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Authors:
Andrea Boscà Robledo, Eva María Montalvá Orón, Rafael López-Andújar

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Liver transplantation for neuroendocrine tumor metastases

Andrea Boscà Robledo, Eva M. Montalvá Orón, Rafael López Andújar

Hepato-Biliary-Pancreatic and Liver Transplantation Surgery Unit. Hospital Universitari i Politècnic La Fe. Valencia, Spain

Correspondence:

Andrea Boscà Robledo

bosca.robledo@gmail.com

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Neuroendocrine tumors (NETs) are a heterogeneous group of rare neoplasms that arise from neuroendocrine cells present in the gastrointestinal tract, pancreas, and lung (1). Most are asymptomatic and slow-growing, which means they are often diagnosed at advanced stages. The most common site of metastasis for gastroenteropancreatic NETs is the liver, accounting for more than 77 % of cases, followed by bones and lung (2,3). Eighty percent of tumors show abundant expression of somatostatin receptors, although less than half can secrete bioactive substances (2). The management of liver metastases from NETs requires a multidisciplinary approach and should be based on tumor grade, somatostatin receptor expression, and intrahepatic spread. These data will determine their biological behavior and define the most appropriate treatment (4).

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Treatment options include somatostatin analogs, locoregional treatments (ablation, chemoembolization, radioembolization), peptide receptor radionuclide therapy (PRRT), conventional chemotherapy, kinase inhibitors, and surgical resection (5). Sometimes, several modalities can be combined to control and cure the disease.

Initially, when resectable liver disease is present, the treatment of choice is surgical resection with curative intent in well- or moderately-differentiated cases (G1-G2) (6,7). However, recurrence is common, reaching 70-90 % during the first two years. The reason for these results is probably because liver disease is underestimated preoperatively (7), leading to early liver recurrence (8,9).

However, most patients have unresectable liver lesions at diagnosis, with this percentage reaching up to 80 % of cases (10,11). These patients would only be candidates for palliative treatment with systemic therapies or locoregional treatments in order to try to improve their quality of life and control the progression of the disease. It is in this group of patients and in very select cases (1 %) that liver transplantation has a potentially curative role (3,12).

CANDIDATE SELECTION

Pre-transplant imaging is crucial for selecting candidates. Liver lesions must meet typical NET characteristics on multiphase multislice computed tomography (CT) and magnetic resonance imaging (MRI) with hepatobiliary phase (13). In addition, to locate other possible metastatic foci before transplantation, a ^{68}Ga-DOTATE PET scan should be performed, as its specificity reaches 98 % for ruling out extrahepatic disease, especially bone lesions. It is more effective and diagnostically safer than ^{111}In pentetreotide (Octreoscan®) scintigraphy, which is the classic scan for these tumors (14,15).

Since Mazzaferro published the first Milan criteria in 2007 (16), modifications have been made as a result of a better understanding of the peculiarities of these tumors, such as the ENETS (European Neuroendocrine Tumor Society) criteria in 2012 (3) and the United Network for Organ Sharing (UNOS) criteria (13).

The main objective of liver transplantation is to prolong overall survival and disease-free survival compared to systemic treatments. The selection criteria currently accepted by most groups are (3,13):

- *Characteristics of the primary tumor:* it must originate in the gastroenteropancreatic tract and drain via the portal vein. Primary tumors located in the lower rectum, esophagus, lung, adrenal gland, thyroid gland, or of unknown origin are not recommended. Surgery on the primary tumor must be performed before transplantation and must be a radical surgical resection with clear margins (R0) and standard lymphadenectomy. In order to evaluate the transplant, the pathological study of the specimen must include the degree of tumor differentiation (G1 or G2), the percentage of ki67 (< 10 %, some centers accept up to 20 %), and the mitotic index must be < 20 per high-power field (HPF) (3,13).
- *Extent of liver involvement:* lesions must be unresectable and occupy less than 50 % of the total volume of the liver parenchyma or less than 75 % in patients with refractory hormonal symptoms (3,16).
- *Disease stability/response to therapies:* disease stability must be achieved for at least 6 months prior to transplantation (3,11,16,17). This minimum waiting period has lower post-transplant recurrence rates, and compliance with it favors more favorable tumor biology (18). The behavior of the disease in the first few months determines whether it is a slow or fast-progressing disease, which will influence the results. Cases accepted for transplantation should be included on waiting lists as exceptions to MELD. Once included, updates must be made every 3 months and, in the event of liver progression, treatment can be given, waiting another 6 months for stability. Lymph node metastases that have been treated and are negative in functional studies could be included again, waiting 6 months without progression. Metastases in other solid organs are definitive exclusion criteria, even if they have been treated or resected (3,13).
- *Age:* although early publications recommended an age below 55, this is now considered a relative criterion and it has been proposed to raise the age to

60 (12,19).

RESULTS

Given that these are rare and slowly progressive neoplasms, there are no randomized clinical trials in the literature comparing medical treatments with surgical treatments. Although systemic treatments have been shown to improve progression-free survival (PFS), their administration has not been shown to confer any benefit in terms of overall survival (OS) (20-22).

With regard to publications on liver transplantation, studies show benefits in both OS and DFS in favor of transplantation in highly selected patients. One of the first large retrospective series based on the European Liver Transplant Registry reported an OS of 52 % and disease-free survival (DFS) of 30 % at 5 years according to different prognostic factors (23). However, it specified that less than half of its transplant recipients met the Milan criteria; analysis of this subgroup achieved an OS of 79 % and DFS of 57 % at 5 years (23).

The series published by Mazzafero a few years later, using the Milan criteria defined by his group, prospectively compared two groups of patients who were candidates for transplantation, with striking 5-year OS results of 97.2 % in those who underwent transplantation versus 50.9 % in those treated with systemic therapies, and SLE of 86.9 % compared to 16.5 % at 5 years (11). Although the transplant group was younger, had smaller tumors, and had received more locoregional treatments prior to transplantation, the trend in results was very striking in favor of transplantation. In addition, the magnitude of the benefit of transplantation, calculated as the difference in survival over the years between the two groups, increased over time and peaked after 10 years (11).

It should not be forgotten that surgical risk must be assessed in patients who are candidates for transplantation, since morbidity and mortality are high in the first few months and the initial risk assumed is higher than with systemic therapies, which ultimately has a negative impact on overall survival data (11).

As for the analysis of post-transplant recurrences, there is also no comparative evidence between treatments, and only descriptive series exist, the longest being that of Sposito et al., with OS figures after post-transplant recurrence of 76.3 % and 45.5 % at 5 and 10 years (24). The most striking finding in this study was that the time between liver transplantation and recurrence had a significant impact on OS, which was 89.5 % at 5 years if recurrence was diagnosed more than 2 years after transplantation, compared with 0 % for recurrences within 2 years after transplantation. Furthermore, in selected cases with resectable recurrences, the authors advocated attempting surgical rescue, especially if they were late (24).

POST-TRANSPLANT MANAGEMENT AND FOLLOW-UP

There are no clinical guidelines on the management of transplant recipients with liver metastases from NETs that address the issue of which immunosuppressive drugs should be used. Nor has it been demonstrated that monitoring with chromogranin is useful for predicting recurrence, nor do its values appear to indicate prognosis, although other markers such as 5-hydroxyindoleacetic acid in urine or other hormones may be useful if the original tumor was functioning (24). The imaging studies that can provide the most information for follow-up are ^{68}Ga-DOTATE PET and Octreoscan® (14,15).

FUTURE

The role that certain treatments such as PRRT or radioembolization may play in the future, used as bridge therapy prior to transplantation, could potentially benefit some candidates, but this remains unanswered, although there are already promising series describing PRRT as neoadjuvant therapy in locally advanced tumors (12,25).

For all these reasons, the potentially curative option of liver transplantation in this subgroup of patients should not be overlooked, and there is evidence of the benefit of referring cases to transplant centers with experience in this indication and multidisciplinary teams with expertise in the management of NETs.

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