UPMC
STARZL TRANSPLANTATION INSTITUTE
LIVER TRANSPLANT POLICIES AND PROCEDURES

POLICY LT-NET
LIVER TRANSPLANTATION IN PATIENTS WITH METASTATIC NEUROENDOCRINE TUMOR (NET)

PURPOSE

This policy is intended to guide the selection, transplantation, and postoperative follow-up patients with the diagnosis of unresectable neuroendocrine hepatic metastases.

BACKGROUND

Neuroendocrine tumors encompass a range of heterogenous neoplasms that comprises about 2% of all GI tract malignancies. Most of these neuroendocrine tumors are metastatic at the time of diagnosis. The liver is the most common site of metastasis. Surgical resection is usually not an option due to the high incidence of bilobar disease. Prior to presentation to the transplant center, most patients with hepatic metastasis have already undergone multiple procedures, such as chemoembolization, to attempt local-regional control. In selected patients, liver transplantation may be an option, where 5-year patient survival is approaching 90%. Many of these patients, however, develop recurrent disease. For this reason, careful patient selection pretransplant and close follow-up post-transplant are important for good outcomes and long-term patient survival.

GUIDELINES FOR MELD EXCEPTIONS

The UNOS Liver Committee released guidelines for liver transplantation in patients with metastatic neuroendocrine tumors. These are guidelines for to direct the Regional Review Boards in the granting of MELD exception for patients without a potential living donor. “Guidelines for NET were developed following a review of the literature. Candidates with NET are expected to have a low risk of waiting list drop-out. Initial recommendations included age less than 60. Older patients with a lot of disease burden may be referred to transplant as a last resort, leading to poor outcomes, while data presented at the AASLD show that very young patients with NET and early-stage disease do well. Committee members felt that these initial guidelines could include strict criteria that could be liberalized based upon the experience of the RRBs.

- Transplant Programs should also be aware of these criteria when submitting exceptions for NET. RRBs should consider the following criteria when reviewing exception applications for candidates with NET.
  1.) Recipient age <60 years

2.) Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence at least six months prior to MELD exception request.
3.) Liver-limited Neuroendocrine Liver Metastasis (NLM), Bi-lobar, not amenable to resection. Tumors in the liver should meet the following radiographic characteristics:
    - CT Scan: Triple phase contrast
        i. Lesions may be seen on only one of the three phases
        ii. Arterial phase: may demonstrate a strong enhancement
        iii. Large lesions can become necrotic/calcified
    - MRI Appearance:
        i. Liver metastasis are hypodense on T1 and hypervascular in T2 wave images
        ii. Diffusion restriction
        iii. Majority of lesions are hypervascular on arterial phase with wash –out during portal venous phase
        iv. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense lesions are characteristics of NET
4.) Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin tumors with portal system drainage. Note: Neuroendocrine tumors whose primary is located in the lower rectum, esophagus, lung, adrenal gland and thyroid are not candidates for automatic MELD exception.
5.) Lower - intermediate grade following the WHO classification. Only well differentiated (Low grade, G1, Ki-67<2%) and moderately differentiated (intermediate grade G2, Ki-67 3-20%). Mitotic rate <20 per 10 HPF with less than 20% ki-67 positive markers.
6.) Lower - intermediate grade following the WHO classification. Only well differentiated (Low grade, G1, Ki-67<2%) and moderately differentiated (intermediate grade G2, Ki-67 3-20%). Mitotic rate <20 per 10 HPF with less than 20% ki-67 positive markers.
7.) Negative metastatic workup should include one of the following:
    - Positron emission tomography (PET scan)
    - Somatostatin receptor scintigraphy
    - Gallium-68 (68Ga) labeled somatostatin analogue 1,4,7,10-tetraazacyclododedcane N, N', N",N'"-tetraacetic acid (DOTA)-D-Phe1-Try3–octreotide (DOTATOC), or other scintigraphy to rule out extra-hepatic disease, especially bone metastasis.

Note: Exploratory laparotomy and or laparoscopy is not required prior to MELD exception request.

8.) No evidence for extra-hepatic tumor recurrence based on metastatic radiologic workup at least 3 months prior to MELD exception request (submit date).
9.) Recheck metastatic workup every 3 months for MELD exception increase consideration by the Regional Review Board. Occurrence of extra-hepatic progression – for instance lymph-nodal Ga68 positive locations – should indicate de-listing. Patients may come back to the list if any extra-hepatic disease is zeroed and remained so for at least 6 months.
10.) Presence of extra-hepatic solid organ metastases (i.e. lungs, bones) should be a permanent exclusion criterion”

CONSIDERATIONS SPECIFIC TO CANDIDACY AT UPMC

1.) Patients with extrahepatic disease (this should not include those with enlarged/involved hilar lymph nodes) will be excluded, unless the patient has had stable extrahepatic disease for greater than one year and is expected to be able to continue suppressive therapy (eg., Octreotide, Lutathera) post-transplant. **Note that in these cases, the patient will not be eligible for UNOS MELD exception points.

2.) Patients with non-GI NET will be excluded.

3.) Patients with poorly differentiated tumors (ki-67>20%, mitotic rate >20) will be excluded.

4.) Primary tumor should be resected prior to transplant if possible, or at time of transplant.

FOLLOW-UP AFTER TRANSPLANTATION

- Cross-sectional imaging (Contrast CT or MRI of abd/pelvis) at 6 months, 1 year, and then annually until year 5
- Non-contrast CT chest at 6 months, 1 year, and then annually until year 5
- Chromogranin A should be measured every 3 months for first year then every 6 months until year 5. Other tumor markers should be ordered on the same schedule if elevated prior to transplant.
- PET, NETSPOT, or Octreotide scan annually until year 5.

POST-TRANSPLANT RECURRENCE

Any post-transplant recurrence identified will be presented to UPMC's multidisciplinary Hepatobiliary Tumor Board for review and development of a treatment plan. Treatment options include:

- Chemotherapy
- Locoregional therapy (TACE or RFA)
- Surgical resection
- Radionuclide-targeted therapy with, e.g., lutetium-117-DOTA-octreotate

IMMUNOSUPPRESSION AFTER TRANSPLANT

Efforts should be made to switch to mTOR inhibitor (Everolimus) early post-transplant as literature suggests mTOR inhibitors may have some action against these tumors.

REFERENCES

UNOS Liver Committee Guidelines for Liver Transplantation in Patients with Metastatic Neuroendocrine Tumors.

Rossi RE, et al. Liver Transplantation for UnresecStable Neuroendocrine Tumor Liver Metastases. Ann Surg Onc, 2014, 21(7), 2398–2405.S