term outcomes[32].

Some patients in this group will have had resection of primary a long time before the appearance of the liver metastases. There should have been no recurrence at the primary site or elsewhere outside the liver for the patients to be eligible for consideration of liver transplantation. Despite this, only those who had radical surgery without vascular reconstruction and with a negative resection margin will be considered in the initial phase (of first 10 patients).

Patients presenting with synchronous primary and liver metastases: These patients are usually not considered for resection of the primary. However, if such patients are deemed to be suitable for liver transplantation, primary resection can be considered.

Patients will have demonstrated good biological behaviour in order to be considered for liver transplantation. This will usually mean disease stability for 6 months or more. In such cases, and following careful counselling of the patient, the primary will be removed. A further 6 months will be needed to allow recovery from pancreatic surgery and to demonstrate lack of local recurrence. Patients will then be assessed for liver transplantation.

Patients with vascular involvement requiring reconstruction will be excluded. Radical surgery, including local lymphadenectomy, should be performed to deal with the primary.

Simultaneous resection of primary at the time of liver transplant is not allowed as it is associated with significantly poorer outcomes.

Patients needing Total pancreatectomy for the clearance of primary disease:
Patients with multiple intra-pancreatic primaries will need total pancreatectomy. This results in significant endocrine and exocrine depletion requiring replacement for both. For these reasons, this group of patients will be excluded from phase I of the pilot programme – the initial 10 patients. Thereafter, careful consideration will need to be given as to the likely transplant benefit for individual patients.

Special investigations that may be required prior to pancreatic NET LM patients entering the liver transplant assessment pathway:

- All patients should be considered for diagnostic laparoscopy to look for any obvious peritoneal disease. This may be more readily feasible in patients with previous laparoscopic resection and the risk of such laparoscopy needs to be assessed individually for each patient.

- EUS to be performed to exclude obvious 2nd primary in the pancreatic stump and also to look for any significant lymphadenopathy. Endoscopic and histological findings have to considered together to assess the possibility of disease recurrence.

Management on the waiting list
Selected patients will need to demonstrate good tumour biology in terms of radiological disease stability, with or without treatment, for 6 months prior to being listed and reasonable disease control whilst on the waiting list.

On the waiting list they shall need to be reassessed in the following manner:
Clinical assessment [3 monthly] to ensure remains in adequate physiological condition without rapid, unmanageable changes in health
Biochemical assessment [3 monthly] to monitor for fluctuations in hormone symptoms, liver and renal function, and development of carcinoid heart disease.
Radiological assessment [6 monthly since relatively slow growing cancers] using CT TAP, MRI liver and Ga-68 DOTA SSTA PET to look for disease progression.

Delisting criteria:

- Overall deterioration in patient's condition making transplantation unsafe.
- Rapid radiological disease progression within liver [slow progression may be acceptable for remaining on the list].
- Recurrence of extra-hepatic disease.

Outcome measures:
Participating Centres [ENETS CoE and Transplant Centres] shall provide data <u>in order to remain within the pilot programme.</u>

1. There will need to be robust data capture on ***all*** patients from when they are referred by the NET specialist to the National Board for an opinion on suitability for the liver transplant pathway. Since this is a single arm evaluation and there are so many points at which patients can drop out, a comprehensive database, ***that includes patients not transplanted***, will add to evidence for best management of patients with NETs. Need funding to be able to do this proactively – using a part-time data manager.
2. Overall survival: 3 months, 1 year, 5 years, 10 years
3. Disease Free Survival in transplanted: 3 months, 1 year, 5 years, 10 years
4. Survival of 'not transplanted': 3 months, 1 year, 5 years, 10 years
5. QoL measures: CLQ C30, GINET Q21, psychological wellbeing GHQ9 [possibly other tools to be decided], and EQ5D for health economics. These measures will be assessed for all patients referred to the advisory group so that we have data for an intention to treat analysis.

Prioritisation on the waiting list:
Method for timely allocation has been agreed by the LAG committee.
The National MDT could make recommendations on prioritising given patients, should the need arise.

Figure 1: morphological and topological distribution of 8,726 neuroendocrine neoplasms diagnosed in England, 2013 and 2014

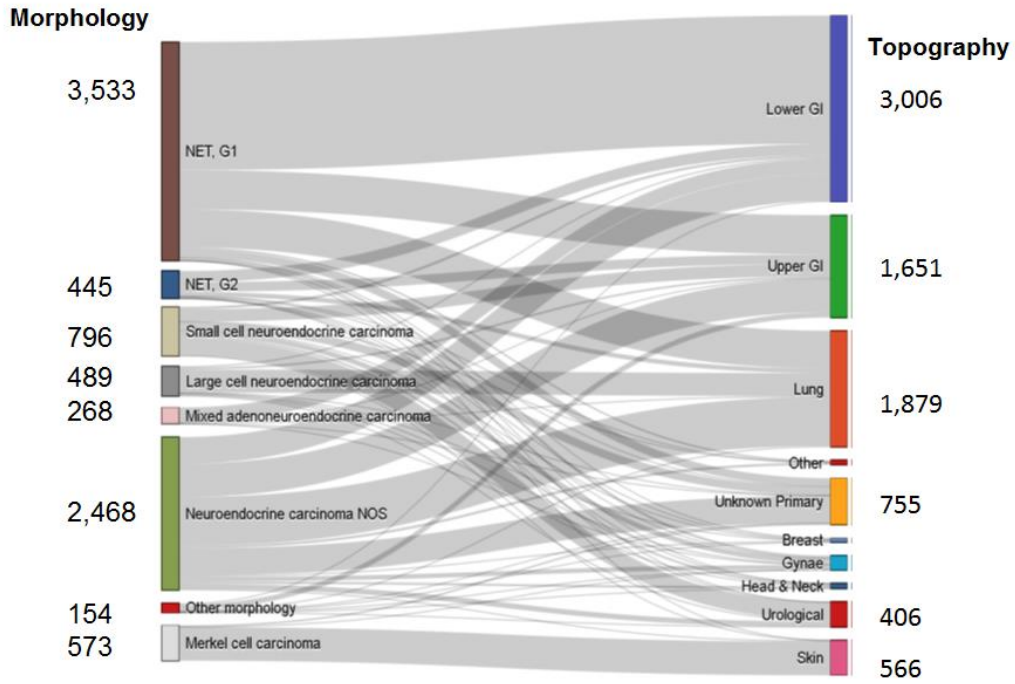


Figure 2: One year survival for neuroendocrine neoplasms diagnosed in England, 2013-2014.

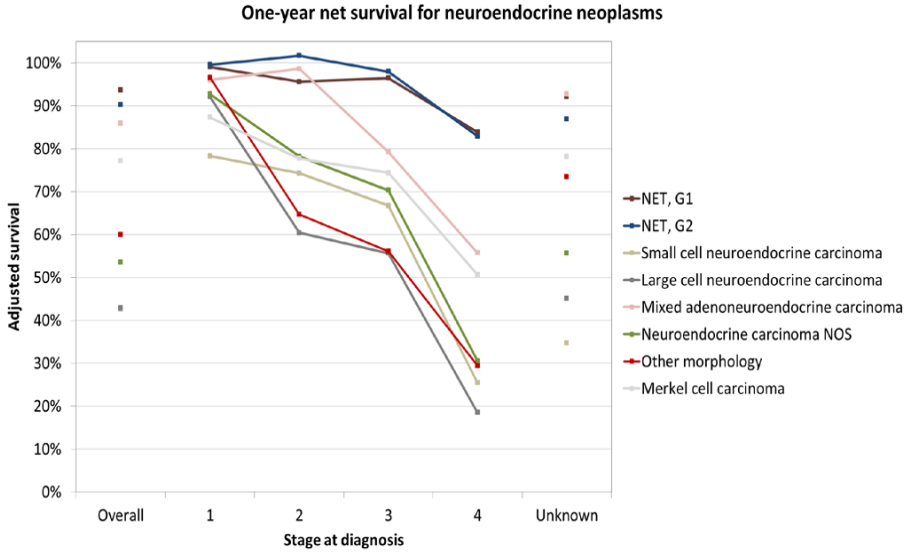
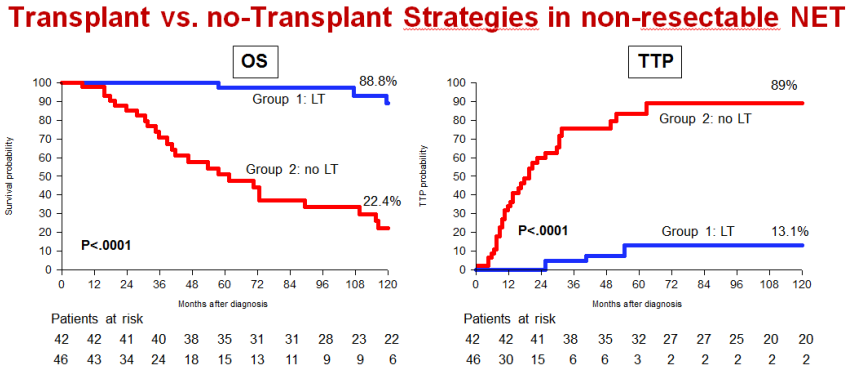


Figure 3: Overall and disease free survival in transplant v standard of care

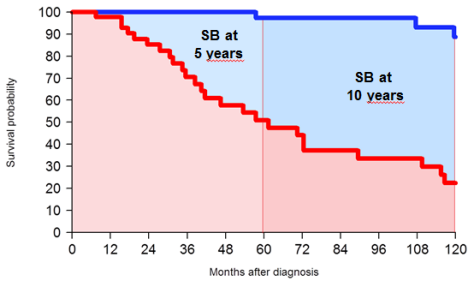


	GROUP 1: LT	GROUP 2: no LT
5-yr OS	97.2%	50.9%
10-yr OS	88.8%	22.4%
Median OS	NR	62 months
Median TTP	NR	20 months

Mazzaferro V et al Am J Transpl 2016

Figure 4: Transplant benefit, at 5 and 10 years, measured in months

Survival Benefit estimation of LT for NET



	SURVIVAL BENEFIT ESTIMATION			
	Univariable model		*Multivariable model (adjusted for propensity score)*	
	D-MST (CI)	p	D-MST (CI)	p
At 5 years Group1 vs Group 2	12.79 (7.95,17.63)	**<0.0001**	6.82 (1.10,12.54)	**0.019**
At 10 years Group1 vs Group 2	48.62 (35.49,61.75)	**<0.0001**	38.43 (21.41,55.45)	**<0.0001**

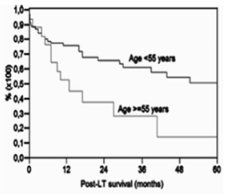
Mazzaferro V et al Am J Transpl 2016

Figure 5: It should be possible to expand criteria whilst maintaining transplant benefit

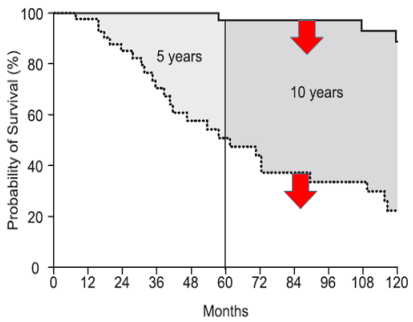
Acceptable Expansion

Decrease in Overall Survival with maintained Survival Benefit

- Age
- pNET
- Time (stability period)
- Higher Ki-67 cutoff



French experience with 89 transplanted patients
Synchronous primitive resection with LT is associated with low OS. Poor result from LT in patients > 55 yrs



Parallel decrease in OS in both "arms"

Not expected changes in survival benefit

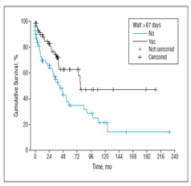


Table 2. Five-Year Survival Rates in Liver Transplantation Patients for Neuroendocrine Tumors by Quartile of Wait Time

Wait Time, d	No. of Patients	5-Year Survival, Mean (SE), %
≤22	37	33 (9)
23-67	36	40 (12)
68-170	37	52 (11)
≥171	36	74 (9)

Rosenau J et al, Transplantation. 2002
Frilling A et al, Br J Surg. 2009 ; Gedaly R Arch Surg 2011

Table 1: Selection criteria for liver transplantation as accepted by various international bodies.

Table 1 Milan criteria, UNOS guidelines, and ENETS guidelines on LT for pNETLM

Index	Milan criteria (6.15. 35) (1)	UNOS guidelines 2015 (2)
Histology grade	G1–G2*	G1–G2*
Primary tumor site	Drained by the portal system	Drained by the portal system
Tumor involvement	<50% of the liver volume	<50% of the liver volume
Primary tumor resection and interval of stable disease	Resection of primary tumor and all extra-hepatic tumor deposits and stable disease/good response to therapies for at least 6 months	Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence at least 6 months
Recipient age	<60 years (relative criteria)	<60 years
Others	None	Neuroendocrine liver metastasis limited to the liver, bi-lobar, not amenable to resection

Coppa JC et al, Transpl Proc 2001 ; Stutcliffe et al. Am J Surgery 2003; Mazzaferro V et al. J Hepatology 2007; Shimata et al. Gland Surg 2018

Table 1A: Proposed UK&I selection criteria for eligibility for liver transplantation in patients with liver metastases from neuroendocrine tumours (NET)

Pilot phase	I [0-10 liver transplants]	II [11-50 liver transplants]
Histology	G1/G2 WD NET	G1/G2 WD NET
Primary site	GEP	GEP + Other
Primary and associated lymphadenopathy	Completely resected before liver transplant surgery	Can be left in-situ if small volume and stable
Liver metastatic burden	<50% by volume	< or > 50% by volume
Disease stability	Stable disease/response to therapies for at least 6 months prior to transplant consideration	Stable disease/response to therapies for at least 6 months prior to transplant consideration
Patient age	< 60 (relative criteria)	< 60 (relative criteria)

Table 2: Single centre evidence on the role of liver transplantation in NEN liver metastases

	Type of study	Site of NEN	Number of patients	5y survival PT/DF	Adjuvant therapy	MVT included	Note
Makowoka 1989	Retrospective	SB Pancreas	5	NR	Selective chemotherapy	No	
Routley 1995	Retrospective	SB Pancreas Lung Anorectal Unknown	11	57%	Selective systemic and LRT	No	
Dousset 1996	Retrospective	Stomach SB Pancreas	9	NR	Selective neoadjuvant systemic and LRT	No	Concomitant resection of extrahepatic disease in around half of cases. High perioperative death rate
Coppa 2001	Retrospective	SB Pancreas	9	70%/53%	Neoadjuvant systemic therapy	No	Clear selection criteria
Rosenau 2002	Retrospective	Stomach SB Caecum Pancreas Lung Anorectum Unknown	19	80%/21%	Selective neoadjuvant systemic therapy	No	Ki67 is a prognostic indicator for survival. Liver resection performed pre OLT in some cases
El Rassi 2002	Retrospective		5	60%		Yes	
Florman 2004	Retrospective	SB Pancreas Appendix Anorectum	11	36%	Unclear	No	Living donor transplants included. Liver resection performed pre OLT in some cases
Fernandez 2005	Retrospective	SB Pancreas Lung	8	NR		No	
van Vilsteren 2006	Retrospective	SB Pancreas Unknown	19	NR	Selective neoadjuvant systemic and LRT	No	Minimum 6 month observation between primary resection and transplant. Liver resection performed pre OLT in some cases
Frilling 2006	Prospective	SB Colon Pancreas Lung Unknown	15	67%/48%	Selective neoadjuvant systemic and LRT	Yes	Liver resection performed pre OLT in one cases
Olausson 2007	Retrospective	SB Pancreas Anorectum Lung Unknown	15	90%/20%	Selective neoadjuvant systemic and LRT	Yes	Less strict inclusion criteria. Age, tumour burden, Ki67, and time from diagnosis had no significant influence on recurrence. Liver resection performed pre OLT in two cases
Marin 2007	Retrospective	SB Pancreas Lung	10	NR	Unclear	No	Concurrent resection of primary performed in two cases
Dhupar 2009	Retrospective	Pancreas	5	NR	None	All MVT	Concurrent resection of primary in all cases
Stauffer 2009	Retrospective	Pancreas	5	NR	Unclear	No	Concurrent resection of primary in two cases
BonaccorsiRiani 2010	Retrospective	SB Pancreas Lung Unknown	9	33%/11%	Selective neoadjuvant systemic and LRT	No	Liver resection performed pre OLT in one case
Grat 2014	Retrospective	SB Pancreas Colon Unknown	12	79%/52%	Unclear	Unclear	Tumour grade, Ki67 and intraoperative blood transfusion are associated with DFS
Mazzafero 2016	Prospective	Stomach SB Colon Pancreas	42	97%	Selective neoadjuvant systemic and LRT	No	Selection based on Milan-NET criteria

Table 3: Present location of Liver Transplant and ENETS certified Centres of Excellence in UK and Ireland.

Liver Transplant Centre	**Co-located ENETS CoE**	**Nearest ENETS CoE**
Birmingham QEHB	Birmingham QEHB	Coventry, Oxford, Liverpool
Cambridge Addenbrooks	Addenbrooks [soon]	Southampton and Portsmouth
Dublin St Vincent's	Dublin St Vincent's	
Edinburgh Royal Infirmary		Glasgow Beatson Oncology Centre
Leeds St James's		Manchester Christie, Sheffield Teaching Hospitals
London King's	London King's	Imperial Hammersmith
London Royal Free	London Royal Free	Oxford, Imperial Hammersmith
Newcastle Freeman	Newcastle Freeman	

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