Neuroendocrine Cancer UK
Incorporating The Ann Edgar Trust

in partnership with

NHS
University Hospitals Birmingham
NHS Foundation Trust

This Patient Information Leaflet has been written for a select group of patients only.
It is for those patients, diagnosed with Neuroendocrine Tumour Liver Metastases,
who are being considered for liver transplantation by their specialist 'NET' team.

UK and Ireland Programme for Liver Transplantation in Selected Patients with Neuroendocrine Tumours

Liver transplantation for cancer is evolving offering new opportunities for selected Neuroendocrine Cancer patients in terms of improvements in survival and quality of life.

Neuroendocrine Cancer is divided into 2 key types:

- Neuroendocrine Tumours (NETs)
- Neuroendocrine Carcinomas (NECs)

This programme focusses on those who have developed Neuroendocrine Tumour liver metastases.
Emerging evidence from global experience has now allowed us to identify a small sub-group of NET patients who may benefit from liver transplantation.

This programme will help determine the feasibility and usefulness of liver transplantation for those, in the UK and Ireland, who are in that sub-group.
It is also hoped that it will spur greater research into the understanding and treatment of Neuroendocrine Tumours resulting in better outcomes for all Neuroendocrine Cancer patients.

Further information on Neuroendocrine Cancer can be found at www.neuroendocrinecancer.org.uk

What is liver transplantation?

Liver transplantation is an operation to remove a damaged or diseased liver and replace it with a healthy one. The medical name for the procedure is orthotopic liver transplant (OLT).

People who have a liver transplant will need to take medicines for the rest of their life to prevent their immune system from reacting to and possibly rejecting their new liver.
They will also need to have regular appointments with their transplant and specialist care teams to check that the new liver is working well and to monitor overall health.

In the UK, survival following liver transplantation, is over 90% at 1 year and more than 80% at 5 years.

Most livers used in liver transplantation come from people who have just died, called deceased donors.

Adult recipients typically receive the entire liver from a deceased donor. However, surgeons may split a deceased donor's liver into two parts: the larger part may go to an adult, and the smaller part may go to a smaller adult or child.

Sometimes a healthy living person will donate part of his or her liver. This type of donor is called a living donor. In the UK, almost 1,000 liver transplants are performed every year - more than 80% use livers from deceased donors.

Liver transplantation can offer a potential cure - however certain diseases, including cancer, may return. It is, therefore, important that part of the follow up care includes surveillance for this so that early detection and intervention, such as further treatment, can be discussed, planned, and given, as needed.

A liver transplant is a major operation, the assessment and selection phase, the 'waiting list' period and the recovery process afterwards can each take time to complete. It is not without risk and there are several factors that need to be considered before transplantation can be discussed.

Considerations relating to Liver Transplantation in Neuroendocrine Tumours

Diagnosis:
It is always important to make an accurate diagnosis so that the right treatment is provided.

Histology:
In Neuroendocrine Cancer - confirming diagnosis and what the cancer cell looks like, under the microscope can help predict its likely behaviour – and suitability for consideration for liver transplantation.

- Is it a Neuroendocrine Tumour (NET) or Neuroendocrine Carcinoma (NEC)?
- If it is a NET - what grade is it?

Neuroendocrine Tumour	Neuroendocrine Carcinoma
Well-differentiated neuroendocrine cells	Poorly differentiated neuroendocrine cells: either small cell or large cell in appearance.
Grade 1 = Ki67 is less than 3%	
Grade 2 = Ki67 between 3-20%	
Grade 3 = Ki67 is more than 20%	Ki67 is more than 20% - usually above 50%

For the purposes of this pilot programme, only those with **grade 1 and some low grade 2 NETs (where the Ki67 is less than 10%)** will be considered.
This is because the evidence and global experience shows that those with moderate to high grade cancers do not benefit from liver transplantation.

Primary site:
The site of origin of the cancer has been shown to have a bearing on outcomes and overall survival.

Best outcomes were seen in patients with cancers starting in the pancreas or other parts of the digestive tract (e.g., GEP-NET*s) - who had all extra-hepatic (non-liver) disease identified and removed, prior to liver transplantation.
*GEP-NET*s includes Neuroendocrine Tumours of the pancreas or other parts of the gastrointestinal tract, such as the stomach, small bowel, large bowel, rectum, and appendix.*

NETs originating from other sites, have not appeared to gain the same benefit and will not, initially, be included in the liver transplant pilot programme, though this may be reviewed over time.

For the purposes of this pilot, discussion about transplantation **may** occur before surgery to remove the primary (and/or associated lymph nodes) takes place.

However, for liver transplantation to take place, it will be very important to demonstrate that all cancer outside of the liver (extra-hepatic disease) has been completely removed.

The best way to reassuringly achieve extra-hepatic disease clearance will be through detailed imaging investigations prior to primary site (and/or lymph node) surgery and then a careful assessment of the disease and its removal by a surgeon experienced in operating on NET patients.

Following surgery, you will need to be scanned using the best available methods: these may include CT scan, MRI scan and DOTA PET scan.

To continue to proceed further along the assessment pathway for liver transplantation, it will be important to demonstrate that no extra-hepatic disease has recurred and that the cancer within the liver is stable: in other words, shows no significant evidence of new growth or new tumours. You may remain on some of your treatments and will have any extra treatments, as needed, to maintain disease stability, and help keep you within transplant criteria.

The amount of cancer within the liver (intra-hepatic disease)
This may also be referred to as liver "metastatic burden" or "volume of disease": and refers to how much of the liver contains cancer, for example, 10%, 25%, etc . . .
Volume (or burden) considers both the number and size of tumours and assesses the total amount of cancer compared to the overall size of the liver. Liver and tumour volume measurements (volumetrics) have been found to be important in making decisions about transplantation.

Evidence shows that if total cancer volume takes up less than half of the liver total volume, patients will do better post-transplantation.

Age at time of transplantation
With increasing age comes the reality of decreasing years of life expectancy alongside increasing risk of developing age-related health concerns. We are living longer, but public health records also show that we are doing so with an increasing number of age-related health concerns and conditions.

As previously stated, a liver transplant is a major operation, and the recovery process can be long. There is evidence, that despite improvements in overall health and healthcare, older age is associated with poorer survival during and/or following liver transplantation.
Age-related risk starts slowly to rise in the 5th decade (late 40s), rising more sharply thereafter.

For the purposes of this programme there is an age restriction of **less than 60 years.** The benefits of liver transplantation have only been demonstrated in this relatively young patient group.
There may be exceptions, but these will be carefully reviewed on a case-by-case assessment and national board discussion.

Other considerations
Include overall health status, the presence of NET-associated health conditions - for example Carcinoid Heart Disease, the presence of other health conditions/risks: a complete medical / treatment history and assessment.

Alongside discussion about the possibility, suitability, and availability of other treatment options instead of transplantation.

There are also psychosocial considerations - issues that may occur or be re-ignited during transplant assessment, the transplant listing process and/or after transplantation: for example, managing anxiety and/or uncertainty - concerns may arise about the donor, the process, waiting time and / or treatment plan.

Careful assessment of whether transplantation is appropriate for you is key - and must address all physical and psychosocial well-being concerns.

Transplant assessment takes place to ensure that:

- Medically suitable patients are placed on the transplant list in a timely manner.
- Patient education and counselling can take place to explore and discuss both physical and psychosocial concerns. (Where consent given, this should include next of kin / patient named support)
- Patients are able to make an informed choice and share decision making about transplantation.

If at any time during the assessment, selection and listing process you change your mind, speak to your team, and let them know.

You can withdraw your consent and participation in this process at any time.

Liver Transplant Assessment & Listing Process

1. **NET specialist team identifies potential candidates for liver transplantation.**

Inclusion criteria for this programme:

Histology	Neuroendocrine Tumour: well-differentiated
Grade	Grade 1 and Grade 2 (with Ki67 less than 10%)
Primary Site	Gastro-entero-pancreatic (GEP)*
Primary Site Treatment	Primary is potentially amenable to complete surgical clearance** or has already been resected.
Liver disease burden/volume	Less than 50% (volumetric measurement)
Disease status	Stable disease/response to therapies for at least 6 months prior to transplant consideration
Age	Less than 60 (relative criteria)

**GEP-NETs include Neuroendocrine Tumours of the pancreas or other parts of the gastrointestinal tract, such as the stomach, small bowel, large bowel, rectum, and appendix.*
*** Resection needs to take place before liver transplantation*

2. **Discussion with you** - to include reason for consideration, risks and benefits, likely wait times and completion of any further tests / scans that may be required for **National MDT (nMDT)** discussion. There should also be a chance to explore the implications of a potential Yes or No from the nMDT and what the next steps would be, should transplant not be recommended.
Written information about the topics covered in this discussion will be made available to you.

3. **Referral made to the virtual nMDT**: referral NET team will present 'case' at the nMDT.

4. **Decision by nMDT and agreement on next steps**
   - If outcome is that you are suitable for transplantation, this will be confirmed with you, and with your consent the "NET" team will refer to you to the transplant team
   - If outcome is that you are potentially suitable for liver transplantation, but further tests are required - the "NET" team will discuss this with you and arrange further tests. Once completed the results will be rediscussed at the nMDT and ongoing care will depend on outcome.
   - If the decision is that you are not suitable for liver transplantation, then the "NET" team will discuss this with you and agree a plan of ongoing care.

5. **Referral to transplant team and completion of liver transplant assessment.**
   - If transplant assessment confirms that transplantation **would** be suitable for you, then with your consent, you will be placed on the waiting list and a schedule of scans and appointments will be agreed with you.
   - If transplant assessment confirms that transplantation **would not** be suitable for you, the reason(s) why will be explained and discussed with you. Your "NET" team will also discuss and, with you, confirm plan for your ongoing care.

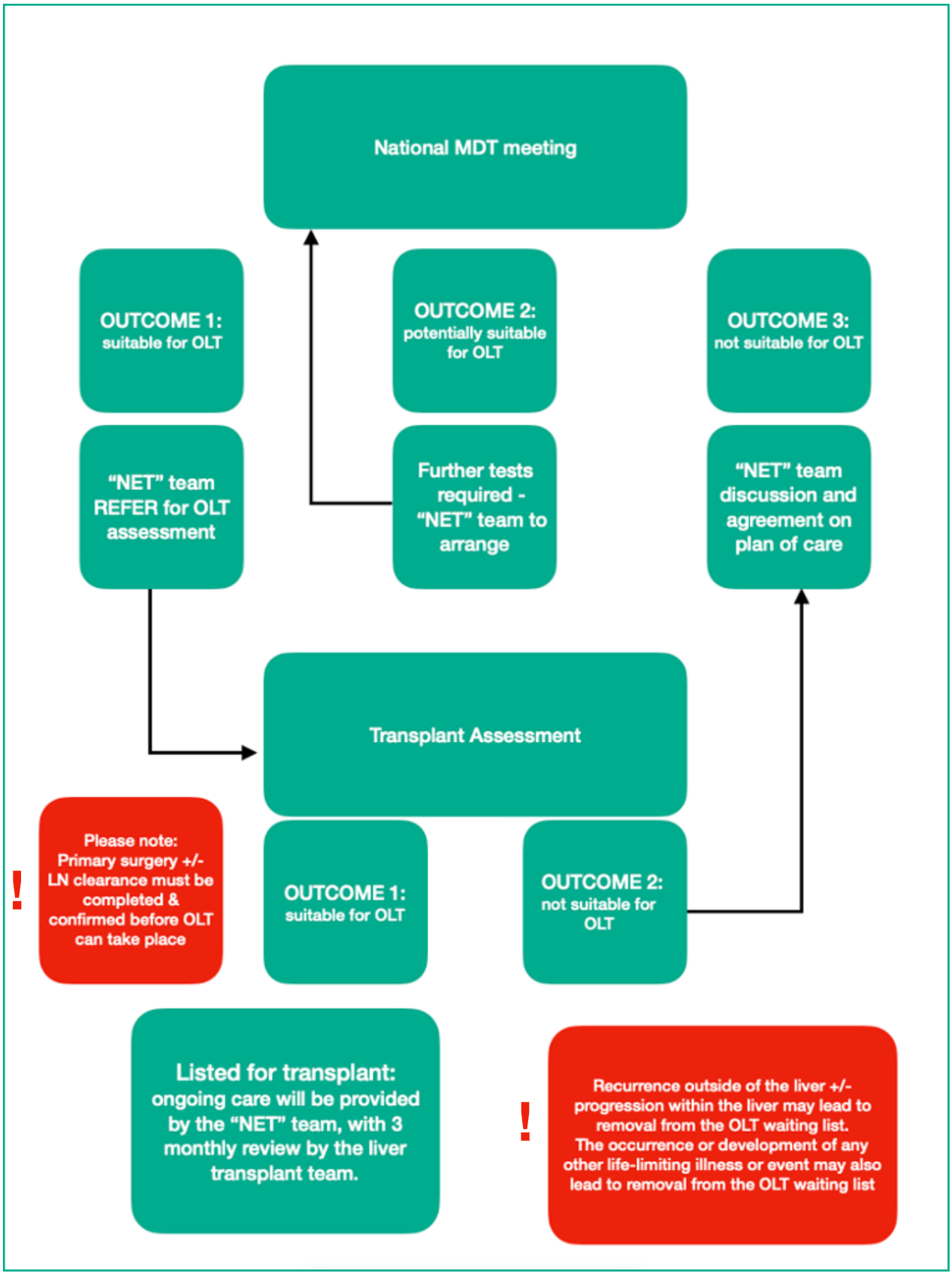
6. **Once listed for liver transplantation:** patients accepted on to the wait list will likely wait 6-12 months for a suitable liver to become available for them. During this time, you will be regularly seen by your "NET" team as well as 3 monthly by your liver transplant team. Your cancer will continue to be actively managed on the waiting list: you may remain on some of your treatments and will have any extra treatments, as needed, to maintain disease stability, and help keep you within transplant criteria.

Removal from the waiting list:

! **Any sign of recurrence outside liver or significant progression within the liver will lead to removal from the transplant waiting list.** !

Any other event that might severely affect survival (such as a heart attack or stroke, development of another cancer, etc.) will also lead to removal from the waiting list.

Process Flow Chart



Waiting List:

As previously mentioned, patients accepted on to the wait list will **likely wait 6-12 months** for a suitable liver to become available for them. During this time you will be seen regularly by both your "NET" team and your liver transplant team: to monitor your health, your cancer and also to ensure you are kept up to date and have the information you may need or want: for example, you may want further information about the medication you will need to keep your new liver healthy and reduce the risk of rejection.

While on the waiting list, you will receive any additional information and support you may need.
A donor liver may become available at any time, day or night and you will need to go to the transplant centre as soon as possible after receiving the call to come in.
It is important that you are prepared to respond to the call - and have arrangements in place to make the journey quickly and safely.

It is also important that you are psychologically (emotionally and mentally) prepared - support, information and counselling is available, through both your "NET" and transplant teams - including your specialist nurse and transplant co-ordinator.

This preparation may include thinking about how you would manage 1 or more 'false starts.'
Even when you are called in for a transplant, there may be reasons why it might not go ahead - which can be incredibly disappointing and emotionally difficult to deal with - even if you completely understand the reason(s) why. We talk about why this might happen in the next section.

While waiting - you may find it useful to speak with others who are also waiting, or those who have had a liver transplant: shared experience(s), learning from others and peer support can help.

Support group information is available through your team(s) and from patient organisations and charities, such as Neuroendocrine Cancer UK (www.neuroendocrinecancer.org.uk) and the British Liver Trust (www.britishlivertrust.org.uk).

Transplant operation and hospital stay:

This is covered in great detail through the patient information booklets and education sessions provided by all transplant centres.

However, it is worth noting that your operation can only go ahead once your surgeon and anaesthetist are satisfied that, when you are called in for surgery, you are well enough to have the operation, and that the donor liver is right for you.
Sometimes, the operation may not be able to go ahead. This may be because:

- Your admission tests show that you have a new health problem - for example you may have an infection. Even if you have no symptoms, this may mean that going ahead with surgery would be too high risk.
- There may be a problem with your donor's health or with the liver itself, that may not have been known when the liver was accepted for you.

If your transplant cannot go ahead, the reasons for this will be talked through with you. This does mean you will need to go home and restart waiting again.

If your transplant can go ahead, you will be prepared for surgery. Your anaesthetist will come and see you before the operation. If you have any questions about the anaesthetic and how you may feel afterwards, this visit is a good opportunity to ask them.

A liver transplant can take up to 12 hours to complete - and you may need to go to the intensive care or high dependency unit, for the first 24-48 hours following surgery.

As you recover, you will then be transferred to the ward, where you may stay for a further 5-14 days, before being discharged home.
During your hospital stay, your transplant co-ordinator, team and nursing staff will go through your medication, answer any questions you may have and agree your discharge date, alongside follow up arrangements.

There is a free and very informative booklet about "Having a Liver Transplant", available to download or order from the British Liver Trust (www.britishlivertrust.org.uk)

Clinical follow-up after liver transplant:

Follow-up by the transplant teams begins quite quickly –but the frequency of appointments starts to slow down as you healthily achieve 3 months, 6 months, and 12 months milestones.
The number of different and/or new medications you may have been started on may also reduce over time, though some medications, especially those to help prevent rejection, will need to be continued long-term.

Your "NET" team will also want to see you and continue to monitor your health and well-being; usually every 3-6 monthly initially.

For the purposes of the pilot programme, throughout your follow-up appointments, your overall health and quality of life will be assessed and monitored. This will allow the programme leads to determine any and all identified benefits or concerns that could affect length of life, quality of life and psychological well-being.

In Summary:

Liver transplantation for cancer is evolving with some Neuroendocrine Cancer patients now being considered for this procedure.
This programme offers new opportunities, not only in determining the feasibility and usefulness of liver transplantation for appropriately selected patients, but also in encouraging further advances, including research, into the understanding and treatment of Neuroendocrine Tumours, with the aim to promote and improve better outcomes for all Neuroendocrine Cancer patients.

Further information and support resources:

British Liver Trust: www.britishlivertrust.org.uk
Helpline: 0800 652 7330 (Monday to Friday - 9:00am to 3:00pm)

Neuroendocrine Cancer UK: www.neuroendocrinecancer.org.uk
Helpline: 0800 434 6476 (Tuesday to Thursday - 10am to 4pm)

NET Patient Network (Ireland): www.netpatientnetwork.ie
Email: help@netpatientnetwork.ie

Neuroendocrine Cancer Centres of Excellence in UK and Ireland is available from the ENETs website: www.enets.org

UK Liver Transplant Centres is available from the Organ Donation and Transplant website: www.odt.nhs.uk
Ireland - National Liver Transplant Centre is at St Vincent's University Hospital in Dublin: www.stvincents.ie

NHS Blood and Transplant liver transplant resources: www.nhsbt.nhs.uk/organ-transplantation/liver

HSE Organ donation and transplant Ireland: www.hse.ie

A Page for your own notes

Acknowledgements

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World Neuroendocrine Cancer Day is held on 10th November each year, events and information shared by Neuroendocrine Cancer UK coordinated by the International Neuroendocrine Cancer Alliance (INCA) https://incalliance.org/

Information on organ donation week - usually September - and other related events can be found on the NHS blood and transplant website: www.organdonation.nhs.uk/get-involved/organ-donation-campaigns/

Organ Donation

Neuroendocrine Cancer UK
Incorporating The Ann Edgar Trust

Neuroendocrine Cancer UK is a UK wide charity solely dedicated to providing support and information to those affected by Neuroendocrine Cancer.

Contact Email: hello@nc-uk.org
Nurse & Peer Support Helpline: 0800 434 6476 (Tuesday-Thursday, 10am - 4pm)
Website: www.neuroendocrinecancer.org.uk