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Controversy Over Liver Transplantation or Resection for Neuroendocrine Liver Metastasis

Tumor Biology Cuts the Deal

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Background: In patients with neuroendocrine liver metastasis (NELM), liver transplantation (LT) is an alternative to liver resection (LR), although the choice of therapy remains controversial. In this multicenter study, we aim to provide novel insight in this dispute.

Methods: Following a systematic literature search, 15 large international centers were contacted to provide comprehensive data on their patients after LR or LT for NELM. Survival analyses were performed with the Kaplan-Meier method, while multivariable Cox regression served to identify factors influencing survival after either transplantation or resection. Inverse probability weighting and propensity score matching was used for analyses with balanced and equalized baseline characteristics.

Results: Overall, 455 patients were analyzed, including 230 after LR and 225 after LT, with a median follow-up of 97 months [95% confidence interval (CI): 85–110 months]. Multivariable analysis revealed G3 grading as a negative prognostic factor for LR [hazard ratio (HR) = 2.22, 95% CI: 1.04–4.77, $P = 0.040$], while G2 grading (HR = 2.52, 95% CI: 1.15–5.52, $P = 0.021$) and LT outside Milan criteria (HR = 2.40, 95% CI: 1.16–4.92, $P = 0.018$) were negative prognostic factors in transplanted patients. Inverse probability-weighted multivariate analyses revealed a distinct survival benefit after LT. Matched patients presented a median overall survival (OS) of 197 months (95% CI: 143–not reached) and a 73% 5-year OS after LT, and 119 months (95% CI: 74–133 months) and a 52.8% 5-year OS after LR (HR = 0.59, 95% CI: 0.3–0.9, $P = 0.022$). However, the survival benefit after LT was lost if patients were transplanted outside Milan criteria.

Conclusions: This multicentric study in patients with NELM demonstrates a survival benefit of LT over LR. This benefit depends on adherence to selection criteria, in particular low-grade tumor biology and Milan criteria, and must be balanced against potential risks of LT.

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D.E. and D.J.S. are joint senior authors.
No third-party financial funds or materials were accepted or necessary for the execution of this research project.
The authors report no conflicts of interest.
Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.annalsofsurgery.com.

ISSN: 0003-4932/23/27705-e1063
DOI: 10.1097/SLA.0000000000005663

Keywords: liver metastases, liver resection, liver transplantation, NET, neuroendocrine tumors

(*Ann Surg* 2023;277:e1063–e1071)

The incidence of gastroenteropancreatic neuroendocrine tumors (NETs) increased over recent years to the point that this entity is no longer a rarity for general surgeons.[1,2] We have learned that for this heterogenous group of tumors, both the prognosis and biological behavior mostly rely to the site of the primary tumor, stage, and grading.[1,3] When NELM (neuroendocrine liver metastases) are already present at the time of diagnosis, which is seen in about half of the cases due to the portal venous drainage, the 5-year survival is poor, ranging between 20% and 40%.[4–6]

Treatment options for metastatic NET evolved over the last years as displayed by current international guidelines and recommendations.[2,7–12] Despite some benefit regarding progression-free survival (PFS), none of the treatments demonstrated an overall survival (OS) benefit in these patients.[13–16] For example, peptide receptor radionuclide (PRRT), which showed promising results after treatment with ^{177}Lu-DOTATATE in patients with metastatic midgut NET, failed to provide a survival benefit in the final analysis.[17,18] In patients with resectable NELM, resection remains the first choice,[12,19,20] although complete (R0) liver resection (LR) is feasible in only a minority (7%–15%) of patients and recurrence is almost the rule (70%–90%), mostly occurring within the 2 first years after surgery due to residual microscopic disease.[21–23] This limitation is largely underestimated by preoperative or even intraoperative imaging.[24] Liver transplantation (LT) has therefore been introduced for selected patients with NELM, like the situation in hepatocellular carcinoma, to maximize surgical radicality and minimize early recurrence in and outside the liver.[25] Selection of patients with NELM for LT relies on a disease limited to the liver, a moderate disease load and a stable behavior over the last few months, reflecting a low-grade biology.[26]

The choice between LR and LT remains a debated topic, with limited and unconvincing data favoring one or the other approach.[2,10,11,27] While LR and LT have been explored separately, a comparative analysis is missing and the recommendation in guidelines only depends on expert consensus.[12,23] This shortcoming is mostly due to the heterogeneity of patient cohorts. The aim of this multicentric study was to compare patient outcomes after LR versus LT through the loupe of a matched analysis.

METHODS

Fifteen large international centers were identified and contacted following a systematic literature search, to provide comprehensive long-term data on patients after LR or LT for NELM. The search strategy for the identification of international centers was provided in Supplementary Material 1 (Supplemental Digital Content 1, http://links.lww.com/SLA/E183). Data were collected retrospectively between 1988 and 2021, including demographics, patient outcomes, types of treatment (resection or transplantation), recurrence, and survival status at the last follow-up. The primary tumor location (if available), presence of extrahepatic metastasis, histology including differentiation, the extent of liver metastasis, and management of the primary tumor were included. NET grading was performed according to the WHO classification into G1 (< 2% Ki-67 positive cells or mitotic figures per 10 HPF), G2 (2%–20%), or G3 (> 20%). Patients who did not undergo LR or LT were excluded from the study. The primary aim of the study was to evaluate the association between the type of curative treatment (resection or transplantation) and patient OS. Secondary aims were to study the association between the type of treatment and PFS and to identify prognostic factors for survival after LT. Imaging for preoperative workup included computerized tomography, magnetic resonance imaging, or different kinds of sandostatin receptor imaging (octreotide scan or Gallium-68-DOTATOC-PET), whenever possible. Patients were discussed in separate interdisciplinary tumor boards of each participating center. If available in a specific center, the decision for LT was based on center-specific criteria (Table 2). Patients were followed up using repeated abdominal imaging every 6 to 12 months or whenever clinically indicated. The respective local authorities approved the use of patient-level data for this analysis.

Statistical Analyses

OS was defined as the time interval between the date of LR or LT and the death of any cause. Patients alive at the last follow-up were censored and median follow-up time calculated with the reversed Kaplan-Meier method. Survival probabilities were calculated using the Kaplan-Meier method, and curves compared with the log-rank test with Benjamini+Hochberg correction for multiple comparisons. Univariable and mixed-effect multivariable Cox proportional hazard regression model analyses was performed to identify predictive factors associated with survival after either transplantation or resection, with center implemented as a random variable. The concordance statistic served to assess the goodness of fit of multivariate models. To account for underlying differences and minimize bias due to the expected heterogeneity of the collected data, inverse probability weights based on logistic regression distance were calculated and weighted multivariate analyses performed including all patients. Furthermore, 1:1 ratio propensity score matching was performed using the nearest neighbor method (logistic regression distance, caliper: 0.1) based on age, primary tumor location, and tumor grade. Statistical significance was defined as P value <0.05. Numerical variables are expressed as mean ± SD or median ± interquartile range as appropriate, and their distributions were compared by Student t test (after checking the assumption of normal distribution by the Shapiro-Wilk test) or Wilcoxon rank-sum test. Categorical variables are presented as number (n) and percentage (%), and their distributions were compared with the Fisher exact test. R V4.0.2 and R-Studio V1.3.1093 were used for statistical analyses, calculations, and graphical representations.

RESULTS

Baseline Characteristics

Two hundred twenty-five (49.5%) patients undergoing LT and 230 (50.5%) resected patients were included. Their median follow-up was 93 months [95% confidence interval (CI): 80–107 months] and 102 months (95% CI: 77–127 months), respectively. Baseline patient characteristics are given in Table 1. In summary, most primary NET were located in the pancreas or small bowel without difference between the 2 groups. Transplanted patients were younger, had a higher proportion of G1 NET, and had more, but smaller liver lesions. Selection for LT was performed according to center-specific criteria, with most centers using a modified version of the Milan criteria[25] (Table 2). Most patients received long-term immunosuppression with tacrolimus alone.

Survival Outcomes in Unmatched Patients

Overall, the whole cohort of patients with NELM after LR or LT demonstrated a PFS of 42 months (95% CI: 35.0–54.8 months) and an OS of 127 months (95% CI: 120–151 months). In a first step, PFS and OS were stratified

TABLE 1. Patient Characteristics

	Median (IQR) or n (%)		
	LR (N = 230)	LT (N = 225)	*P* Value
Age at diagnosis	58.0 (50.0, 66.8)	47.0 (38.0, 55.0)	< 0.001
Sex			
Female	105 (46)	105 (47)	0.851
Male	125 (54)	120 (53)	
Primary tumor location			
Small bowel	104 (45)	101 (45)	
Pancreas	94 (41)	80 (36)	0.226
Other	32 (14)	44 (20)	
Grade			
Grade 1	78 (34)	100 (44)	
Grade 2	97 (54)	54 (24)	< 0.001
Grade 3	19 (8)	10 (4)	
Unknown	9 (4)	61 (27)	
Ki-67 index (%)	5.00 (2.00, 10.0)	3.00 (1.90, 8.20)	0.059
Lesions largest size	26.5 (15.0, 55.0)	17.3 (7.88, 40.0)	0.01
Lesion number	1.00 (1.00, 3.75)	12.0 (7.00, 100)	< 0.001
Result of hepatic resection margin			
R0	111 (48)	166 (74)	
R1	28 (112)	1 (0.4)	< 0.001
R2	37 (16)	0	
Unknown	54 (24)	58 (26)	
T stage of the primary tumor			
T1	5 (2)	4 (2)	
T2	44 (19)	29 (13)	< 0.001
T3	55 (24)	36 (16)	
T4	28 (12)	20 (9)	
Unknown	98 (43)	136 (60)	
N stage of the primary tumor			
N0	29 (13)	18 (8)	
N+	106 (44)	71 (32)	< 0.001
Unknown	95 (41)	136 (60)	
90-d mortality	3 (1)	13 (6)	0.021
Resection			
Minor	127 (55.2)		
Major	98 (42.6)	—	
Missing	5 (2)		

IQR indicates interquartile range.

between patients undergoing LR versus LT. For transplanted patients, median PFS was 117 months (95% CI: 71.3–169.0 months) with a 5-year PFS of 62.4%. In resected patients, median PFS was significantly reduced with 16 months (95% CI: 11.6–26.1 months) and a 5-year PFS of 18.1% [hazard ratio (HR) = 0.28, 95% CI: 0.21–0.36, $P < 0.001$; Fig. 1A]. Median OS for transplanted patients was 197 months (95% CI: 143–not reached), with a 5-year OS of 74%, while OS in resected patients was again significantly reduced with 119 months (95% CI: 82–130 months) and a 5-year OS of 68.8% (HR = 0.65, 95% CI: 0.48–0.87, $P = 0.004$; Fig. 1B). Postoperative 90-day mortality was 1.3% after LR and 5.8% after LT ($P = 0.021$).

Factors Associated With Survival After Transplantation and Resection

To identify risk factors for OS, univariable and multivariable analyses was performed (Table 3). In resected patients, univariable and multivariable analyses (concordance = 0.600, SE = 0.035) demonstrated G3 grading as the only factor predicting poorer outcomes (HR = 2.22, 95% CI: 1.04–4.77, $P = 0.04$), while age and primary tumor location did not influence long-term survival outcome. In contrast, in transplanted patients, univariable and multivariable analyses (concordance = 0.747, SE = 0.036) revealed G2 grading (HR = 2.52, 95% CI: 1.15–5.52, $P = 0.021$) and exceeding Milan

TABLE 2. Center-specific Selection Criteria for LT in Metastatic NET

	Portal Drainage of Primary	NET G1–G2	Ki-67 Index	No Extrahepatic Disease	< 50% Hepatic Tumor Load	Stable Disease for 6–12 mo	Age <60–65	CI to LT	Additional Criteria
Milan, Italy[25]	+	+	–	+	+	+	+	+	
Brussels, Belgium	+	+	–	+	+	+	+	+	
Hong Kong, China									
Mainz, Germany	–	–	–	+	+	+	–	+	Primary must be known
Mayo Clinic, United States	+	–	–	+	–	–	–	+	Primary must be known
Murcia, Spain	+	+	+ (< 10%)	+	–	+	–	+	Primary must be known. Selected patients: Ki-67 < 20% and age 65–70
Frankfurt, Germany	+	–	+ (< 10%)	+	–	+	–	+	Primary must be known and removed
Oslo, Norway	–	+	+ (< 10%)	+	–	+	+	+	Primary outside abdomen accepted
Warsaw, Poland	–	+	–	+	–	+	–	+	
Zurich, Switzerland	+	+	+ (< 10%)	+	+	+	–	+	

CI indicates contraindication.

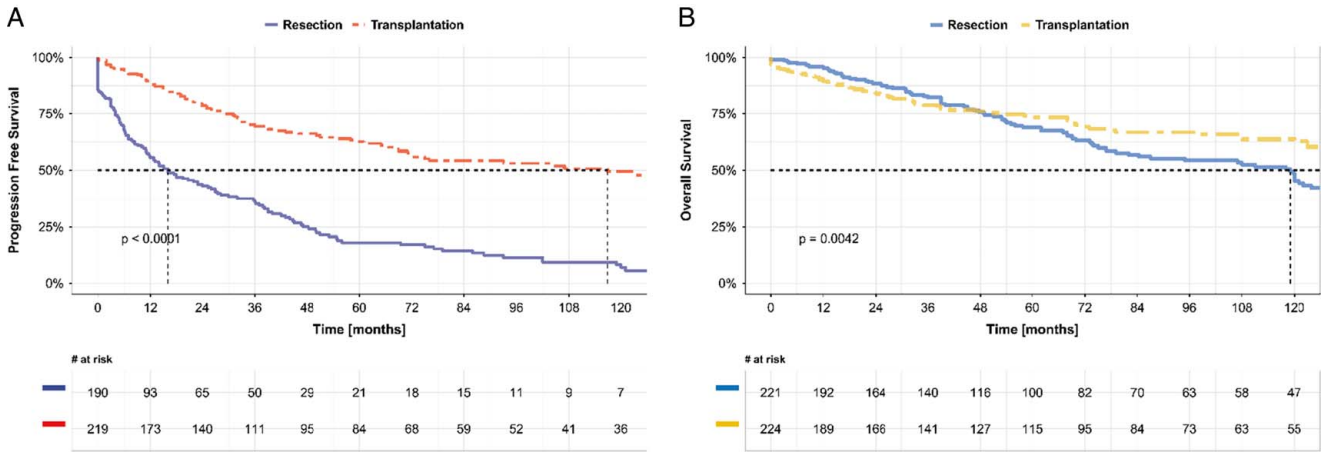

FIGURE 1. A, Kaplan-Meier curves depicting PFS of patients with NELM undergoing LR or LT. B, Kaplan-Meier curves depicting OS of patients with NELM undergoing LR or LT.

criteria (HR = 2.40, 95% CI: 1.16–4.92, $P = 0.018$) as unfavorable prognostic factors. Median OS of patients with G1 NET was 220 months (95% CI: 197–not reached) with 92.9% 5-year survival, compared with 120 months (95% CI: 98–not reached) and a 70.0% 5-year survival in patients with G2 histology (Fig. 2A). Ki-67, a marker for tumor cell proliferation, was assessed and the available population dichotomized at the median value of 5%. LT patients with Ki-67 staining <5% had an OS of 220 months (95% CI: 216–not reached) compared with 120 months (95% CI: 70–not reached, $P < 0.001$) in patients with Ki-67 staining ≥5% (Fig. 2B).

Inverse Probability-weighted Analyses

To account for underlying patient baseline differences and the expected heterogeneity of the collected data and minimize selection bias among centers, we calculated inverse probability weights for receiving LT versus LR based on previously described and above-identified factors influencing outcomes after either both treatments, namely, age, ENETS grade, and primary tumor localization. Based on these weights, age ($P = 0.331$), grade (G2: $P = 0.710$, G3: $P = 0.885$), or tumor localization ($P = 0.930$) did not influence the choice of treatment (LR vs LT).

TABLE 3. Univariable and Multivariable Analyses of Factors Associates With Survival After LT or Liver Surgery for NELM

Variables	N [n (%)]	OS [Median (95% CI)] (mo)	Univariate Analysis [HR (95% CI)]	*P*	Multivariate Analysis [HR (95% CI)]	*P*
LT						
Age			1.02 (1.00–1.04)	0.127	0.99 (0.96–1.02)	0.51
Primary location						
Pancreas	101 (45)	123 (98–NA)	—	—	—	—
Small bowel	79 (35)	216 (151–NA)	0.60 (0.35–1.01)	0.055	0.74 (0.37–1.50)	0.407
Other	44 (20)	143 (78–NA)	0.94 (0.53–1.66)	0.82	1.35 (0.59–3.08)	0.481
Tumor grade						
G1	99 (44)	220 (197–NA)	—	—	—	—
G2	54 (24)	120 (98–NA)	**3.01 (1.53–5.92)**	**0.001**	**2.52 (1.15–5.52)**	**0.021**
G3	10 (4.5)	49 (11–NA)	3.79 (1.55–9.23)	0.003	1.92 (0.67–5.49)	0.222
Milan criteria						
Inside	86 (52)	320 (NA–NA)	—	—	—	—
Outside	78 (46)	107 (69–216)	**3.67 (1.98–6.81)**	**< 0.001**	**2.40 (1.16–4.92)**	**0.018**
LR						
Age			1.00 (0.99–1.02)	0.803	1.00 (0.98–1.02)	0.957
Primary location						
Pancreas	104 (45)	122.1 (84.34–NA)	—	—	—	—
Small bowel	94 (41)	107 (70–130)	1.43 (0.94–2.17)	0.092	1.39 (0.89–2.17)	0.152
Other	31 (14)	79.05 (57.79–NA)	1.56 (0.81–2.99)	0.18	1.39 (0.71–2.74)	0.337
Tumor grade						
G1	77 (34)	123.98 (107–141.58)	—	—	—	—
G2	124 (54)	118 (76.94–155)	0.97 (0.63–1.48)	0.878	1.05 (0.67–1.63)	0.844
G3	19 (8)	39 (19.45–NA)	**2.23 (1.07–4.65)**	**0.032**	**2.22 (1.04–4.77)**	**0.04**
Resection margin						
R0	110 (48)	120 (95–144)	—	—	—	—
R1	28 (12)	111 (53–NA)	1.24 (0.65–2.34)	0.512	1.09 (0.54–2.19)	0.817
R2	37 (16)	87 (62–NA)	1.53 (0.82–2.85)	0.183	1.53 (0.80–2.90)	0.195

Bold indicates a statistically significant.
NA indicates not available.

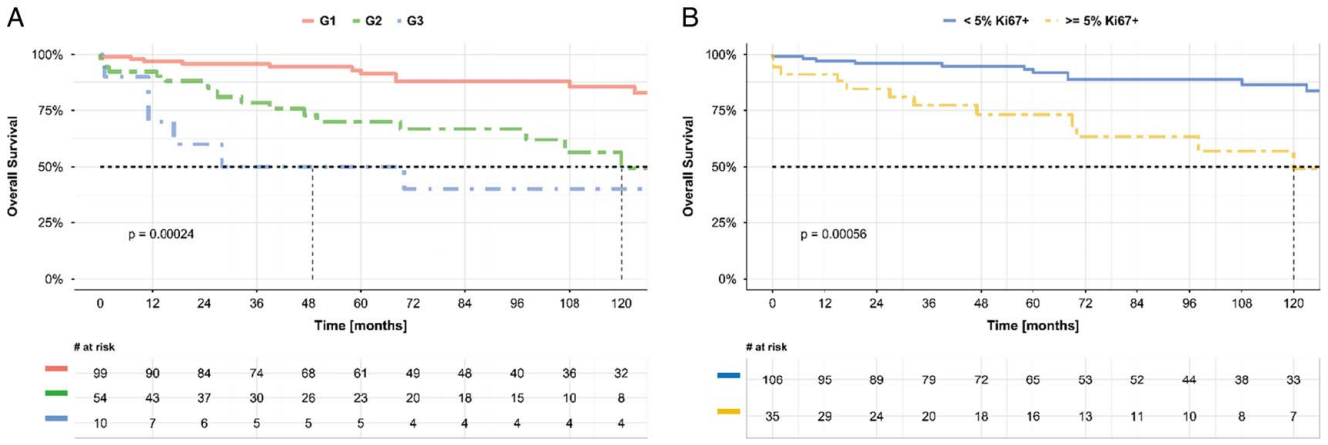

FIGURE 2. A, Kaplan-Meier curves depicting OS of patients with NELM undergoing LT stratified according to ENETS tumor grade. B, Kaplan-Meier curves depicting OS of patients with NELM undergoing LT stratified according to Ki-67 staining (< 5% vs ≥ 5%).

Weighted multivariable logistic regression analyses for 10-year OS, however, revealed a distinct survival benefit for patients undergoing LT compared with LR ($P = 0.0004$), which was more pronounced than in unweighted analyses (0.027). Survival was furthermore reduced by G2 ($P = 0.015$) and G3 grade ($P \leq 0.001$). Similar findings were obtained with weighted multivariable cox regression analysis, with LT showing improved survival ($P = 0.012$), while G3 decreased survival ($P = 0.031$).

Survival Outcomes in Matched Patient Cohorts

Next, a 1:1 propensity score match of R0 resected patients undergoing LT or LR based on age, tumor grade, and primary tumor location was performed to compare long-term outcomes in a comparable patient cohort (n = 192). The match equalized underlying differences in age, tumor grading, median Ki-67 count, and largest tumor lesion size (Table 4). After matching, PFS in LT patients was 107 months (95% CI: 69–216 months), their 5-year PFS was 64.2%, compared with 18 months (95% CI: 12.8–37 months) and 14.2% 5-year PFS in resected patients (HR = 0.25, 95% CI: 0.16–0.39, $P = 0.001$, Fig. 3A). The benefit in PFS translated into a significantly improved OS, which was 205 months (95% CI: 143–not reached) with a 5-year OS of 75% after LT, versus 120 months (95% CI: 74–133 months) with a 5-year OS of 68.3% after resection (HR = 0.56, 95% CI: 0.35–0.90, $P = 0.015$, Fig. 3B). Finally, patients were compared regarding their status inside or outside Milan criteria. In the overall cohort, patients within Milan criteria, OS after LT was 320 months (95% CI: not reached) versus 120 months (95% CI: 95–not reached) after resection (HR = 0.24, 95% CI: 0.11–0.48, $P < 0.001$). This OS benefit was preserved when only matched patients were considered (LT: median survival not reached, 95% CI: not reached–not reached vs LR: 119 months, 95% CI: 75–not reached, HR = 0.18, 95% CI: 0.06–0.52, $P = 0.00042$, Fig. 3C). In contrast, OS was similar after LT and LR for patients outside Milan in the whole cohort (107 months, 95% CI: 69–216 vs 111 months, 95% CI: 69–134, HR = 0.87, 95% CI: 0.55–1.35, $P = 0.54$) as well as for matched patients (LR: 74 months, 95% CI: 52.8–not reached vs LT: 127 months, 95% CI: 69–not reached, HR = 0.64, 95% CI: 0.31–1.33, $P = 0.24$, Fig. 3D).

TABLE 4. Baseline Characteristics of Patients After Propensity Score Matching

	LR (N = 96)	LT (N = 96)	*P* Value
Age at diagnosis	51.0 (42.0, 57.9)	50.5 (41.0, 57.0)	0.628
Sex (female/male) [n (%)]	42 (43.8)/54 (56.2)	43 (44.8)/53 (55.2)	1
Primary tumor location [n (%)]			
Small bowel	32 (33.3)	33 (34.4)	0.829
Pancreas	48 (50.0)	44 (45.8)	
Other	16 (16.7)	19 (19.8)	
Grade [n (%)]			
Grade 1	38 (39.6)	38 (39.6)	
Grade 2	45 (46.9)	44 (45.8)	0.829
Grade 3	6 (6.2)	4 (4.2)	
Grade unknown	7 (7.3)	10 (10.4)	
Ki-67 index (%)	5.00 (2.00, 10.0)	5.80 (2.00, 9.00)	0.094
Lesions largest size (mm)	30.0 (15.0, 55.0)	22.0 (13.0, 60.0)	0.222
Lesion number	1.00 (1.00, 3.00)	10.0 (7.00, 100)	< 0.001
90-d mortality [n (%)]	2 (2.1)	7 (7.3)	0.185

Continuous variables are shown as median (interquartile range).

DISCUSSION

This large multicentric study offers new insights into the surgical management of NELM. LT offers not only a far better PFS than LR in comparable groups of patients but also a significant benefit on long-term survival. The benefit of LT relies on adherence to selection criteria, most notably a low-grade tumor biology. In patients outside Milan criteria, the transplant benefit is lost. Our data highlight the pivotal role of tumor biology as a prognostic factor for NELM, and thus as a key selection criterion for LT.

Several authors have reported encouraging results for LT in patients with NELM, but only one comparative study from Milan is available comparing 42 patients after LT to patients who received medical treatment only.[25] The main criticism with this study was the limited sample size and the inherent heterogeneity of patient cohorts. To minimize this bias, we performed inverse probability weighting and propensity score matching, uniquely possible here due to a large number of patients, which represents the highest available level of evidence and considering that a randomized controlled trial is not feasible in this disease.[25] In addition, the long follow-up time available in our study enabled us to gauge the long-term effects of surgery, which are otherwise difficult to assess due to the slow evolution of low-grade NET.[28,29]

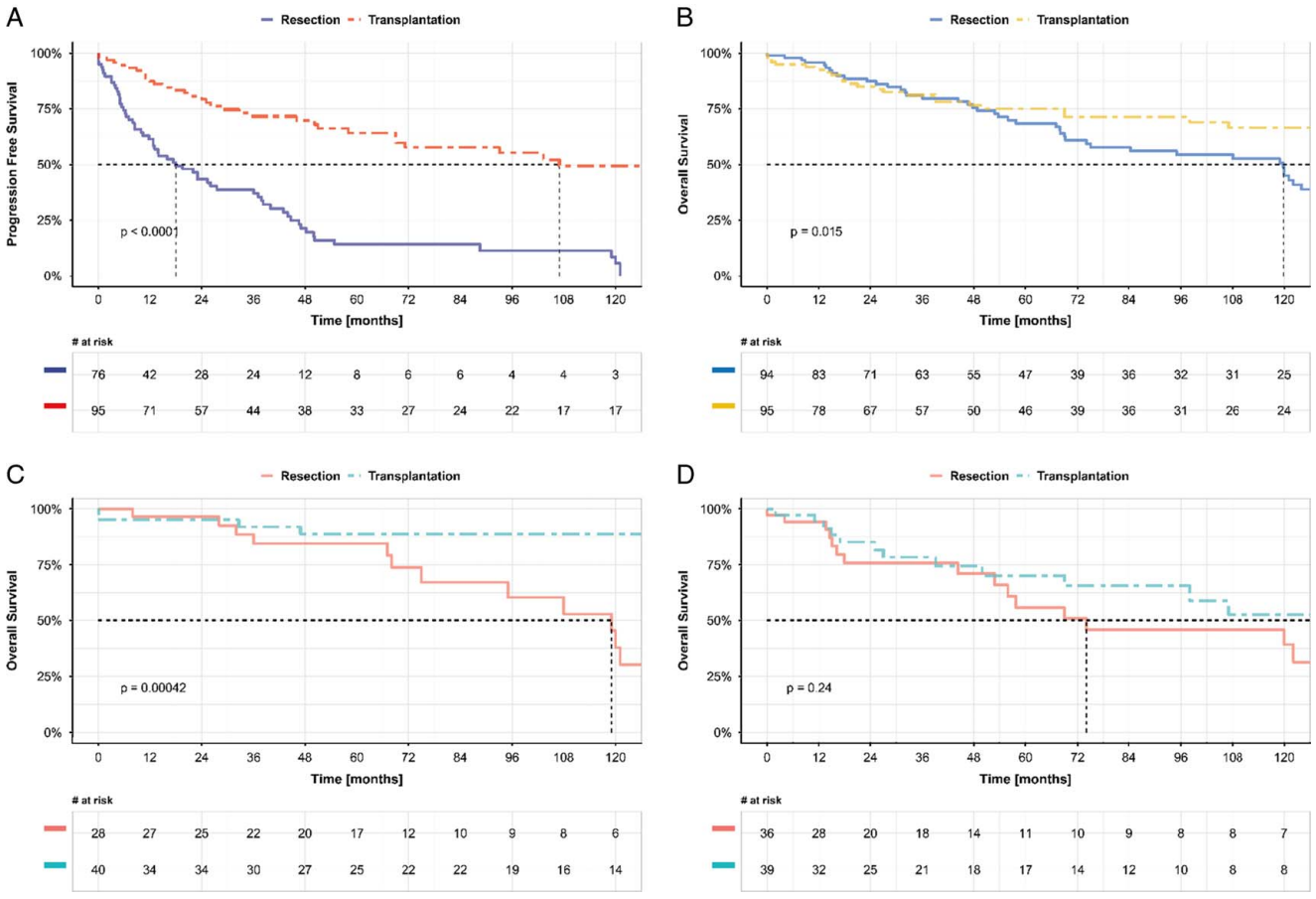

FIGURE 3. A, Kaplan-Meier curves depicting PFS of propensity score–matched patients with NELM undergoing LR or LT. B, Kaplan-Meier curves depicting OS of propensity score–matched patients with NELM undergoing LR or LT. C, Kaplan-Meier curves depicting OS of propensity score–matched patients with NELM inside modified Milan criteria undergoing LR or LT. D, Kaplan-Meier curves depicting OS of propensity score–matched patients with NELM outside modified Milan criteria undergoing LR or LT.

Despite the advent of many innovative treatment modalities, the standard approach to NELM remains resection. In the rare patients with solitary metastasis, where radical (R0) surgery is possible, excellent long-term outcomes can be obtained such as shown by an US multicentric analysis including 581 patients.[12,30] The drawback of an upfront surgical approach is incomplete tumor resection leaving behind microscopic disease in most patients. This relies on 3 different growth patterns of NELM, described by Frilling et al.[31] While type I NELM show isolated single lesions, type II NELM present with a metastatic bulk with smaller surrounding lesions, always involving both hemi livers, and type III NELM grow as disseminated bilobar tumor growth invading near all liver parenchyma. Consequently, radical resection is reserved for patients with type I and some selected patients with type II. Technical advances in liver surgery, such as associating liver partition and portal vein ligation for staged hepatectomy, have been shown to increase the percentage of R0 resection rates of multiple liver metastasis.[32] However, the major drawback of any LR is to leave behind potential microscopic disease, providing the soil for recurrence. Microscopic disease is typically not detected by preoperative imaging or intraoperative ultrasound, but resides in the hepatic parenchyma.[24] This explains the high recurrence rates after resection of NELM.[12,33]

The rationale behind LT to treat unresectable liver tumors was originally conceived by Starzl in his pioneering studies.[34] Despite the technical success, poor oncological outcomes after LT in the 1960–1990s faded away the enthusiasm.[23,34] Over the years, advances in immunosuppression and perioperative patient management, and finally the introduction of better selection criteria, for example, Milan criteria for HCC or the Mayo protocol for perihilar cholangiocellular carcinoma, renewed the interest in transplant oncology. Over time, selection criteria for LT in NELM patients improved. The report on the European Liver Transplant Registry (ELTR), including 213 liver recipients, reported a 5-year OS of 52%.[35] This study was the first to identify several prognostic factors including major resection in addition to LT, poor tumor differentiation, or large involvement of the liver (tumor hepatomegaly).[35] More recently, the Milan group proposed refined selection criteria which allowed for staggering results (94% 5-year survival rate).[25] These encouraging improvements further emphasized the possibility of a curative role of LT in the treatment of selected NELM patients.

The issue today is whether resectable patients might also be transplanted. Macroscopic growth patterns and tumor load are predictive for survival after LR.[31] In the context of LT, tumor biology and stability under medical treatment turned out to be more important. NET represent a very heterogenous group of tumors, so treatment strategies need to be adapted according to prognostic, biologic risk factors. According to the WHO 2017 or ENETS classifications, NET are currently graded on the basis of tumor proliferation (Ki-67, mitotic index).[36,37] In the present study, G3 grading was identified as a risk factor for reduced survival after LR and G2 grading (with a cutoff level $\geq 5\%$) was a risk factor for worse survival after LT. These findings highlight the importance of tumor biology as a critical prognostic factor, and a key selection criterion for LT. Some centers traditionally accept a Ki-67 index of up to 10% as candidates for LT, indicating that the group of G2 NET does not have a uniform prognosis. Indeed, this is a drawback of the current WHO and ENETS grading system which does not optimally discriminate patients with G2 NET.[38,39] In the present analysis, many participating institutions used a Ki-67 index cutoff at 10% for LT, which was defined arbitrarily. In the present analysis, we observed a good cutoff level between good (220 months) and reduced (120 months) survival in our patient cohort at the median (5%) of our cohort, which suggests that LT in patients with NELM $>$G1 requires careful selection, and that the historical cutoff of 10% might be too optimistic.

Treatment modalities for metastatic NET underwent a major evolution, and it may be expected that more effective systemic treatment will further improve the results of LR and LT. Medical treatments such as somatostatin analogs, mTOR inhibitors, tyrosine kinase inhibitors, cytotoxic regimens (eg, temozolomide and capecitabine) and PRRT all have indeed shown in placebo-controlled studies to improve PFS compared with controls.[7,18,40–43] Hence, none of these medical treatments translated into better survival. The randomized NETTER-1 trial, including only midgut tumors for PRRT, demonstrated an 18% response rate indicating that tumor downsizing is possible,[17] and some retrospective studies indicate that PRRT is also effective in the case of metastatic pancreatic NET.[44,45] In this sense, PRRT may help to increase resection rates if used as a neoadjuvant treatment or enable better control of a disease relapse after LR or LT.[46] Likewise, mTOR inhibitors, which demonstrated to improve PFS in metastatic NET, may help to improve tumor control after LT if used in the immunosuppressive regimen.[14] Recently, a multicenter trial identified a benefit for mTOR inhibitors in patients after LT for active hepatocellular carcinoma compared with immunosuppression with a calcineurin inhibitor.[47] Likewise, the use of an mTOR inhibitor may also improve tumor control after LT for NELM, avoiding negative impacts of posttransplant immunosuppression by calcineurin inhibitors. The use of steroid-free, low-dose tacrolimus regimens is another option which needs future evaluation in the context of LT for NELM.[48]

The finding of better survival in patients with low-grade NELM after LT should close the debate about whether LT is justified for this particular indication. The proposed Milan criteria provide a solid and comprehensive basis for patient selection, and selection of patients outside Milan criteria should be avoided. Tumor biology remains the critical parameter and a Ki-67 index $>5\%$ should call for caution. Careful selection of LT candidates remains critical to justify the use of any graft, including split and living donor grafts. NELM patients usually do not present with portal hypertension and can usually well tolerate small size grafts.[34,49,50] These patients, if selected for LT, must benefit from a Model for End-stage Liver Disease exception status to secure timely transplantation, and this can probably best be achieved using partial livers such as split and living donor LT. Public discussions must be avoided such as that seen following the transplantation of Apple CEO Steve Jobs.[34,51,52] Despite superior results of LT on long-term outcomes for a subgroup of NELM patients, the decision in an individual patient remains difficult, mostly due to the higher invasiveness and risks of LT. Despite a better survival in transplanted compared with resected patients, a uniform use of LT for patients with NELM is unlikely to happen for several reasons. First, morbidity and mortality after LT are higher compared with LR, also reflected by the numbers in the present study. It remains, therefore an individual decision whether a patient is willing to undergo LT expecting a benefit on the long-term outcome, which becomes apparent only after many years, at the price of potentially severe complications. The second issue is a more general ethical question. An unrestricted recommendation for LT in the setting of NELM would create significant pressure on the waiting list. The current discussion about the role of LT for various types of liver metastasis must intensify our discussions on how to expand the donor pool, for example, by higher utilization rates or the use of living donors. In addition, waiting list priority of patients with chronic liver failure must be protected from an increasing number of oncologic patients who profit from prioritization by Model for End-stage Liver Disease exception points.

We would like to acknowledge the limitations of this study. There is missing data for N and T stages of the primary tumors due to the retrospective nature of this study. In the metastatic situation, however, tumor grading and tumor load are the main prognostic factors, apart from extrahepatic disease or nonradical resections which were excluded in the present analysis. In contrast, T and N stage did not appear as independent prognostic factors in this or in previous analyses. We, therefore, do not expect the missingness of this data to have an impact on the conclusion of this paper. Second, the time of diagnosis to treatment may differ for LT or LR. We decided not to use the time of diagnosis but the time of surgery to calculate outcomes, to remain conservative, and avoid an overinterpretation and bias in favor of LT patients. Similar, patients might have undergone systemic therapies before surgery, which were not available in detail for this analysis. However, as discussed above, none of these therapies so far demonstrated a benefit on OS. Finally, we decided not to match the patients for the number of metastases, which is obviously higher in patients selected for LT who are considered as nonresectable in most of the cases. The result is a higher number of metastases in the LT group which does not reflect a bias in favor of LT patients and underlines the benefit of LT compared with LR in patients with NELM.

Individualized treatment or precision medicine is the future of surgical oncology. In NELM patients, an important subset remains without recurrence after LR and has a stable disease over a long period of time. Similar, after PRRT, some patients may undergo long-term remission despite the overall negative result from the NETTER trial. One of the future challenges, therefore, is to identify these subgroups, not possible here with the available data, due to the missingness of parameters or the availability of molecular data that are required for further prognostic discrimination. The future challenge will be to identify the subset of patients with a limited number of metastasis but with a high risk of hepatic recurrence, which is likely caused by molecular mechanisms that yet remain to be identified. Until this data is available, our data suggests that LT offers better long-term outcomes than LR. However, this is limited to

highly selected patients and comes at the price of a higher morbidity and mortality.

In conclusion, our study should justify LT as a treatment modality in patients with NELM offering superior PFS and OS on the condition that strict selection criteria are followed.

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