Review Article (Pancreatic Neuroendocrine Tumors)

# Liver transplantation in the treatment of unresectable hepatic metastasis from neuroendocrine tumors

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**Abstract:** Neuroendocrine tumors (NET) are rare neoplasms with generally indolent growth behavior. The liver is the most common site of NET metastasis. The NET metastatic spread to the liver are usually multiple tumors involving bilateral hemilivers. For patients with isolated NET metastasis to the liver, a complete extirpation (R0) resection of both the primary NET and liver metastasis provide the best chance of tumor recurrence-free patient survival. Orthotopic liver transplantation (OLT) presents a viable treatment option for patients with unresectable liver metastasis from NET. Post-OLT outcomes for the patients of NET with liver metastasis (5-year overall survival rate 47–71%) are comparable to those for other indications. However, the high rate of recurrence after OLT (31–57%) remains a clinical obstacle. As such, it is imperative to consider each patient individually and identify prognostic factors that would impact post-OLT outcomes. This article focuses on the role of OLT in the definitive treatment of metastatic liver NET, review patient selection criteria predictive of survival outcomes and post-OLT outcomes for patients.

**Keywords:** Neuroendocrine tumor (NET); liver metastasis; liver transplantation

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## Introduction

Neuroendocrine tumors (NET) are rare neoplasms with generally indolent tumor growth behavior. As such, the initial clinical presentation varies from an asymptomatic incidental diagnosis to an extensive metastatic disease with refractory carcinoid syndrome (1). Among the primary NET, the order of frequency is the small intestine (45%), pancreas (42%), colon (40%), stomach (15%), rectum (6%) and appendix (3%) (2). Compared to NET from other gastrointestinal (3–45%) or lung (28%) origins, pancreatic NET (PNET) shows a high rate of distant metastasis at the time of diagnosis (42–64%) (2,3).

The NET liver metastases may occur from a primary NET of the foregut, midgut and hindgut and generally spread to the liver via the portal venous system. These NET metastatic spread to the liver are usually multiple tumors involving bilateral hemilivers. The common sites of NET metastasis are the liver (40–93%), bone (12–20%) and lung (8–10%) (4). For patients with unresectable liver metastasis from NET without any other organ involvement, orthotopic liver transplantation (OLT) presents a viable treatment option and has been reported to provide survival benefits (2,5-7). This article focuses on the role of OLT in the definitive treatment of metastatic liver NET, review patient selection criteria predictive of survival outcomes and post-OLT outcomes for patients.

## OLT for oncologic indications

There are two oncologic indications for OLT: primary hepatic malignancy and hepatic metastasis. While a

 

**Table 1** WHO grading system for pancreatic neuroendocrine neoplasms

| Grade | Mitotic count per 10 HPF* | Ki-67 index** |
|---|---|---|
| G1 | <2 | <3% |
| G2 | 2–20 | 3–20% |
| G3 | >20 | >20% |

*, high power field at 40× magnification; **, % of 500–2,000 tumor cells in areas of highest nuclear labeling using MIB1 antibody. When two criteria do not agree each other, the highest grade is applied. HPF, high power field.

total hepatectomy with regional lymphadenectomy followed by OLT would theoretically provide the best oncologic extirpation of hepatobiliary malignancy, there are at least two major issues that limit its widespread acceptance and application as the first line of treatment. It is important to weigh the risks and benefits of OLT in terms of patient survival outcomes, the need for life-long immunosuppression and risk of disease recurrence in immunocompromised patients. The ongoing donor organ shortage places the patients at risk for tumor progression while on the transplant waiting list. Furthermore, the transplantation community has adopted a threshold of 5-year post-OLT survival rate of at least 50% in order to justify the utilization of scarce organs.

Hepatocellular carcinoma (HCC) is the most prevalent primary hepatic malignancy, representing 30% of indications of OLT in the United States (U.S.) (8). While OLT for HCC (under various criteria) has achieved 5-year tumor recurrence-free survival rates (65–81%) that are comparable to those for general indications for end stage liver disease (71–81%), the outcomes for metastatic colorectal cancer have been discouraging (12–37%) (9-14). As such, OLT for colorectal cancer liver metastasis is currently only considered in a setting of clinical trials (15). In contrast, OLT is an accepted definitive treatment for patients with unresectable liver metastasis from NET tumors as long as the primary NET has been resected and in the absence of another organ metastasis. Despite metastatic spread to the liver, NET exhibit different tumor biology and behavior compared to gastrointestinal and pancreatic adenocarcinomas: NET typically show specific protracted clinical presentation and course; approximately half of the NET produce hormones and/or amines, which are responsible for the specific clinical signs and symptoms as well as serve as tumor markers; and sensitivity of some NET to specific blocking agents resulting in tumor growth inhibition and symptom relief (2,16-20).

Compared to the total number of OLT performed in the U.S. and Europe, OLT for NET only constitute 0.2–0.3% of the total OLTs (2). According to a recent systematic review, OLT provided a 5-year overall survival rate between 47% and 71% and a 5-year disease-free survival rate between 20% and 32% (7). While the outcomes of OLT in metastatic NET have been better than those in colorectal cancer liver metastasis, the long-term tumor recurrence-free survival outcomes remain inferior to that of HCC. As such, it is imperative to consider each patient individually and identify prognostic factors that would impact post-OLT outcomes.

## Prognostic factors

### *Histologic grade*

The World Health Organization (WHO) grading system subdivided well-differentiated NET into G1 and G2 tumors based on the mitotic and proliferative (e.g., Ki-67) index, and G3 (e.g., mitotic count >20/HPF or Ki-67 index >20%) indicates a poorly differentiated NET (*Table 1*) (21). The Ki-67 index over 10% to 20% has been considered as a poor prognosis marker, and it has been reported that PNET is often involved with Ki-67 index over 15% (19,22-24). The largest registry database regarding the outcome of OLT for NET is available from the European Liver Transplant Registry (ELTR) study (n=213). According to the ELTR study, the 5-year overall survival rates after OLT for well and poorly differentiated NET were 55% and 27%, respectively (5). The histologic grade can be different between primary and metastatic tumors in the liver, and treatment is guided by the worst grade in the available specimen. It is widely accepted that OLT should be reserved only for G1 and G2 NET (4,25).

### *Hepatic tumor burden*

European studies suggested that the amount of hepatic tumor involvement is an important prognostic factor (4,5,7). The degree of hepatic tumor burden has been expressed in various terms, such as “hepatomegaly”, “tumor bulk”, or “estimated tumoral invasion”. The presence of hepatomegaly has been presumed a surrogate for extensive metastatic disease within the liver, and it was an independent predictor of poor outcome (5).

A functional liver parenchyma involvement of 50% was arbitrarily suggested as a cut-off in considering transplantation (4). According to the ELTR study, the

 

5-year overall survival rate after OLT for NET was 42% when the estimated tumoral invasion was over 50%, while it was 61% for tumors under 50% (5). However, when the hepatic lesions are numerous, the estimation becomes subjective and may not represent a strict factor for listing policy. In addition, not all agree that hepatic tumor burden is an important prognostic factor. Interestingly, a Norwegian single-center experience (n=15) demonstrated that a 90% 5-year overall survival rate could be achieved when all patients involved in this study had hepatic tumor involvement over 50% (24).

### *Primary tumor factors*

#### Non-portal drainage of the primary tumor

The Milan group suggested that only liver metastasis from NET with portal venous drainage should be considered for OLT based on the assumption that the liver may be the only hematogenous colonization of the primary tumors for those cases (4). However, data from the ELTR study do not strongly support the idea. Among the patients in the study, 16 underwent pulmonary lobectomy before OLT for bronchial tree origin NET, and their 5-year overall survival rate (53%) was comparable to NET originating from the small bowel (62%), large bowel (40%), and duodenum/pancreas (44%) (5). The site of metastases is not only determined by the mechanical lodgment of cancer cells, but also by the effect of the microenvironment of an organ and dissemination through clinically undetectable micrometastases (26). The effect of venous drainage of the primary tumor on the outcome of OLT in NET requires further validation.

#### Surgical control of the primary tumor

In general, it is recommended that the primary tumor be resected before OLT to monitor the biologic response of the liver metastasis (waiting time, see below) and to avoid surgical complications from conducting two major surgeries at the same time. Primary NET was reported to be resected before OLT in the majority (74–78%) of cases (5,7). The ELTR study showed that the outcome is inferior when primary tumors were resected during OLT compared to those cases in which the primary tumors were resected before OLT (5-year overall survival rate of 22% and 56%, respectively). Of note, nine cases in which primary tumors were resected after OLT showed a 5-year overall survival rate of 75%. Simultaneous primary tumor resection and OLT showed significantly inferior results due to the poor oncologic control or higher risk of extensive surgeries (e.g., combined Whipple and OLT). In the case of a primary tumor that is identified but that cannot be resected until the time of OLT, it is unclear whether it is safe to defer the primary tumor resection until after OLT due to the limited available data.

In 13–14% of cases of NET with liver metastasis, the primary tumor is unidentifiable (3,5). A possible indistinguishable scenario is primary hepatic NET with multiple intrahepatic metastases. In the ELTR study reported a 5-year overall survival rate of 54% after OLT in 17 patients in which the primary tumor was never identified and thus, never resected (5). As such, this report suggests that OLT remains a viable treatment option even in those patients without an identifiable primary NET tumor.

### *Extrahepatic disease*

#### Locally advanced tumors

Total hepatectomy during OLT may not completely remove the tumor burden (e.g., R1 or R2); 5-year survival rates following OLT with positive margins were significantly inferior to those with R0 margins (15% and 56%, respectively). As such, "palliative" OLT with an R2 margin is not recommended (27). Locally advanced tumors, especially in PNET, can also be resected through upper abdominal exenteration at the time of OLT with or without multivisceral transplantation. The median survival of ten patients who underwent upper abdominal exenteration in the ELTR report was only 6 months (5). In a Swedish report, among the five patients who underwent multivisceral transplantation, three patients died and one patient survived 66 months with recurrent disease and the other patient showed no evidence of disease at 12 months after transplantation (24). Based on currently available data, the aggressive approach has been associated with poor outcomes with few exceptions.

#### Extrahepatic metastases

In the case of NET with liver metastasis, evidence of extrahepatic spread precludes transplantation. As NET express somatostatin receptors in 60–100% of cases, functional imaging such as positron emission tomography/computerized tomography (PET/CT) is the main diagnostic tool to identify the presence metastatic disease. It is recommended to utilize PET/CT to rule out extrahepatic metastases, in the bone and lymph nodes in particular (2,7). In PNET, regional lymph nodes of the pancreas are

 

presumed resected at the time of primary tumor resection, while para-aortic, retroperitoneal, retrocrural, and mesenteric lymph nodes are considered signs of metastatic disease (21).

The detection of distant metastasis relies on the sensitivity of functional imaging. Indium-111 octreotide scintigraphy has a lower sensitivity (69–86%), and gallium-68 labelled somatostatin analogues (DOTATOC, DOTATATE, or DOTANOC) showed improved sensitivity (85–96%) in identifying extrahepatic metastases, especially in low grade NET. In the detection of intermediate and high-grade NET, 18F-FDG PET showed higher sensitivity than somatostatin receptor scintigraphy (92% versus 69%, respectively) (2). Furthermore, high uptake in 18F-FDG PET was reported to be associated with an increased risk of disease progression in low grade NET. As such, gallium-68 somatostatin receptor imaging and 18F-FDG PET can be complementary in the assessment of NET with liver metastasis (28).

Somatostatin receptor imaging can also be used to assess the utility of radionuclide therapy with $^{90}$Y or $^{177}$Lu, known as peptide-receptor radionuclide therapy (PRRT) (2). It has been reported that neoadjuvant PRRT decreased the incidence of nodal metastases in pancreas resections for PNET (29). A few cases have been reported in which downstaging for NET with multiple bone metastases could be achieved through PRRT, which would enable hepatectomy for liver metastasis with curative intent (30-32). PRRT was recently approved by the U.S. Food and Drug Administration (FDA), and the role of PRRT in "downstaging" metastatic NET to be eligible for OLT remains to be investigated.

### *Waiting time*

According to an analysis of the Organ Procurement and Transplantation Network /United Network for Organ Sharing (OPTN/UNOS) database, patient survival was inferior when the waiting time was too short (less than 2 months), especially in elderly patients (33). It is difficult to interpret the results, as the time point of listing may vary anywhere after primary tumor resection. The poor outcomes of cases with a short wait time may be partly due to the frail physical conditions of the patients and the insufficient recovery time following the major surgery for the primary tumor. In addition, the waiting time may provide an opportunity to monitor the biologic behavior of NET after resection of the primary tumor. Two months may be too short for this purpose, and other authors recommend arbitrarily choosing 6 months as a wait time to observe the tumor's behavior with possible extrahepatic recurrences (4,34). In contrast, the interval between the diagnosis and OLT was not identified as a prognostic factor in the ELTR study, and the authors suggested that OLT could be postponed, regardless of the wait time length, until patients become refractory to other treatment (5). The "appropriate" timing of OLT remains debatable.

### *Recipient age*

The mean age of NET patients in general is 62±15 years according to the Surveillance, Epidemiology, and End Results (SEER) registries data (3). The reported mean recipient age of patients who underwent OLT for NET is younger, and it ranges from 45 to 49 years (7). The SEER report included patients at all stages of disease, namely, localized, regional, and distant metastasis, and when the authors divided the patients into three groups based on age at diagnosis (30 or less, 31 to 60, and over 60 years), age was a strong predictor of survival duration.

The effect of age on survival outcomes has also been investigated in the setting of OLT for NET. A systematic review in Europe (n=103) identified an age greater than 50 years and combined upper abdominal exenteration or Whipple's operation as two independent adverse prognostic factors (35). However, more recent OPTN/UNOS and ELTR data did not concur that recipient age is a prognostic factor when 55 and 50 years were used as cutoff ages, respectively (5,33). In the ELTR study, when a separate multivariate analysis was performed on data after the year 2000, an age over 45 years, hepatomegaly, and resection in addition to OLT were independently significant adverse prognostic factors (5). At present, there is no consensus regarding the significance and most reasonable cut-off age for OLT.

## Patient selection criteria for OLT

The patient selection criteria for OLT in the treatment of unresectable hepatic metastasis from NET should be based on the patient's survival benefits as well as stewardship of scarce organs. While simultaneously achieving these two goals is clearly defined, the patient selection criteria remain vague due to multiplicity of factors that may impact post-OLT outcomes and organ availability. Several groups have proposed their patient selection criteria.

 

**Table 2** Milan-NET selection criteria (2007, revised in 2016)

| |
|---|
| Absolute |
| Histologic grade G1 or G2 |
| Portal drainage of the primary tumor |
| Pre-transplant curative resection of all extrahepatic lesions |
| Hepatic tumor invasion under 50% |
| Duration of stable disease over 6 months |
| Relative |
| Age under 60 years |

NET, neuroendocrine tumors.

**Table 3** Summary of UNOS guidelines for LT in NET

| |
|---|
| Common criteria with Milan-NET |
| Histologic grade of G1 or G2 |
| Gastro-entero-pancreatic origin tumors with portal system drainage |
| Resection of primary and extra-hepatic disease without recurrence >6 months |
| Tumor replacement <50% of the liver volume |
| Recipient age <60 years |
| Additional criteria |
| Unresectable liver metastasis |
| Radiographic characteristics of NET of the liver lesions |
| Negative metastatic workup by PET scan |
| Lack of extrahepatic tumor recurrence during the past 3 months |
| In the presence of positive findings for lymph node metastases by PET scan, the finding should become negative for 6 months before re-listing |
| In the presence of extrahepatic solid organ metastases (i.e., lungs or bones), the case will be permanently delisted |

NET, neuroendocrine tumors; PET, positron emission tomography.

The group from Milan reported a 5-year overall and disease-free survival rates of 97% and 89%, respectively, with their patient selection criteria (*Table 2*) (4,6). However, among the 280 NET patients referred for OLT, only 88 patients (31%) were waitlisted for OLT while 42 patients (15%) underwent OLT (6). In another report, a subgroup analysis of the ELTR study for patients who underwent OLT (n=106) demonstrated a 5-year overall survival rate was 59%. When the Milan criteria were retrospectively applied, the calculated survival rate increased to 79% at a cost of excluding 64% of patients to OLT. While this study suggests expanding the Milan criteria, a G3 histologic grade is considered a contraindication for OLT (5). In the U.S., the current OPTN/UNOS guidelines regarding OLT for NET with liver metastasis are mainly based on the Milan-NET criteria (36) (*Table 3*).

While there is no currently widely accepted patient selection criteria or policy for OLT for hepatic NET metastasis, it would be prudent to adopt criteria that are not "too" restrictive that would potentially deny the patient's access to a definitive treatment. This is important to consider as several of the proposed criteria were based on prognostic factors that have yet to be validated. In fact, the European-African Hepato-Pancreato-Biliary Association (E-AHPBA) working group on neuroendocrine liver metastases recommended further validation of a variety of criteria including patient age, primary resection before transplantation, hepatic tumor burden, and wait time for disease stabilization (2).

## Outcomes of PNET with liver metastasis

The pancreas is the most common site of the primary tumor among the cases of OLT for metastatic NET (44–53%) (5,7,37). As such, pancreatic resection was the most common surgical procedure for the primary tumor (47%) in the ELTR data [most commonly distal pancreatectomy (64%) followed by the Whipple procedure (28%)] (5). The 5-year overall survival rates after OLT for PNET with liver metastasis have been reported to be between 44% and 53%. PNET has been associated with a high incidence of metastasis (42–64%) and the presence of distance metastasis in PNET significantly affects the outcome (2,3). The 5- and 10-year survival rates of localized PNET were 79% and 58%, while those of distant metastasis were 27% and 11%, respectively (2). The survival outcomes of PNET with liver metastasis are comparably lower than those of OLT in NET with liver metastasis in general, but higher than the historical outcome of non-transplant management for PNET with liver metastasis (5,37).

Approximately 10–40% of PNET are functional tumors (18). Insulinoma is the most common functional form of PNET, but it is rarely (<10%) malignant. Zollinger-Ellison syndrome, VIPoma, or glucagonoma, as well as other rare types of functional PNET, may produce hormonal syndrome as well. Although specific data are

 

unavailable, the hormonal symptom was the indication for OLT in 37% of cases in the ELTR study, and the 5-year overall survival rate of those patients was 57% (5). As such, OLT for control hormonal symptoms may be considered as long as liver lesions are unresectable and the patient meets the oncologic criteria.

## Neoadjuvant or adjuvant therapy: uncharted territory

The high rate of recurrence after OLT for NET (31–57%) remains a clinical obstacle (7). Neoadjuvant or adjuvant therapy could have been considered in OLT for NET metastasis in an effort to reduce the incidence of recurrence. However, available data are scarce. In European studies, 74% to 82% of OLT patients for NET underwent chemotherapy or hormonal therapy before OLT, but no further data to support their role are available (5,7). Most data available are from experience in a non-transplant setting. In a multivariate retrospective study, adjuvant chemotherapy using streptozotocin and 5-fluorouracil for patients who underwent liver resection for metastatic NET did not affect disease-free survival (38). An investigation into the role of neoadjuvant PRRT has also begun in a non-transplant setting to increase the resectability of primary NET (31). A few case reports are also available showing that PRRT was used to make PNET with liver metastasis curatively resectable (39,40).

Targeted therapies using everolimus (5 mg daily) or sunitinib (37.5 mg daily) have been used mostly for G1 or G2 PNET in a palliative setting to improve progression-free survival (2,41,42). Importantly, everolimus has been used as a part of maintenance immunosuppression after OLT, and it is approved by the FDA for the treatment of locally advanced, unresectable, or metastatic PNET (43). Calcineurin inhibitor (i.e., tacrolimus or cyclosporine)-based immunosuppression has been mainly applied in OLT for NET in the literature, and the mammalian target of rapamycin (mTOR) inhibitors (i.e., everolimus or sirolimus) have not been utilized empirically as primary immunosuppressant drugs to prevent recurrence after OLT (6,7).

## Conclusions

For patients with unresectable liver metastasis from NET tumors without any other organ involvement, OLT presents a viable treatment option and provides acceptable long-term patient survival benefits. At present, favorable outcomes of OLT for NET and PNET can be achieved by meticulous risk-stratification of the tumor biology of the primary NET, burden of the liver metastatic disease, feasibility of a R0 resection, patient's physiologic status, and anticipated waiting time for OLT. The advances in genetic and epigenetic sciences may guide the application of novel approaches, such as neoadjuvant PRRT, the selection of immunosuppression, or adjuvant targeted chemotherapy.

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