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Liver Resection for Neuroendocrine Tumor Liver Metastases Within Milan Criteria for Liver Transplantation

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Abstract

Background The role of liver transplant (LT) for neuroendocrine liver metastasis (NELM) has not been completely defined. While international guidelines included LT as a potential treatment for highly selected patients with advanced NELM, recently, LT has been proposed as an alternative curative treatment for NELM for patients meeting restrictive criteria (Milan criteria).

Methods Using a multi-institutional cohort of patients undergoing liver resection for NELM, the long-term outcomes of patients meeting Milan criteria (resected NET drained by the portal system, stable disease/response to therapies for at least 6 months, metastatic diffusion to < 50% of the total liver volume, a confirmed histology of low-grade, and ≤ 60 years) were investigated.

Results Among the 238 patients included in the study, 28 (12%) patients met the Milan criteria for LT with a 5-year OS of 83%. Furthermore, among patients meeting Milan criteria, subsets of patients with favorable clinic-pathological characteristics had 5-year OS rates greater than 90% including G1 patients (5-year OS, 92%), patients undergoing minor liver resection (5-year OS, 94%), patients with low number of NELM (1–2 NELM), and small tumor size (< 3 cm) (for both groups of patients, 5-year OS, 100%).

Conclusions In our series, only 12% of patients met Milan criteria, and the 5-year OS after liver resection for this small selected group of patients was comparable with that reported in the literature for patients undergoing LT for NELM within Milan criteria. While LT might be the optimal treatment for patients with unresectable NELM, surgical resection should be the first option for patients with resectable NELM.

Keywords Neuroendocrine liver metastasis · Liver surgery · Liver transplant

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors arising from neuroendocrine cells in the gastrointestinal (GI) tract or in the tracheo-bronchopulmonary (TB) complex.[1] In the last decade, the incidence of NETs has increased to more than 5 per 100,000 people-years and NETs representing about 5% of all gastro-enteropancreatic tumors.[2–4] While NETs can present different biological behaviors ranging from indolent well-differentiated tumors to undifferentiated cancers associated with poor prognosis, NETs have been associated with high risk of distant metastasis at initial diagnosis (15–35% of patients) and during the follow-up following treatment of primary NET (about 40% of patients).[5–9] In particular, the liver is the most common site of distant metastasis for GI NETs and liver failure due to massive hepatic replacement has been reported as the leading cause of death in NET patients.[10] The optimal treatment for NET liver metastasis (NELM) has not been completely defined. In fact, while surgery with curative intent has been included in international guidelines for the management of NET patients (i.e., ENET and NCCN), liver transplant (LT) has been proposed as an alternative curative treatment for NELM.[5,11–13] In a recent review of the studies on LT for NELM published between 2002 and 2013, Fan et al. reported a 5-year overall survival (OS) from the time of diagnosis of approximately 70% which decreased to about 50% when calculated from the time of LT.[14] While these results might question the actual benefit of LT for NELM, more recently, Mazzaferro et al. investigated the long-term outcomes of 88 patients with bilobar unresectable NELM eligible for LT according to specific criteria comparing LT versus non-LT treatments and reported a significant advantage for the LT group over nontransplant strategies in terms of OS (5-year OS: LT, 97% vs. non-LT, 51%, respectively; $p < 0.001$).[12] After defining the Milan criteria for LT in patients with hepatocellular carcinoma (HCC) in 1994, Mazzaferro and colleagues introduced a specific protocol for LT in patients with bilateral unresectable NELM as "Milan criteria for NELM".[12,15–17] According to the Milan criteria for NELM, selection criteria for eligibility for LT included (a) confirmed histology of low-grade (G1-G2) NET, (b) primary tumor drained by the portal system and removed, (c) metastatic diffusion to < 50% of the total liver volume, and (d) stable disease/response to therapies for at least 6 months prior to transplant consideration.[12,16,17]

Based on these results, the authors suggested that the LT should be offered with a curative rather than palliative intent to patients with limited tumor burden and no extrahepatic spread.[12] To further investigate the outcomes of patients meeting the Milan criteria for NELM, a multi-institutional national database was used to analyze the survival of patients undergoing liver resection whether or not their clinico-pathological characteristics were complying with the proposed restrictive criteria for LT (Milan criteria for NELM).

Methods

Study Population

Patients undergoing hepatic resections for NELM between January 1990 and December 2014 at one of the seven tertiary referral hepato-biliary-pancreatic centers participating in the Italian NET group were included in our analysis (G. B. Rossi Hospital, University of Verona, Verona; Sant'Orsola Hospital, University of Bologna, Bologna; San Raffaele Hospital, Milan; Catholic University of the Sacred Heart, Rome; Mauriziano Umberto I Hospital, Turin; Istituto Clinico Humanitas, Milan; and Regina Elena National Cancer Institute, Rome). Patients who underwent non-surgical treatments or diagnostic laparoscopy for a disease that was unsuitable for radical surgery or who had macroscopic disease after debulking (R2) were excluded from the analysis. The institutional review board of the participating institutions approved the study.

Demographic and clinicopathological data collected for each patient included age, gender, tumor functional status, presence of genetic syndrome, primary tumor site, timing of metastasis diagnosis (synchronous vs. metachronous), extrahepatic metastatic disease at diagnosis, tumor grade, Ki-67 index, simultaneous hepatic treatment, number and size of metastasis, and type of liver resection. Tumor grade was defined according to the World Health Organization (WHO) 2010 classification of tumors of the digestive system.[18] Operative-specific characteristics included the type of hepatic resection (minor versus major hepatectomy), receipt of lymphadenectomy, final margins status, and receipt of associated resection or local ablation. Major hepatectomy was defined according to Brisbane's classification as the resection of three or more liver segments.[19] Moreover, NELMs were classified according to Frilling's classification.[20] The primary outcome of interest was the overall survival that was defined as the time interval between the date of surgery and the date of death. Time was censored at the date of the last follow-up assessment for patients who were found to be alive.

Milan and Extended Milan Criteria Groups

Patients were included in the Milan Criteria groups when they had a NET drained by the portal system and removed, stable disease/response to therapies for at least 6 months, metastatic diffusion to < 50% of the total liver volume, a confirmed histology of low-grade (G1-G2) tumor, Ki67 proliferation index of < 10% and had ≤ 60 years (Table 1).[12,16,17] Given that, in Italy, the current age limit for deceased donor LT is 70 years,

Table 1 Milan criteria for liver transplantation in patients with neuroendocrine liver metastasis[12,16,17]

Inclusion criteria
• Confirmed histology of neuroendocrine tumor (low-grade neuroendocrine tumors, G1-G2, WHO 2010) with or without syndrome
• Primary tumor drained by the portal system
• Metastatic diffusion to liver parenchyma ≤ 50%
• Good response or stable disease for at least 6 months
• Age ≤ 60 years
Exclusion criteria
• Small-cell carcinoma and high-grade neuroendocrine carcinoma (non--carcinoid tumors)
• Other medical/surgical conditions contraindicating liver transplantation, including previous tumors
• Non-gastrointestinal carcinoids or tumors not-drained by the portal system

we defined Extended Milan Criteria to include patients within Milan criteria and age ≤ 70 years.

Statistical Analysis

Continuous variables were reported as medians with interquartile ranges (IQR) while categorical variables were reported as whole numbers and percentages. Survival curves were estimated using the Kaplan-Meier method, and differences between the curves were compared with the log-rank test. For statistical analysis, the STATA software (StataCorporation, 2011, MP-Parallel Edition), and R CRAN software (v. 3.2.2, 2015)[21] with the "survival"[22], and "Hmisc"[23] packages were used.

Results

Baseline Characteristics

Among the 238 patients included in the study, a majority of patients was male ($n = 133$, 55.9%) and ≤ 65 years ($n = 143$, 61.4%) (Table 2). Primary NETs were symptomatic (functional NETs) in 73 (32.6%) patients while 9 (6.0% of 150 patients with available data) patients had an underlying genetic syndrome (MEN-1, $n = 5$; VHL, $n = 4$). In 84 (35.3%) patients, the primary NET was in the pancreas while 154 (64.7%) patients had a NET in other organs including jejunum/ileum ($n = 76$, 31.9%), colon/rectum ($n = 17$, 7.1%), and stomach ($n = 9$, 3.8%). A total of 195 (81.9%) patients had a G1-G2 NELMs while the median Ki-67 index was 5% (IQR, 2–10). In particular, 83 (34.9%) patients had a < 3% Ki-67 index, 118 (49.9%) a Ki-67 index value between 3% and 20%, while 37 (15.6%) patients had a Ki-67 index >20%. A total of 55 (23.1%) patients had a single NELM, while 155 (65.1%) and

Table 2 Baseline characteristics of the study population ($n = 238$)

Variables	*N* (%)
Age, median (IQR)	62 years (51–70)
Gender	
Male	133 (55.9%)
Female	105 (44.1%)
Symptomatic	
No	151 (67.4%)
Yes, functional	73 (32.6%)
Not available	14
Genetic syndrome	
No	141 (94.0%)
Yes	9 (6.0%)
Not available	88
Primary NET site	
Pancreas	84 (35.3%)
Other organs	154 (64.7%)
Synchronous metastatic hepatic disease	
No	64 (27.5%)
Yes	169 (72.5%)
Not available	5
Synchronous metastatic extrahepatic disease	
No	217 (93.1%)
Yes	16 (6.9%)
Not available	5
Associated surgical procedures	
No	208 (87.4%)
Yes	30 (13.6%)
Grade	
G1-G2	195 (81.9%)
G3	43 (18.1%)
Ki 67, median (IQR)	5% (2–10)
Ki 67	
≤ 3%	83 (34.9%)
3–20%	118 (49.6%)
> 20%	37 (15.5%)
Number of hepatic lesions, median (IQR)	3 (2–7)
Number of hepatic lesions	
1	55 (23.1%)
2–10	155 (65.1%)
> 10	28 (11.8%)
Tumor size, median (IQR)	45 mm (25–75)
Tumor size	
< 3 cm	70 (29.4%)
≥ 3 cm	168 (70.6%)
Frilling classification	
Type I	55 (23.1%)
Type II	183 (76.9%)
Major liver resection	
No	157 (65.9%)
Yes	81 (34.1%)
Meet Milan Criteria	
No	210 (88.2%)
Yes	28 (11.8%)
Meet extended Milan Criteria	
No	197 (82.8%)
Yes	41 (17.2%)
Recurrence	
No	96 (40.3%)
Yes	142 (59.7%)
Follow-up, median (IQR)	3.7 years (2.0–6.9)
Status	
Alive	157 (65.9%)
Dead	81 (34.1%)

28 (11.8%) patients had 2–10 and > 10 NELMs, respectively. The median tumor size was 4.5 cm (IQR, 2.5–7.5); 70 (29.4%) patients had NELM < 3 cm; and 168 (70.6%) patients had NEML ≥ 3 cm. While 183 (76.9%) patients had type II NELM according to the Frilling classification, 55 (23.1%) patients had type I NELM. Major and minor liver resections were performed on 81 (34.1%) and 157 (65.9%) patients, respectively. While 28 (11.8%) of patients met the Milan Criteria for liver transplant, 41 (17.2%) patients had a transplantable disease according to the Extended Milan Criteria.

Survival Analysis

Among the whole study population, 5- and 10-year overall survival (OS) were 67.1% (95% CI, 59.3–73.8) and 52.4% (95% CI, 43.3–60.7), respectively. Of note, among patients meeting Milan criteria, 5- and 10-year OS were 83.3% (95% CI, 55.1–94.6) and 71.4% (95% CI, 36.2–89.5), respectively (Fig. 1a). Similarly, among patients meeting the Extended Milan criteria, 5- and 10-year OS were 80.9% (95% CI, 58.6–92.0) and 64.8% (95% CI, 36.4–82.9), respectively (Fig. 1b). In comparison, 5-year OS was 63.8% (95% CI, 55.1–71.3) for patients not meeting Milan criteria and 63.2% (95% CI, 54.2–70.9) among patients not meeting Extended Milan criteria. Among patients meeting Milan criteria, subsets of patients with specific clinic-pathological characteristics had a median 5-year OS greater than 80% (Table 3). In particular, female patients meeting Milan criteria had a 5-year OS of 84.6% (95% CI, 51.2–95.9) while no patients with non-functional and non-pancreatic NELM meeting Milan criteria died within the first 5 years following liver surgery (all $p \leq 0.10$). Similarly, while G1 patients meeting Milan criteria had a 5-year OS of 91.7% (95% CI, 53.9–98.8; $p = 0.12$), no patients with a small number of NELM (1–2 NELM) and small tumor size (< 3 cm) meeting Milan criteria died within the first 5 years following liver surgery (all $p \leq 0.062$). Patients meeting Milan criteria and undergoing minor liver resection had a 5-year OS of 93.8% (95% CI, 63.9–99.1; $p = 0.053$). Similarly, among patients meeting extended Milan criteria, patients with non-functional and G1 NELM had a 5-year OS of 96.0% (95% CI, 51.2–95.9) and 93.3% (95% CI, 61.3–99.0), respectively ($p \leq 0.05$). Moreover, patients meeting extended Milan criteria with a small number of NELM (1–2 NELM), small tumor size (< 3 cm), and who underwent minor liver resection had a 5-year OS of 78.9% (95% CI, 31.8–95.2), 94.1% (95% CI, 65.0–99.2), and 86.9% (95% CI, 63.3–95.8), respectively (all $p \leq 0.10$).

Discussion

During the last decade, significant advances in therapeutic options for patients with NET have been reported that might change our current management of NELM. In particular, while somatostatin analogs (SSAs) and everolimus demonstrated to improve long-term outcomes of patients with advanced NET, peptide receptor radionuclide therapy (PRRT) has been proposed as a new treatment modality for inoperable or metastasized gastro-enteropancreatic NET patients delivering radionuclides (lutetium-177-DOTATATE) to tumor cells expressing high levels of somatostatin receptors.[24–29] Moreover, the multitargeted tyrosine kinase inhibitor sunitinib demonstrated to improve progression-free survival, overall survival, and the objective response rate among patients with advanced pancreatic NET.[30] Despite these progresses, national and international (i.e., NCCN and ENETS) guidelines for the management of NET still suggest surgical resection as the treatment of choice for both locoregional NET disease and NELM. Even though Gurusamy et al. performing a Cochrane review in 2009 reported lack of good quality evidence showing superiority of surgery versus other non-surgical treatments for NELM, an increasing number of retrospective studies have described a 5-year survival of about 70% following liver resection for NELM.[5,31–35] Moreover, after the publication of the prospective study performed by Mazzaferro et al. in which the authors compared the long-term outcomes

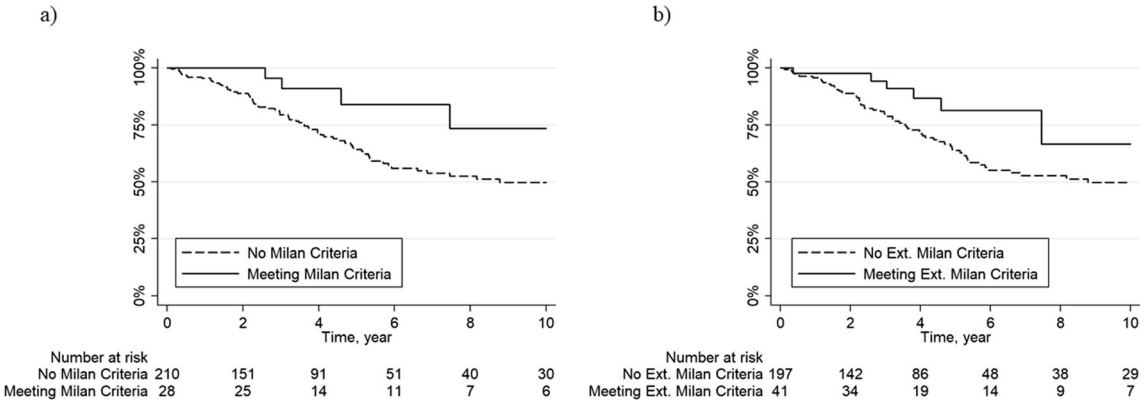

Fig. 1 Kaplan-Meier curves for overall survival of the study population stratified by **a** Milan Criteria and **b** extended Milan Criteria

Table 3 Univariate analysis for overall survival

	Meeting Milan Criteria		Meeting extended Milan Criteria	
Variables	5-year OS 95% CI	*p* value[a]	5-year OS 95% CI	*p* value[b]
Gender				
Male	75.0% (12.8–96.1)	0.31	78.9% (31.8–95.2)	0.19
Female	84.6% (51.2–95.9)	0.07	79.9% (49.0–93.2)	0.15
Functional				
Functional	57.1% (17.2–83.7)	0.74	60.0% (25.3–82.7)	0.88
Non-functional	100.0%	0.033	96.0% (74.8–99.4)	0.029
Primary tumor				
Non-pancreas	100%	0.10	87.7% (56.9–96.9)	0.13
Pancreas	74.0% (38.2–91.0)	0.19	75.8% (40.4–91.9)	0.19
Tumor grade				
G1 tumors	91.7% (53.9–98.8)	0.12	93.3% (61.3–99.0)	0.051
G2 tumors	72.9% (27.6–92.5)	0.18	67.7% (34.1–86.8)	0.41
Number of hepatic metastasis				
1–2 hepatic lesions	83.3% (27.3–97.5)	0.062	78.9% (31.8–95.2)	0.074
3–9 hepatic lesions	90.0% (47.3–98.5)	0.15	85.1% (52.3–96.1)	0.17
Tumor size				
< 30 mm	100%	0.051	94.1% (65.0–99.2)	0.10
≥ 30 mm	75.0% (39.4–91.5)	0.26	76.7% (48.2–90.8)	0.19
Type of surgery				
Minor liver resection	93.8% (63.2–99.1)	0.053	86.9% (63.3–95.8)	0.051
Major liver resection	66.7% (19.5–90.4)	0.43	71.4% (25.8–91.9)	0.58

[a] Compared with patients non-meeting the Milan Criteria

[b] Compared with patients non-meeting the extended Milan Criteria

of 88 patients with bilobar unresectable NELM who underwent LT ($n = 42$) versus non-LT therapies ($n = 46$), an increasing interest has been risen regarding the possibility to include LT as a reliable curative treatment for a subset of patients with NELM. Given the complex and evolving framework for the treatment of NELM, in this study, a multi-institutional cohort of 238 patients was analyzed to identify the subgroup of patients who might be considered eligible for LT according to Milan (≤ 60 years) and extended Milan (≤ 70 years) criteria and to investigate their prognosis after surgical resection. While only a minority of patients undergoing liver resection for NELM met the Milan ($n = 28$, 11.7%) and extended Milan criteria ($n = 41$, 17.2%), those patients demonstrated a better prognosis compared with patients without Milan and extended Milan criteria. Moreover, among patients in the Milan and extended Milan criteria groups, subsets of patients characterized by favorable clinic-pathological characteristics had 5-year survival > 80–90%, no significantly inferior to the 5-year OS reported in the literature for patients undergoing LT and meeting Milan criteria for NELM.[12]

In the ENETS 2008 guidelines, LT was considered an appropriate treatment for patients with diffuse unresectable liver metastases or for patients suffering from life-threatening hormonal disturbances refractory to medical therapy.[36] These recommendations were only partially changed in the ENETS 2016 guidelines suggesting that LT might be "generally not recommended as a treatment option in advanced NEN" while it may be "an option in highly selected patients with carcinoid syndrome or other functional NET and extended liver disease, early refractory to multiple systemic treatments including SSA, interferon (IFN)-alpha, locoregional therapies and PRRT".[37] The survival outcomes of patients undergoing LT for NELM ineligible to surgery due to widespread hepatic involvement as suggested by the ENETS guidelines have been reported in studies using national or regional databases that showed similar results.[5,14]

Gedaly et al. used the United Network for Organ Sharing (UNOS), a database recording data from every organ donation and transplant event occurring in the USA, to investigate the prognosis of patients undergoing LT for NELM from 1988 to 2008.[38] During the study period, among the 87,280 LT performed in the USA, only 150 (0.2%) transplants were performed for NELM with a 5-year OS calculated from the date of LT of 49%.[38] A comparable result was reported by Le Truet et al. who investigated outcomes and indications of patients undergoing LT for NELM using the European Liver

Transplant Registry (ELTR).[39] Among the 213 patients who underwent LT for NELM in 35 centers in Europe between 1982 and 2009, 5-year OS was 52% from the date of LT while the 5-year OS increased to 59% considering only those patients who underwent LT since 2000.[39]

In our series, while among the 238 patients who underwent surgical resection for NELM, 5-year OS resulted 67.1%; among the 55 (23%) patients with a Frilling I disease (NELMs involving < 25% of the liver), 5-year OS resulted 74.2%. Similarly, Mayo et al. analyzed a multi-institutional international cohort of 339 patients undergoing hepatectomy for NELM and reported that among the 129 (38%) patients with a Frilling I disease (NELMs involving < 25% of the liver), 5-year OS was 74%.[34]

While these results seem to confirm the current guideline for the management of NELM (surgical resection as first option for patients with resectable NELM and LT for selected patients with advanced disease), a different approach has been proposed by Mazzaferro and colleagues. In 2001, Coppa et al. reported a 5-year OS of 53% for the 9 patients who underwent LT between 1987 and 1999 for NELM meeting the proposed specific Milan criteria for NELM.[17] More recently, Mazzaferro et al. presented the updated series of 42 patients who underwent LT according to the Milan criteria between 1995 and 2010 comparing LT versus non-LT palliative treatments.[12] The authors reported a clear benefit for LT compared with non-LT palliative treatments in both univariate and multivariable models after propensity score matching (non-LT vs. LT, HR 7.4, $p = 0.001$).[36] Even though the authors compared the outcome of LT in the setting of palliation (patients with unresectable disease), the 5-year OS for patients meeting Milan criteria was 97% questioning the opportunity to include LT as a curative treatment for patients with a diagnosis of resectable NELM.

In our analysis, only a small subset of patients who underwent surgical resection met the Milan criteria for LT (Milan criteria, $n = 28$, 11.7%; extended Milan criteria, $n = 41$, 17.2%), and for these patients, the 5-year OS resulted > 80% (Milan criteria, 83%; extended Milan criteria, 81%). Furthermore, among patients meeting Milan criteria, subsets of patients with specific clinic-pathological characteristics demonstrated long-term survival reaching 5-year OS rates greater than 90% including G1 patients (5-year OS, 92%), patients undergoing minor liver resection (5-year OS, 94%), patients with a small number of NELM (1–2 NELM), and small tumor size (< 3 cm) (for both groups of patients, 5-year OS, 100%).

Several limitations should be considered when interpreting the results of our study. The retrospective and multicentric nature of this study did not allow to standardize the criteria used to define patients' operability, the surgical technique, the perioperative management as well as the patients' follow-up. On the other hand, the large study sample size might allow to generalize the results and permitted to perform multiple sub-analysis on a significant number of patients. Moreover, while in the international guidelines, LT and surgery are treatments suggested for different stage of disease (unresectable advanced disease vs. resectable disease), objective definitions of "resectable" and "unresectable" disease have not been identified (i.e., Frilling and Pavel classifications of NELM).[20,40] For this reason, in our cohort including 76% of patients with Frilling II disease, a subset of patients might have been considered unresectable when evaluated in other centers with more restrictive clinical practice guideline. Importantly, a recent report on the long-term outcomes of patients meeting Milan criteria and undergoing LT for NELM suggested that the risk of recurrence/disease progression might be almost null for those patients who did not experience any relapse within the first 5 years from the LT.[12] In comparison, patients meeting Milan criteria in our series were still at risk of recurrence and death after 5 years from the surgical resection (5-year OS, 83%, 10-year OS, 71%). These results might be strongly influenced by the small sample size of patients still at risk of recurrence after 5 years and should be confirmed in studies specifically designed to investigate the "very long-term" survival of patients undergoing LT and surgical resection for NELM.

In conclusion, while there was not a direct comparison of surgical resection and LT, the present study was designed to assess the long-term outcomes of a selected cohort patients who underwent surgical resection and met the Milan criteria for NELM. In our series, the OS of the subset of patients meeting Milan criteria had an improved long-term survival that was > 90% at 5 years in patients with favorable clinico-pathological characteristics. The results of our study confirmed that surgical resection should be the first option for patients with resectable NELM. While LT might be the optimal treatment for patients with unresectable NELM, the low availability of liver graft, the increased risk of perioperative mortality (i.e., waiting list and 1-year post-transplant death), and the quality of life following LT should be considered when evaluating patients with NELM for LT. Of note, clinical tools (i.e., nomogram) should be used to more objectively identify the morphological (i.e., number of NELM and tumor size) and biological (i.e., Ki67 label index and grade of tumor differentiation) characteristics of disease allowing comparison between treatments within "homogeneous" groups of patients.[6] Further studies investigating the impact of the novel treatments (i.e., somatostatin analogs, everolimus, sunitinib, and peptide receptor radionuclide therapy) combined with surgical resection and LT for patients with NELM are needed to better elucidate the optimal treatment of patients with advanced NET.

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- Revising it critically for important intellectual content: all authors.
- Final approval of the version to be published: all authors.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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