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

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**This edition also contains guidance on post-transplant management**

## EXECUTIVE SUMMARY:

In 2020 the Liver Advisory Group agreed to a pilot scheme to determine the benefits of liver transplantation for unresectable neuroendocrine tumour liver metastases [NET LM]. A national delivery framework was set up in mid-2021 and has been selecting patients for the pilot programme through a national MDT meeting held once monthly. The nMDT provides oversight and guidance on taking patients through the patient selection and liver transplant assessment pathway.
Patients only meeting the Milan criteria for NETs are being selected initially, with plans for expansion of criteria during second phase [Table 1A].

- ***The service evaluation will deliver liver transplantation for 50 patients with a NET diagnosis.***
- ***Allocation of organ within 6 months has been agreed 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.***
- ***Guidance on post-transplant follow-up is provided***
- ***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 bespoke immunosuppression and increasing 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 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]. However, they are not being routinely applied to patients who would qualify for this treatment. They nevertheless provide the best basis for a programme in UK, Ireland and rest of Europe. The criteria can likely 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 cancer with ***increasing prevalence***.

**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 significant proportion of NETs are found incidentally and at an early stage within the stomach, duodenum, appendix or rectum. They can usually be managed with

curative local resections. About 40-50% of newly diagnosed cases however 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. Several 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 have 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 and immunosuppression 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 NET (Ki67 index of less than 10%) regardless of function, a primary tumour (with venous drainage via the portal system) that 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, this has been without presentation of 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 $^{177}$Lutetium-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 management 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 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. NTproBNP 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 presented at the national MDT.

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.

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***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 its associated lymphadenopathy.
CT TAP, MRI liver, and Ga-68 DOTA PET +/- EUS pancreas are needed for assessing NETs of pancreatic origin.
CT TAP, MRI liver, and 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 should be viewed in conjunction with a surgeon with expertise and experience of managing GI-NETs. Most 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 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 bowel syndrome as a consequence of obtaining clear margins. Further risk of short 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 trans-coelomic 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 gastrointestinal or pancreatic surgery 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' tumours will have demonstrated an indolent course 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 when resecting 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 be needed for predicting 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 quantified for each patient.

- EUS to be performed to exclude obvious 2$^{nd}$ primary in the pancreatic stump and to look for any significant lymphadenopathy. Endoscopic and histological findings must be 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. There needs to be 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.
***Quality of life*** [3 monthly].
***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.
***Chemotherapy whilst on the waiting list*** please see Appendix 1

**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 in order to remain within the pilot programme.

1. Robust data capture is required 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 prospectively and 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.

**Post transplantation follow-up:**
Immediate post transplantation management is unlikely to require additional NET-specific measures since the patient should now be cancer free. There should not be any risk of carcinoid crisis for instance. Patients shall no longer require long-acting somatostatin analogue treatment.
The peri-operative octreotide infusion should be weaned down and stopped once the patient has stabilised and off all inotropes.

The patients shall receive the transplantation Centre's standard immunosuppression. Complications such as acute rejection shall be managed utilising the transplant centre's standard protocols.

Patients shall have a NET team review at 1 month to ensure restaging investigations are arranged to take place at 3 months post-transplant. These shall include CT TAP and tumour markers.

Patients shall be reviewed at appropriate intervals by the liver transplant and NET teams. Ideally this shall be within a specialist combined MDT clinic, but some centres may do so in separate liver transplant and NET clinics, depending on local expertise and arrangements.

The NET imaging follow-up should be CT TAP at 3 months, and 6 months, with a DOTA PET scan at 12 months (unless indicated earlier if abnormal CT). Patients are to have 6 monthly CT TAP for the second year. The interval could subsequently be

increased to 12 monthly if no concerns raised. Additional imaging can be arranged if clinically indicated.
Immunosuppression, including dosing and monitoring, shall be the remit of the transplant specialist with monitoring for cancer recurrence being the responsibility of the NET specialist. Centres are to find their own solutions for managing these two aspects efficiently.

**Immunosuppression:**

All patients shall be given standard immunosuppression as per Centre protocol.

Should cancer recur then consideration may be given to using Everolimus as the main immunosuppressant.

**Post-transplant surveillance for cancer recurrence:**
A proportion of patients may experience neuroendocrine tumour recurrence; with the median time to recurrence in the Milan cohort being 7 years. Recurrence has been shown to occur mainly in lymph nodes, most commonly in the intra-abdominal region. Recurrence was often multi-focal but did not involve the transplanted liver.

At present there are no protocols for surveillance for recurrence. Given the knowledge regarding recurrence in the Milan cohort, regular imaging with CT of thorax / abdomen / pelvis seems to be the best method for surveillance. Although median time to recurrence was 7 years following liver transplantation, survival outcomes were worse when it occurred within 2 years. It would therefore seem appropriate to perform CT scans at 6 monthly intervals for 2 years after liver transplantation and yearly thereafter.

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

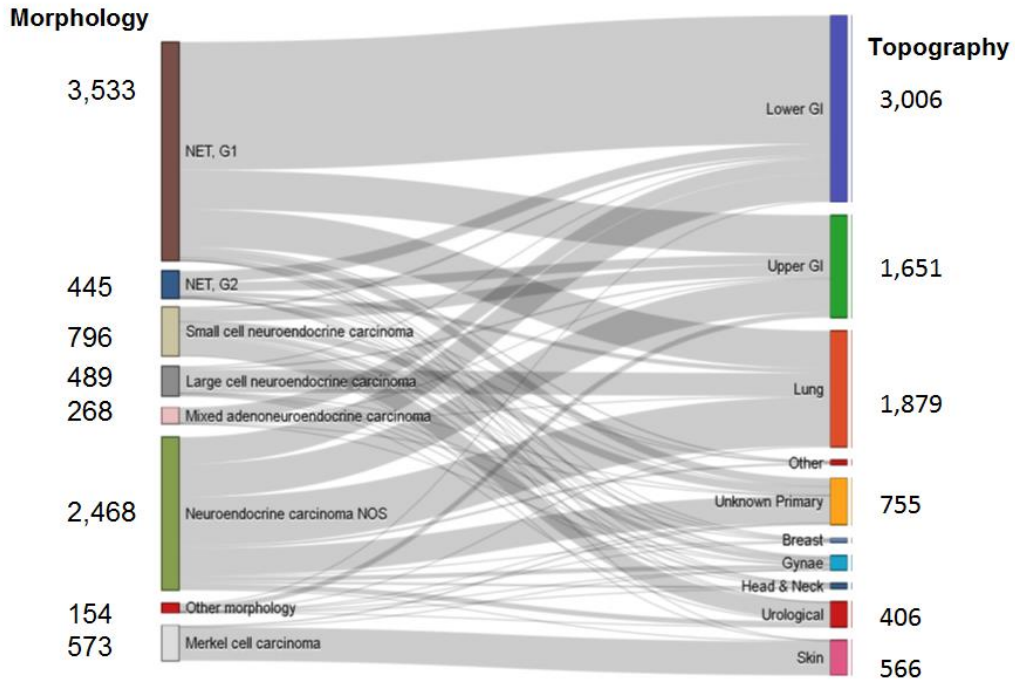



*Figure 2: One year survival for neuroendocrine neoplasms diagnosed in England, 2013-2014.*

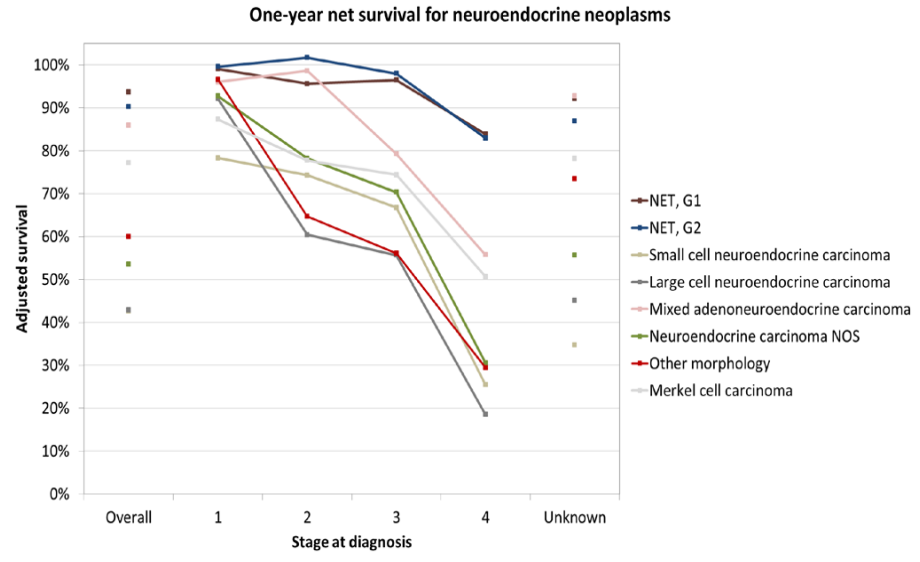
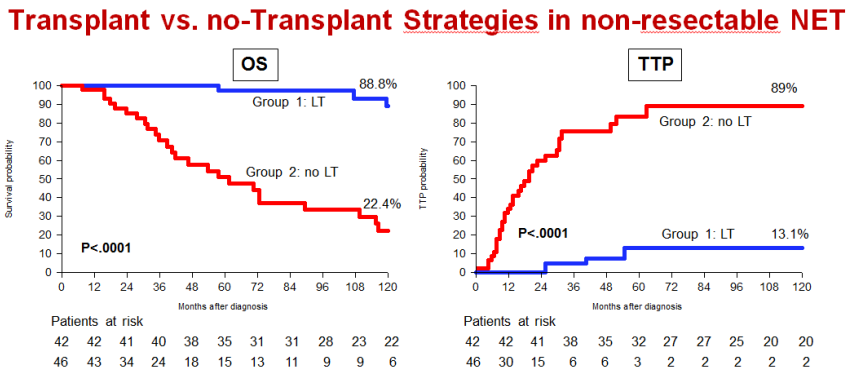


*Figure 3: Overall and disease free survival in transplant v standard of care*




| | 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 |

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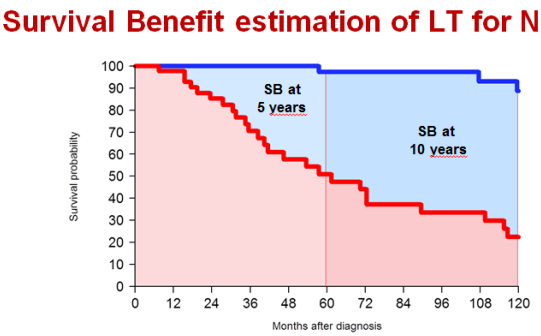
*Figure 4: Transplant benefit, at 5 and 10 years, measured in months*




| | 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** |

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

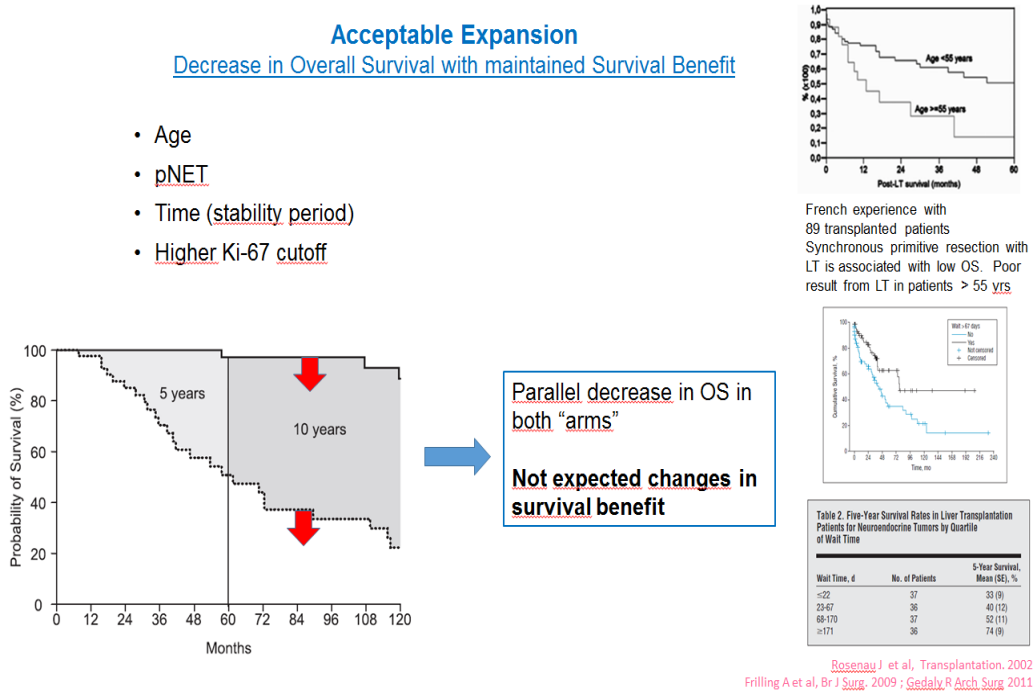


*Table 1: Selection criteria for liver transplantation as accepted by various international bodies.*

**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<br>Pancreas | 5 | NR | Selective chemotherapy | No | |
| Routley 1995 | Retrospective | SB<br>Pancreas<br>Lung<br>Anorectal<br>Unknown | 11 | 57% | Selective systemic and LRT | No | |
| Dousset 1996 | Retrospective | Stomach<br>SB<br>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<br>Pancreas | 9 | 70%/53% | Neoadjuvant systemic therapy | No | Clear selection criteria |
| Rosenau 2002 | Retrospective | Stomach<br>SB<br>Caecum<br>Pancreas<br>Lung<br>Anorectum<br>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<br>Pancreas<br>Appendix<br>Anorectum | 11 | 36% | Unclear | No | Living donor transplants included. Liver resection performed pre OLT in some cases |
| Fernandez 2005 | Retrospective | SB<br>Pancreas<br>Lung | 8 | NR | | No | |
| van Vilsteren 2006 | Retrospective | SB<br>Pancreas<br>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<br>Colon<br>Pancreas<br>Lung<br>Unknown | 15 | 67%/48% | Selective neoadjuvant systemic and LRT | Yes | Liver resection performed pre OLT in one cases |
| Olausson 2007 | Retrospective | SB<br>Pancreas<br>Anorectum<br>Lung<br>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<br>Pancreas<br>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<br>Pancreas<br>Lung<br>Unknown | 9 | 33%/11% | Selective neoadjuvant systemic and LRT | No | Liver resection performed pre OLT in one case |
| Grat 2014 | Retrospective | SB<br>Pancreas<br>Colon<br>Unknown | 12 | 79%/52% | Unclear | Unclear | Tumour grade, Ki67 and intraoperative blood transfusion are associated with DFS |
| Mazzafero 2016 | Prospective | Stomach<br>SB<br>Colon<br>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** | **Linked ENETS CoE** |
|---|---|---|
| Birmingham QEHB | Birmingham QEHB | Coventry, Oxford, Liverpool, Cardiff |
| 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, Belfast |
| London Royal Free | London Royal Free | Oxford, Imperial Hammersmith, Cardiff |
| Newcastle Freeman | Newcastle Freeman | |

***Appendix I:***

Considerations for Capecitabine/Temozolomide chemotherapy in the pre-liver transplant setting

Both capecitabine and temozolomide have short half-lives and are therefore cleared quite quickly from the body. The elimination half-life (t1/2 in hours) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL (capecitabine metabolites) are 0.85, 1.11, 0.66, 0.76 and 3.23, respectively[1]. Assuming five half-lives for the drug to effectively drop to relatively undetectable levels, the maximal washout time is approximately 17 hours. The elimination half-life of temozolomide (t1/2) in plasma is approximately 1.8 hours[2]. Assuming five half-lives for the drug to drop to relatively undetectable levels, the washout time is approximately 9 hours. Once a liver offer has been received and transplant is likely to proceed, the patient should stop capecitabine/temozolamide.

The incidence of grade 3 or 4 neutropenia (i.e. neutrophils <1) with capecitabine/temozolomide chemotherapy is 13%3. The incidence of grade 3 or 4 thrombocytopenia with capecitabine/temozolomide chemotherapy has been recorded as 10%[3]. Patients who are on capecitabine/temozolamide chemotherapy may be on empirical GCSF during the cycle, though the decision to continue with empirical GCSF in the immediate post-transplant period should be considered in accordance with the degree of bone marrow toxicity previously experienced and weighed up against the possible slight increased risks of rejection with GCSF therapy in the post-transplant setting[4].

Patients should be closely monitored for new onset of bone marrow suppression on transplant immunosuppression that is likely to include anti-metabolites.

Overall, the decision to proceed with transplant close to chemotherapy (i.e. within 6 weeks of the last chemotherapy cycle) must be made on a case-by-case basis.

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