Outcomes Following Liver Transplantation for Metastatic Neuroendocrine Tumors

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ABSTRACT

Introduction. Metastatic disease is generally considered as an absolute contraindication for liver transplantation. However, due to relatively low aggressiveness and slow progression rates, liver metastases from neuroendocrine tumors (NETs) form an exception to this rule. Given the scarcity of available data, the purpose of this study was to evaluate long-term outcomes following liver transplantation for NET metastases.

Material and Methods. There were 12 primary liver transplantations in patients with NET metastases out of 1334 liver transplantations performed in the Department of General, Transplant and Liver Surgery (Medical University of Warsaw) in the period between December 1989 and October 2013. Overall survival (OS) and disease-free survival (DFS) were set as primary and secondary outcome measures, respectively.

Results. Median follow-up was 7.9 years. For all patients, OS rate was 78.6% at 10 years and DFS rate was 15.5% at 9 years. Intraoperative transfusions of packed red blood cells ($P = .021$), Ki-67 proliferative index more than 2% ($P = .048$), and grade 2 tumors ($P = .037$) were identified as factors significantly associated with worse DFS. Notably, loss of E-cadherin expression ($P = .444$), mitotic rate ($P = .771$), extent of liver involvement ($P = .548$), primary tumor site ($P = .983$), and recipient age ($P = .425$) were not significantly associated with DFS.

Conclusions. Excellent long-term OS rates support liver transplantation for unresectable NET metastases despite almost universal post-transplantation tumor recurrence. Selection of patients with G1 tumors with Ki-67 index not exceeding 2% and reducing the requirement for intraoperative blood transfusions might improve DFS rates.

NEUROENDOCRINE TUMORS (NETs) are rare malignancies mainly arising from the neuroendocrine cells of the pancreas, gastrointestinal tract, and bronchopulmonary tree [1,2]. Despite a relatively indolent course of the disease, approximately 30%–45% of patients with NETs develop metastases, which are a major contribution to morbidity and mortality [2,3]. Moreover, a significant proportion of NET patients suffer from tumor-related symptoms, attributable to either tumor bulk or secretion hormones and/or amines. Metastatic NETs predominantly occur within the liver, hence special focus is given to the rationale for applicability of liver-targeted therapies [3]. In patients with metastatic NETs limited to the liver, resection and transplantation remain the only potentially radical therapeutic options. Nevertheless, numerous studies on the use of transarterial chemoembolization and radioembolization, tumor ablation, and various systemic therapies have also brought promising results either in terms of oncological outcomes or control of tumor-related symptoms [4–9].

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Outcomes following liver resection for metastatic NETs are characterized by 10-year overall survival (OS) and disease-free survival (DFS) rates of approximately 42.0% and 1.0%, respectively [10]. In fact, results of a recent study by Elias et al indicate that as much as 50% of metastatic lesions are missed on preoperative imaging, particularly those smaller than 10 mm [11]. Therefore, liver transplantation might be the only option to achieve a "true R0" resection for many patients with metastatic NETs. However, its use is currently limited by the shortage of donors and the scarcity of data available in the transplantation literature regarding post-transplantation outcomes of these patients. The aims of this study were to evaluate outcomes of patients undergoing liver transplantation for nonresectable NET metastases and, potentially, to establish factors associated with poor outcomes.

METHODS

There were 1334 liver transplantations performed in the Department of General, Transplant and Liver Surgery at the Medical University of Warsaw in the period between December 1989 and October 2013. Of those, 12 (0.9%) were identified as primary liver transplantations for metastatic NETs and subsequently analyzed in this retrospective study. General information on operative technique and immunosuppression used has been provided previously [12,13].

First, post-transplantation outcomes were evaluated for all 12 patients included in the study. Then, associations between post-transplantation outcomes were assessed with respect to the following factors: recipient age and gender, donor age, intraoperative packed red blood cells (PRBC) transfusions, primary tumor site, extent of hepatic involvement, presence of extrahepatic metastases, tumor differentiation, mitotic index, Ki-67 proliferative index, and E-cadherin expression. Extent of liver involvement was defined as the ratio of the sum of each metastatic tumor volume to the entire liver volume. Volumetric assessment was based on computed tomography scans in all cases except 1, in which it was based on magnetic resonance imaging. E-cadherin expression was characterized using previously introduced "histoscore," defined as intensity of staining (0, negative; 1, weak; 2, moderate; 3, strong) multiplied by the category of percentage of cells with positive staining (0, <5%; 1, 6%–25%; 2, 26%–50%; 3, 51%–75%; 4, >76%) [14]. Intact E-cadherin expression was defined as a histoscore of 8 or more, whereas lower values indicated loss of E-cadherin expression. OS and DFS were set as primary and secondary outcome measures, respectively. Observations were censored at the date of last available follow-up visit. Kaplan-Meier method was used for calculation of survival estimates. Log-rank test was used for survival comparisons. Level of statistical significance was set at .05. STATISTICA version 10 (StatSoft Inc., Tulsa, Okla, United States) was applied for computing statistical analyses.

RESULTS

Characteristics of the 12 liver transplant recipients included in the study are shown in Table 1. At the median follow-up of 7.9 years 2 patients died, both with no evidence of tumor recurrence, and 6 developed post-transplantation tumor recurrence. One patient died 2.7 years after primary transplantation in the postoperative period after retransplantation for graft failure in the course of de novo hepatitis C virus infection and the second died 10 days after primary transplantation due to sudden cardiac arrest of unknown reason. The most common site of recurrence was abdominal lymph nodes (n = 4) followed by bones (n = 3), graft (n = 2), peritoneum (n = 2), and pancreas (n = 1). Accordingly, OS rates were 91.7% at 1 year and 78.6% at 3, 5, and 10 years, whereas DFS rates were 82.5% at 1 year, 61.9% at 3 years, 51.6% at 5 years, and 15.5% at 9 years, for the entire study group.

Ki-67 index >2% (P = .048), G2 tumors (0.037), and intraoperative PRBC transfusions (P = .021) were significantly associated with decreased DFS rates (Table 2). Notably, the association between Ki-67 index and DFS were above the level of significance if the cut-off was increased to either >5% (P = .158) or >10% (P = .289). Similarly, the associations between PRBC transfusions and DFS did not reach the level of significance if the cut-off was increased from no transfusions to ≤2 (P = .088), ≤3 (P = .257), or ≤4 (P = .804) units. Such associations were not observed for recipient age (P = .425) or gender (P = .642), donor age (P = .963), primary tumor site (P = .983), extent of NET metastases (P = .548), presence of extrahepatic metastases (P = .261), mitotic rate (P = .771), and expression of E-cadherin (P = .444).

DISCUSSION

The major finding of the present study is that despite almost universal post-transplantation tumor recurrence, outcomes of patients after liver transplantation for NET metastases are

Table 1. Characteristics of the 12 Patients After Liver Transplantation for NET Metastases

	Median or Number	Range or %
Recipient gender		
Female	8	66.7
Male	4	33.3
Recipient age (y)	47	27–60
Donor age (y)	36.5	20–58
PRBC transfusions (U)	4	0–10
Primary tumor site		
Pancreas	6	50.0
Small bowel	3	25.0
Colon	2	16.7
Unknown	1	8.3
Extrahepatic metastases	4	33.3
Extrahepatic metastases localization		
Abdominal lymph nodes	2	16.7
Abdominal lymph nodes + mediastinum	1	8.3
Peritoneum	1	8.3
Extent of liver involvement (%)	7.0	1.8–47.7
Tumor differentiation		
Well (G1)	6	50.0
Moderate (G2)	6	50.0
Ki-67 index (%)	2	2–16
Mitotic index	1	1–8
E-cadherin expression		
Intact expression	6	50.0
Loss of expression	6	50.0