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Predictors of Long-Term Outcomes After Liver Transplantation for Unresectable Metastatic Neuroendocrine Tumors

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF 1 Mikołaj Kuncewicz
BCDE 1 Igor Piotr Jaszczyszyn
BCDE 1 Kacper Karaban
DEF 1 Paweł Rykowski
ADE 1 Maciej Krasnodębski
EF 1 Marcin Morawski
B 1 Emilia Kruk
BC 2 Łukasz Koperski
EF 1 Krzysztof Zieniewicz
AEF 1 Marek Krawczyk
AEF 1 Michał Grąt

1 Department of General, Transplant, and Liver Surgery, Medical University of Warsaw, Warsaw, Poland
2 Department of Pathology, Medical University of Warsaw, Warsaw, Poland

Corresponding Author: Paweł Rykowski, e-mail: pawel.ryk@gmail.com
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Background: Malignant and benign neuroendocrine tumors (NET) share many histopathological features. Liver transplantation (LT) is one of the liver-directed therapies for neuroendocrine liver metastases (NELM). The aim of this study was to determine the outcomes of patients undergoing LT for NELM.

Material/Methods: This was a retrospective study that included 19 patients who underwent LT for unresectable NELM between December 1989 and December 2022 in the Department of General, Transplant, and Liver Surgery of the Medical University of Warsaw. Kaplan-Meier estimator and Cox proportional hazards regression were used for statistical analyses.

Results: The primary tumor was located most frequently in the pancreas. The median follow-up was 72.5 months. The overall survival (OS) was 94.7%, 88.0%, 88.0%, 70.4%, and 49.3% after 1, 3, 5, 10, and 15 years, respectively. Accordingly, the recurrence-free survival (RFS) rates were 93.8%, 72.9%, 64.8%, 27.8%, and 27.8% after 1, 3, 5, 10, and 15 years, respectively. Ki-67 index ≥5% was found as a risk factor for both worse OS (hazard ratio (HR) 7.13, 95% confidence intervals (95% CI) 1.32-38.63, *P*=0.023) and RFS (HR 13.68, 95% CI 1.54-121.52, *P*=0.019). Recipient age ≥55 years was a risk factor for worse RFS (*P*=0.046, HR 5.47, 95% CI 1.03-29.08). Multivariable analysis revealed Ki-67 ≥5% as the sole independent factor for worse OS (HR 13.78, 95% CI 1.48-128.56, *P*=0.021).

Conclusions: Patients with unresectable NELM achieve great OS and satisfying RFS after LT. The risk factors associated with worse outcomes are attributed to primary tumor aggressiveness.

Keywords: Liver Transplantation • Neoplasm Metastasis • Neuroendocrine Tumors • Surgical Oncology • Liver Neoplasms

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Background

Neuroendocrine tumors (NET) are a heterogeneous group of tumors with an incidence of more than 5 per 100 000 people [1]. The neoplasms derive from neuroendocrine cells present in the bronchopulmonary complex, gastrointestinal tract, and pancreas [2]. There is a huge variety of clinical presentations within the group. The histological appearance of NET is not strictly associated with metastatic potential. Disease progression is often asymptomatic for nonfunctioning tumors and manifest with metastases. Functioning NET produce hormones resulting in endocrinopathies, which worsen quality of life and may be life-threatening. The burden of both functioning and nonfunctioning NET relies on the combined size of tumors. Lesions can metastasize to different organs, including the liver, bones, and lungs. In the vast majority of cases, NET are detected in the metastatic phase (40-80%), of which neuroendocrine metastases to the liver (NELM) are the most common [3].

The goal of treatment is to prolong overall and symptom-free survival. Treatment of NELM relies on cytoreduction, achieved with liver-directed therapy and pharmacological treatment. Pharmacological treatments include somatostatin analogs (SSAs), everolimus, sunitinib, and peptide receptor radionuclide therapy (PRRT) [4]. Invasive methods such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), radiofrequency ablation (RFA), cryoablation, brachytherapy, and hepatic artery embolization are commonly applied [5-8]. However, the 5-year overall survival (OS) reported for these treatment modalities vary from 17% to 57% for selected patients [9-11]. In a study by Roche et al, the 5-year OS for patients with NELM after TACE was reported to be 83% [12]. The median RFS for NELM can also vary from 11 to 15 months [6,13]. Currently, liver resection (LR) allows the best treatment results in patients with resectable disease [14]. However, due to tumor biology and insufficient preoperative imaging techniques, complete cytoreduction is difficult to obtain, especially with bilobar liver metastases. A multicenter study by Eshmuminov et al found the 5-year OS of patients treated with LR was 68.8%, with a 5-year RFS of 18.1% [15]. Liver transplantation (LT) is generally regarded as the best method for complete tumor clearance. However, strict selection of patients is needed to outweigh risks by potential benefits [15]. The number of donors is insufficient; therefore, appropriate organ allocation is necessary [16,17]. The Milan Criteria, United Network for Organ Sharing guidelines, or European Neuroendocrine Tumor Society criteria can be used to assess patient eligibility for LT [18].

Direct comparison of the various treatment modalities is difficult. Patients undergoing LT for NELM usually have already benefited from other treatment modalities prior to transplantation. Nevertheless, factors for selection of an appropriate therapy are unclear [19]. That is especially meaningful in light of newly reported research stating that selected patients undergoing LT can achieve better outcomes than parallel patients undergoing LR [15].

Among risk factors, the Ki-67 index is reported to be the most important for patient stratification. However, an exact value has yet to be determined, as it varies among studies [15,20-22]. The aim of the present study was to assess long-term outcomes after LT in patients with NELM and to define prognostic factors.

Material and Methods

This was a retrospective observational study. There were 2680 LTs performed in the Department of General, Transplant, and Liver Surgery of the Medical University of Warsaw between December 1989 and December 2022. According to the internal register of the department, 19 (0.7%) of them were identified as primary transplantations for NELM. The eligibility criteria in our center require grade 1 (G1) or grade 2 (G2) in the 2019 World Health Organization (WHO) NEN Classification, stable disease for 6-12 months, and no sign of extrahepatic disease at the time of LT, but patients who had previously removed metastases are accepted. Contrary to the practice of some centers, we do not require portal drainage of the primary lesion, and older patient age is not a contraindication nor are liver involvement or Ki-67 value, as long as it does not exceed 20%, which is defined as G1 or G2. During patient selection for LT, results based on primary lesion or biopsy of liver metastases were used to assess the Ki-67 value. However, further evaluations of post-transplantation outcomes were based on pathological examination of the explanted liver as the most reliable and suitable for description of neoplasm aggressiveness. The criteria are summarized in **Table 1** [15]. The lesions were

Table 1. Eligibility criteria for LT in patients with NELM.

Portal drainage of primary	NET G1/G2	Ki67	No sign of extrahepatic disease	Liver involvement	Stable disease for 6-12 months	Recipient age
–	+	≤20%	+	–	+	–

"+" – required in our center, "–" – not required in our center

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defined as unresectable during multidisciplinary team (MDT) meetings by the experienced hepatobiliary surgeons and radiologists, based on computed tomography (CT), magnetic resonance imaging (MRI), or intraoperative finding of liver dissemination. During analysis, associations with outcomes were tested for numerous factors listed in **Table 2**. Liver involvement was defined as the volume revealed in imaging technique lesions relative to the total volume of the liver. Volumetry was based on either CT or MRI scans. E-cadherin expression was characterized by the previously described histoscore, determined by the pathologist by multiplying the intensity of staining (negative – 0; weak – 1; moderate – 2; strong – 3) and percentage of cells with positive staining (0-5% – 0; 6-25% – 1; 26-50% – 2; 51-75% – 3; 76-100% – 4) [20,23]. Scores of 8 or higher were accepted as intact E-cadherin expression, while lower values signified a loss of expression (**Figure 1**).

In most cases, the classic technique of cavo-caval anastomosis was applied, with end-to-end biliary anastomosis. Prior to LT, most patients had undergone numerous types of systemic treatment and liver resections, along with other modalities (**Table 3**). Data on disease recurrence were censored on the last follow-up visit or control imaging examination. OS was set as the primary outcome and RFS as the secondary outcome. Kaplan-Meier method was used for survival estimate calculations. The Cox proportional hazards ratio was applied for risk factor analysis. Univariable analyses were performed. Subsequently, a model for multivariable analysis was built with backward elimination out of factors, which obtained *P* values less than 0.150 in the univariable model. Backward elimination was stopped when none of the variables met the *P*>0.1 criteria. The level of significance was defined as a *P* value less than 0.05. All computations were carried out using STATISTICA version 13.3 (StatSoft Inc., Tulsa, OK, United States). The study protocol was approved by the local ethics committee of the Medical University of Warsaw (AKBE/227/2022).

Table 2. Factors and analyses results.

		Univariable		Multivariable	
		HR (95% CI)	p-value	HR (95% CI)	p-value
OS	Recipient age	1.01 (0.92-1.11)	0.792		
	≥50	1.60 (0.35-7.34)	0.542		
	≥55	4.08 (0.63-26.28)	0.139		
	Recipient male gender	2.74 (0.54-14.04)	0.226		
	Donor age (per year)	0.96 (0.90-1.02)	0.207		
	Donor male gender	1.06 (0.19-5.89)	0.943		
	Intraoperative PRBC transfusions (per unit)	1.29 (0.98-1.71)	0.074		
	Primary pancreatic location	1.67 (0.37-7.60)	0.506		
	Extent of liver involvement	1.02 (0.97-1.07)	0.444		
	≥10%	2.80 (0.45-17.46)	0.270		
	≥40%	2.62 (0.36-19.32)	0.344		
	Mitotic index	1.00 (0.69-1.45)	0.994		
	≥2	0.17 (0.20-1.51)	0.113	0.09 (0.01-1.27)	0.090
	Ki-67	1.17 (1.01-1.35)	**0.035**		
	≥3%	6.82 (1.25-37.34)	**0.027**		
	≥5%	7.13 (1.32-38.63)	**0.023**	13.78 (1.48-128.56)	**0.021**
	≥10%	2.83 (0.61-13.19)	0.184		
	Loss of E-cadherin expression	0.26 (0.05-1.36)	0.110		
	Extrahepatic metastases in history	0.29 (0.03-2.39)	0.248		

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Table 2 continued. Factors and analyses results.

		Univariable		Multivariable	
		HR (95% CI)	p-value	HR (95% CI)	p-value
RFS	Recipient age	1.07 (0.99-1.17)	0.105		
	≥50	1.91 (0.47-7.67)	0.364		
	≥55	5.47 (1.03-29.08)	**0.046**		
	Recipient male gender	0.56 (0.12-2.74)	0.476		
	Donor age (per year)	0.98 (0.93-1.02)	0.326		
	Donor male gender	1.11 (0.26-4.69)	0.889		
	Intraoperative PRBC transfusions (per unit)	1.00 (0.79-1.27)	0.999		
	Primary pancreatic location	0.48 (0.12-2.00)	0.315		
	Extent of liver involvement	1.03 (0.99-1.07)	0.132		
	≥10%	3.96 (0.72-21.83)	0.114		
	≥40%	4.81 (0.80-28.99)	0.087		
	Mitotic index	1.13 (0.92-1.39)	0.254		
	≥2	2.22 (0.54-9.17)	0.271		
	Ki-67	1.20 (1.03-1.41)	**0.022**		
	≥3%	12.80 (1.42-115.11)	**0.023**		
	≥5%	13.68 (1.54-121.52)	**0.019**		
	≥10%	6.88 (1.24-38.09)	**0.027**		
	Loss of E-cadherin expression	0.93 (0.25-3.49)	0.916		
	Extrahepatic metastases in history	0.36 (0.07-1.77)	0.210		

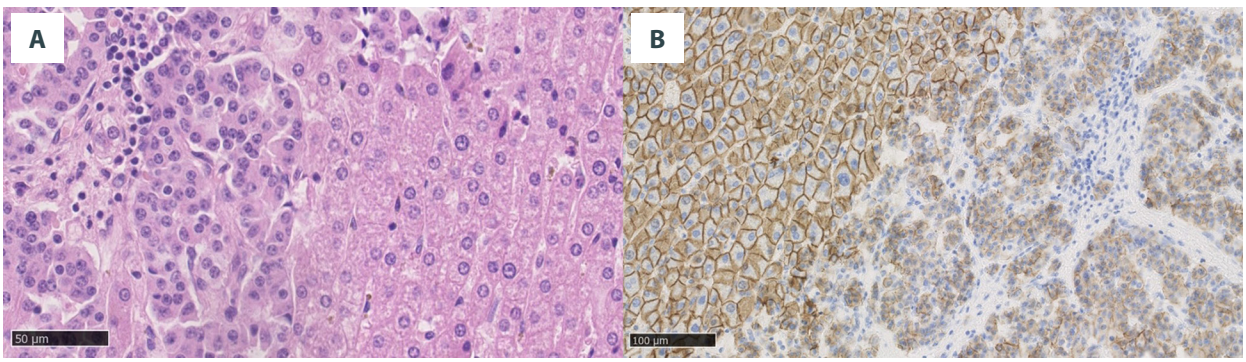

Figure 1. (**A**) Neuroendocrine liver metastases, hematoxylin and eosin staining, showing a well-differentiated tumor on the left side. (**B**) Neuroendocrine liver metastases, E-cadherin staining, showing loss of E-cadherin expression in tumor cells on the right side. *Created using NDP.view2 (U12388-01), version 2.9.29, Hamamatsu Photonics.*

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Table 3. Characteristics of the study group.

	Number of missing data (%)	Median or number	Range or %
Follow-up (months)	0 (0%)	72.5	0.3-235.1
Recipient Gender	0 (0%)		
Female		11	57.89%
Male		8	42.11%
Recipient BMI	4 (21.05%)	24.9	17.2-31.0
Recipient age (y)	0 (0%)	51	27-66
Donor age (y)	1 (5.26%)	46	20-75
Time from primary lesion resection (months)	4 (21.05%)	19.5	1-82
Systemic treatment prior to LT	0 (0%)	15	78.95%
Surgical treatment prior to LT	0 (0%)	9	47.37%
LR		3	33.33%
RFA		3	33.33%
LR+RFA		1	11.11%
TACE		2	22.22%
Caval anastomosis	0 (0%)		
Piggy-back		6	31.58%
Classic		13	68.42%
Biliary anastomosis	0 (0%)		
End-to-end		17	89.47%
Roux-en-Y		2	10.53%
PRBC transfusions (U)	1 (5.26%)	2.5	0-10
Primary tumor site	0 (0%)		
Pancreas		8	42.11%
Small bowel		6	31.58%
Colon		3	15.79%
Stomach		1	5.26%
Unknown		1	5.26%
Extrahepatic metastases in history (previously resected)	0 (0%)	7	36.84%
Abdominal lymph nodes		5	71.43%
Abdominal lymph nodes+mediastinum		1	14.29%
Peritoneum		1	14.29%
Extent of liver involvement (%)	3 (15.79%)	7.5	1-60
Number of tumors	0 (0%)		
Numerous		13	
Countable		6	

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Table 3 continued. Characteristics of the study group.

	Number of missing data (%)	Median or number	Range or %
Number of countable tumors	1 (5.26%)	4	2-4
Size of tumor (mm)	0 (0%)		2-200
Ki67 index (%)	0 (0%)	2	2-16
Mitotic index	0 (0%)	1	0-10
MELD	0 (0%)	7	6-18
Cold ischemia (min)	0 (0%)	510	240-720

BMI – body mass index; LT – liver transplantation; LR – liver resection; RFA – radiofrequency ablation; TACE – transarterial chemoembolization; PRBC – packed red blood cells; MELD – model for end-stage liver disease.

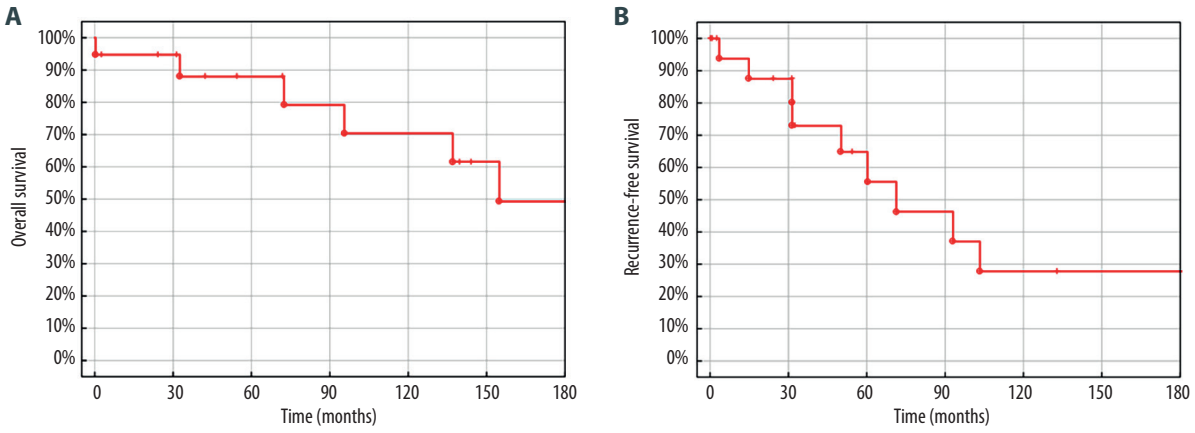

Figure 2. (**A**) Overall survival of liver transplantation for neuroendocrine liver metastases. (**B**) Recurrence-free survival of liver transplantation for neuroendocrine liver metastases. *Created using STATISTICA, version 13.3, StatSoft, Inc., Tulsa, OK, United States.*

Results

Characteristics of the 19 recipients are presented in **Table 3**. There were 11 (57.9%) females and 8 (42.1%) males. The primary tumor was located most frequently in the pancreas (42.1%), followed by the small bowel (31.6%). The median follow-up was 72.5 months (0.3-235.1 months). There were 3 (17.6%) patients beyond the Milan Criteria. During the observation period, there were 3 (15.8%) re-transplantations: the first directly after primary LT due to primary nonfunction, the second at over 2 months after primary transplantation because of hepatic artery thrombosis, and the third after 3 years for de novo hepatitis C virus infection and liver failure.

Because the metastatic tumors in the liver were described as "numerous" or "multiple" in some of the pathological reports, the data on tumors were difficult to analyze. Nevertheless, the information on number of disseminated and countable tumors, their maximal and minimal length, and number for countable tumors are presented in **Table 3**.

The OS was 94.7%, 88.0%, 88.0%, 70.4%, and 49.3% after 1, 3, 5, 10, and 15 years, respectively, and the RFS was 93.8%, 72.9%, 64.8%, 27.8%, and 27.8% after 1, 3, 5, 10, and 15 years (**Figure 2**).

Univariable analysis revealed that Ki-67 ≥5% was a risk factor for worse OS – hazard ratio (HR) 7.13 and 95% confidence intervals (95% CI) 1.32-38.63, *P*=0.023. Ki-67 ≥5% (HR 13.68, 95% CI 1.54-121.52, *P*=0.019) and recipient age ≥55 years (HR 5.47, 95% CI 1.03-29.08, *P*=0.046) were found to be risk factors for RFS. The survival of patients who had one or both risk factors concerning RFS, compared to patients with none of them, was significantly worse (HR 9.74, 95% CI 1.09-98-7.02, *P*=0.042) (**Figure 3**). Notably, liver involvement as a continuous variable was not significantly associated with OS (*P*=0.444) or RFS (*P*=0.132).

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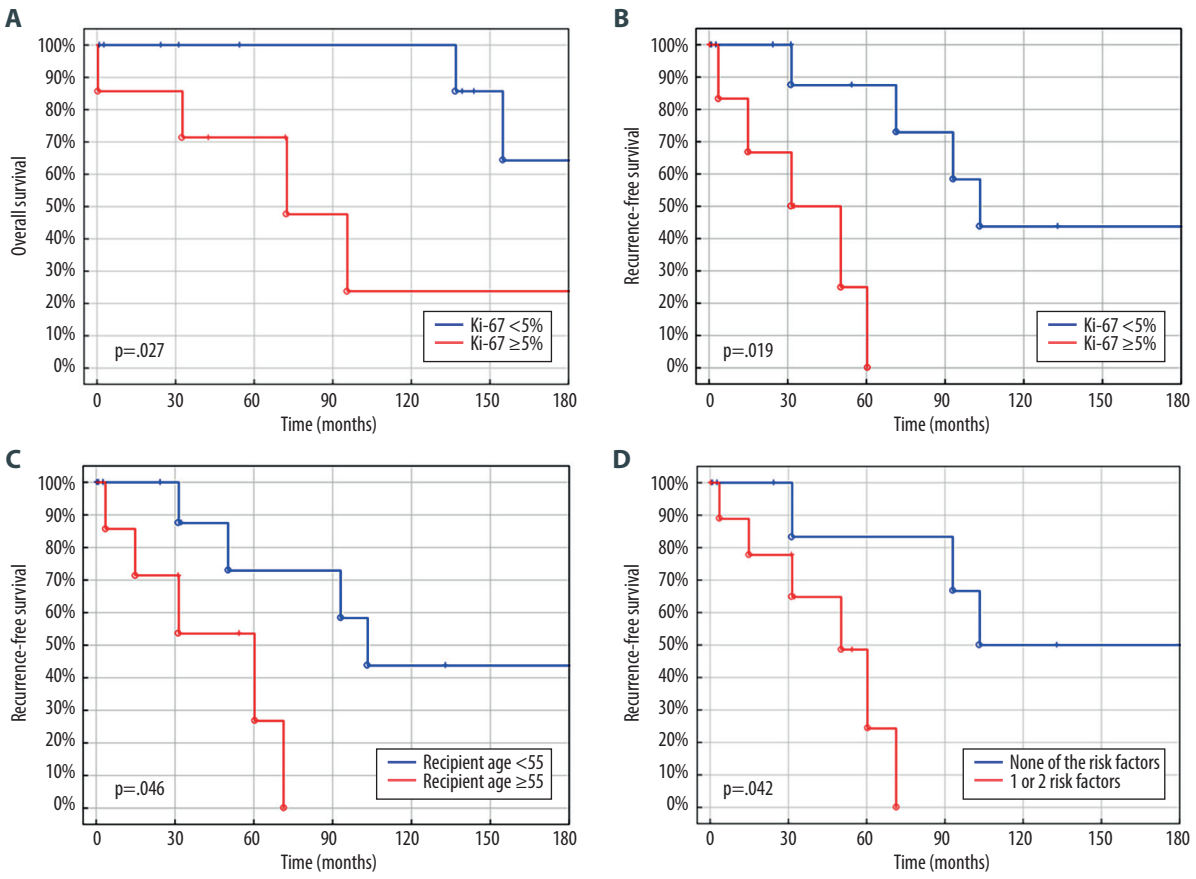

Figure 3. (**A**) Overall survival of liver transplantation for neuroendocrine liver metastases. (**B**) Recurrence-free survival of liver transplantation for neuroendocrine liver metastases. (**C**) Recurrence-free survival of liver transplantation for neuroendocrine liver metastases. (**D**) Recurrence-free survival of liver transplantation for neuroendocrine liver metastases. *Created using STATISTICA, version 13.3, StatSoft, Inc., Tulsa, Oklahoma, United States.*

Backward elimination left 2 variables (**Table 2**) in multivariable analysis, which revealed Ki-67 ≥5% was an independent factor for worse OS (HR 13.78, 95% CI 1.48-128.56, *P*=0.021).

Discussion

Similar to the outcomes of a multicenter study of NELM Eshmuminov et al, the patients in our study were young, with a median age of 47, but most patients had the primary lesions located in the pancreas as opposed to the small bowel [15].

The results presented in the present study are comparable to those reported by other centers. According to the literature, the 5-year OS varies from 33% to 97.2%, and the 5-year RFS ranges from 11% to 86.9% [21,24-29], but results and eligibility criteria differ significantly among centers [30]. The best outcomes are achieved in the Milan center, where the most commonly applied criteria come from [28]. In our group, there were 3 patients beyond the Milan Criteria: one of them was over 60 years old, another had liver involved by neoplasm in over 50%, and the last one exceeded both of these criteria, but the exclusion of those patients did not change our outcomes significantly.

Searching for risk factors, we set the Ki-67 cut-off points as 3%, 5%, and 10%. The strongest effect, defined as the highest HR and the lowest *P* value, was achieved for 5% both for OS and RFS. That value does not overlap with the current,2019 WHO NEN Classification, in which a Ki-67 value of 3% is the cut-off for differentiation of G1 and G2 tumors [31]. Still, a Ki-67 cut-off value of 5% was considered in previous data series [15,32].

Older recipient's age was found to be a risk factor for worse RFS, but is not usually a contraindication for LT [33]. Some studies show it as a predictor of survival following LT for NELM, but there is no consensus on the precise age [22,34,35]. The most commonly accepted is 60 years, which is included in the widely applied Milan Criteria [28]. Because only 2 patients in our

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study were over 60 years old, we decided to use age 55 years as a cut-off point, similar to the cut-off point previously used in the literature [36]. Age ≥55 years was found to be associated with significantly worse RFS, but not with OS. Importantly, age ≥50 was not significantly associated with worse outcomes, contrary a previous study [34].

In broader context, age is not unequivocally associated with risk of neoplastic disease recurrence. In some types of tumors, younger patients are more susceptible to disease relapse, as neoplasms in that group are often more aggressive [37,38]. Previous studies found no association between age and disease recurrence after primary lesion resection in NEN [39-41], but recipient age under 60-65 is one of eligibility criteria for LT in some centers because it raises concerns about achievable outcome [15]. However, NEN are very rare tumors and these patients tend to have very good long-term survival, so it should be considered a chronic disease. Additionally, tumors cells are evolving, getting more aggressive over time [42]. For instance, in our group, one patient had LT for G2 tumor, and on disease relapse was diagnosed with a G3 lesion. The disease in older patients typically takes more time to develop, which may result in worse RFS.

Patients who met both risk factors for RFS had significantly worse outcomes. However, the HR for such division is lower than for Ki-67 separately, which is a much stronger predictor of survival than age. Therefore, Ki-67 should be treated as a key factor in LT eligibility criteria. Even older patients can benefit from LT as long as the Ki-67 index stays low, as reflected in the Milan Criteria, in which age over 60 is only a relative contraindication for LT for NELM [28].

Some of the tested factors, contrary to our expectations, turned out to be insignificant. The mitotic count is one of the fundamental factors included in the 2019 WHO NEN classification, but some authors report it has no advantage over use of Ki-67 alone [43]. However, the most astonishing example is the insignificance of liver involvement, which is included in the Milan Criteria [28]. In our study, patients had a wide range of liver involvement, from 1% to 60%, but it did not have a significant impact on outcomes.

Because this was a retrospective study, we were unable to retrieve all the data for some patients (missing data are reported in **Table 3**). Given that only 19 patients were included in this study, the insignificance of tested factors should be treated cautiously. Another limitation is difficulty in uniform assessment and classification of neoplasms. According to the literature, this problem especially affects borderline tumors with Ki-67 values of 2-5% in the commonly used eyeball estimation technique (EE). As a result, true G1 tumors, defined as Ki-67 <3% obtained in digital image analysis (DIA), achieve in EE an average Ki-67 of 4.5±2.0% [44]. Also, there are suggestions that only cells above some intensity of staining should be included in the assessment. That assumption considers Ki-67 protein functions in cells and can change the classification of borderline tumors [45]. Another aspect of Ki-67 assessment is its huge heterogeneity, not only between primary tumors and metastases, but also between simultaneous metastatic lesions and inside a particular lesion [46-48]. The conclusions of previous studies emphasize the complexity of the issue and the problems affecting all research on NET, which may lead to differences in clinical outcomes.

Conclusions

In conclusion, patients with NELM tend to have very good outcomes after LT. The factor associated with worse outcomes is tumor aggressiveness. Ki-67 appears to be a valuable indicator of tumor biology and thus of clinical outcome. Nevertheless, measurement is difficult to objectify, which may lead to discrepancies in clinical outcomes.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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