Liver Transplantation for Metastatic Neuroendocrine Tumors

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Dear Editor:

We have thoroughly read the article "Liver Transplant for Metastatic Neuroendocrine Tumors: A Single-Center Report of 15 Cases" by Moradi and colleagues, which was published in *Experimental and Clinical Transplantation*.[1] We would like to congratulate the authors for their success in liver transplant (LT) due to metastatic neuroendocrine tumors (NETs) and their important contribution to the scientific community.

The authors reported 8 LTs, 4 multivisceral transplants, 1 LT associated with a Whipple procedure, 1 liver and pancreas transplant, and 1 LT combined with ileal resection. The inclusion criteria mentioned in the article were nonresectable well-differentiated NETs with confined liver metastases of unknown origin and resectable or resected primary tumor. During the follow-up, all patients who had received multiorgan transplants died and the 8 patients who underwent LT had remained alive and disease free.

Nevertheless, there are different aspects to be considered for discussion. Although the authors mentioned the inclusion criteria, it is not explained which parameters were taken into account to enlist patients as transplant candidates; in addition, not having the primary tumor resected was not considered as a contraindication. Another topic we would like to discuss are the pathological criteria that were considered as contraindications for multivisceral and LT.

The simultaneous resection of the primary tumor and LT has been carefully evaluated by Le Treut and colleagues.[2] They reported 213 LTs for metastatic NETs and stated that primary site tumor resection concurrent with LT was a predictor of poor outcome. Determining the origin of the primary tumor is mandatory before deciding which therapeutic option to proceed with because the primary site of NETs has also been described as a factor associated with outcomes. Some authors have stated that tumors located in the pancreas seem to be more aggressive than those of intestinal origin.[5] In the study from Moradi and colleagues, most transplant recipients had a pancreatic NET, although 6 transplants were performed in patients with primary tumor with unknown origin. The manuscript did not report any information regarding the functional status of the tumors, if patients had received somatostatin analogs as part of the pretransplant management, and if there were any priority criteria for patients on the wait list. These issues must be considered since outcomes can be different for isolated liver transplants compared with multiorgan transplants. We suggest that the authors revise the indications using more selective protocols.

In our center, we have established a very restricted protocol for NETs, using as reference the criteria proposed by Mazzaferro and colleagues[6]: Ki-67 of 0% to 5%, well-differentiated or moderately differentiated tumor (grade 1 or grade 2), disease confined to the liver, primary tumor resected with stable disease for at least 6 months, and, if possible, location of primary tumor limited to the small bowel. As advised by Gedaly and colleagues, patients with non-carcinoid tumors, high-grade neuroendocrine carcinomas, and non-gastrointestinal carcinoids or with tumors not drained by the portal vein are not considered for transplant.[7]

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During patient work-up, we always perform somatostatin receptor positron emission tomography/computed tomography (PET/CT) imaging to identify extrahepatic metastatic disease; this is repeated every 6 months to ensure that the disease remains in control while the patient is on the wait list. In the study from Moradi and colleagues, there was a lack of information regarding pretransplant assessment. The use of somatostatin receptor PET/CT imaging has become an essential tool, not only to better identify primary locations but also to assess grading or follow disease stability to define the next therapeutic step.

From September 2009 to July 2021 at our center, 533 LT were performed: 494 with organs procured from donors after brain death (DBD) and 39 using living related donors, 35 of which were for pediatric recipients. From the total number of LTs performed at our center, 6 (1.13%) were due to nonresectable NET liver metastases; all of these patients received grafts from DBDs.

Among the 6 patients with NETs at our center, no patient was considered for multiorgan transplant. The median age was 42 years (range, 35-61 y), 4 patients were female, and median body mass index (in kilograms divided by height in meters squared) was 23.2 (range, 20-26). All patients had symptoms at the moment of diagnosis. In 5 patients (83%), diagnosis of the primary tumor and the liver metastases was simultaneous; however, in the remaining patient, the diagnosis was made 1 year after the first surgery. Five patients had the primary tumor located in the small bowel: 4 underwent partial enterectomy and 1 had a right hemicolectomy, all having primary anastomosis. The sixth patient had the primary tumor on the tail of the pancreas and underwent a distal pancreatectomy. One patient underwent 2 transarterial chemoembolizations before being listed for LT. No patient underwent liver resection before the transplant. In our country Argentina, additional Model for End-Stage Liver Disease (MELD) score exception (22 points) is usually granted to these patients. The median time on the waiting list was 5.5 months (range, 2-16 months). All patients had received somatostatin analogs before LT.

The 6 patients with NETs received transplants from DBDs: in 4 patients, a whole graft was used, but the other 2 patients had extended right lobe split grafts. The donor risk index was >1.7 in 4/6 cases. The median operation time was 345 minutes (range, 265-513 min). Patients were hospitalized for 6.5 days (range, 5-24 days) with no immediate posttransplant complications. Tacrolimus and mycophenolate mofetil were initially used as immunosuppressive therapy. After liver function had stabilized, patients received everolimus. After a follow-up of 43 months (range, 4-82 months), 1 patient presented with recurrent disease and 1 died of sepsis while waiting for a retransplant due to ischemic cholangiopathy (this was one of the recipients of an extended right lobe graft) (Table 1).

Performing LT in patients with malignant diseases is a new challenge; the latest published data have demonstrated that short-term and long-term outcomes of LT in selected patients with NET liver metastases are comparable to patients transplanted for other malignancies. The results shown by Moradi and colleagues suggested that the selection criteria for multivisceral transplantation might require further discussion, analysis, and worldwide consensus. Criteria should be conservative, aimed at the best long-term outcomes, and with the most conscious use of the limited number of donors available.

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Table 1. Liver Transplant in 6 Patients at Our Center With Hepatic Metastases of a Neuroendocrine Tumor

Patient	Age, y	Sex	MELD Score	PTL	Ki-67, %	Grade	Disease-Free	Outcome	Follow-Up, mo
1	42	M	24	P	<2	G2	Yes	Alive	82
2	35	M	22	SB	2	G2	Pulmonary, bone, and peritoneal spread	Alive	70
3	48	F	22	SB	1	G1	Yes	Alive	49
4	54	F	23	SB	<1	G2	Yes	Alive	42
5	61	F	24	SB	2	G1	Yes	Dead	7
6	41	F	25	SB	<3	G1	Yes	Alive	5

Abbreviations: F, female; G, grade; M, male; MELD, Model for End-Stage Liver Disease; P, pancreas; PTL, primary tumor location; SB, small bowel

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