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ORIGINAL ARTICLE

Early Recurrence of Neuroendocrine Liver Metastasis After Curative Hepatectomy: Risk Factors, Prognosis, and Treatment

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Abstract

Background Early tumor recurrence after curative resection typically indicates a poor prognosis. The objective of the current study was to investigate the risk factors, treatment, and prognosis of early recurrence of neuroendocrine tumor (NET) liver metastasis (NELM) after hepatic resection.

Methods A total of 481 patients who underwent curative-intent resection for NELM were identified from a multi-institutional database. Data on clinicopathological characteristics, intraoperative details, and outcomes were documented. The optimal cutoff value to differentiate early and late recurrence was determined to be 3 years based on linear regression.

Results With a median follow-up of 60 months, 223 (46.4%) patients developed a recurrence, including 158 (70.9%) early and 65 (29.1%) late recurrences. On multivariable analysis, pancreatic NET, primary tumor lymph node metastasis, and a microscopic positive surgical margin were independent risk factors for early intrahepatic recurrence. While recurrence patterns and treatments were comparable among patients with early and late recurrences, early recurrence was associated with worse disease-specific survival than late recurrences (10-year NELM-specific survival, 44.5 vs 75.8%, $p < 0.001$). Among the 34 (21.5%) patients who underwent curative treatment for early recurrence, post-recurrence disease-specific survival was better than non-curatively treated patients (10-year NELM-specific survival, 54.2 vs 26.3%, $p = 0.028$), yet similar to patients with late recurrences treated with curative intent (10-year NELM-specific survival, 54.2 vs 37.4%, $p = 0.519$).

Conclusions Early recurrence after surgery for NELM was associated with the pancreatic type, primary lymph node metastasis, and extrahepatic disease. Re-treatment with curative intent prolonged survival after recurrence, and therefore, operative intervention even for early recurrences of NELM should be considered.

Keywords Neuroendocrine liver metastasis · Recurrence · Hepatectomy · Early · Late

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Introduction

Neuroendocrine tumors (NET) are a rare group of hormone-secreting neoplasms arising from a variety of neuroendocrine cell types within the gastroenteropancreatic and bronchopulmonary systems. Although NETs are mostly considered to be indolent, these neoplasms can display malignant behavior with development of metastatic disease. Furthermore, NETs can cause severe hormonal symptoms and dysfunction of involved organs.[1] Approximately 40–85% of patients with NET have synchronous or metachronous neuroendocrine liver metastasis (NELM), and many of these patients have constitutional symptoms and worse prognoses.[1] Specifically, the 5-year survival of patients with NELM ranges from 13 to 54% compared with 75–99% for patients with non-metastatic NET.[2–4] Among patients with NELM, surgical resection is the only curative option, yet is only feasible in roughly 20–40% of cases.[5] Recurrence after surgery is common and decreases both quality of life and long-term survival of patients. Intrahepatic recurrence following initial curative hepatectomy for NELM can be as high as 70–94% at 5 years.[6–9] Therefore, appropriate management of recurrence is central to improve prognosis of patients after NELM resection.

Shorter time to recurrence has been associated with a worse prognosis after resection of hepatocellular carcinoma (HCC) [10–13] and colorectal liver metastasis (CRLM), [14–16] yet has not been well defined for NELM. The management of recurrent tumors may also be limited and varied with different therapeutic benefits. For example, post-recurrence outcome following repeat hepatectomy for early versus late recurrence was much worse among HCC patients, but was similar among patients with CRLM.[12, 14] In NELM, the correlation between time to recurrence after hepatic resection and patient outcomes has not been specifically investigated. As such, the objective of the current study was to define the time course of recurrence among patients undergoing curative-intent resection of NELM. More specifically, we sought to identify risk factors of early recurrence, as well as characterized the treatment and outcome of patients with early recurrence after curative-intent surgery for NELM.

Materials and Methods

Study Population

A total of 548 patients undergoing simultaneous or staged partial hepatectomy for NELM from 1990 to 2015 were identified from a multi-institutional database. Data from Johns Hopkins Hospital, Baltimore, MD; Scientific Institute San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; Stanford University, Stanford, CA; University of Virginia, Charlottesville, VA; Washington University, School of Medicine, St Louis, MO; Curry Cabral Hospital, Lisbon, Portugal, and Emory University, Atlanta, GA were included. All NELM diagnoses were confirmed histologically; 63 patients with macroscopic positive surgical margins (R2 resection) were excluded. Moreover, four patients who died within 30 days after hepatic surgery (in hospital death, 0.8%) were also excluded. Therefore, a total of 481 patients undergoing R0/R1 resection for NELM were included in the analytic cohort. The Institutional Review Boards of each participating institution approved the study.

Clinical Data Collection and Follow-Up

Demographic and clinicopathological variables were collected for each patient including the characteristics of the primary and hepatic metastatic tumor as well as the operative details for both the primary tumor and NELM (types and extent). The type of hepatic resection was categorized as minor or major resection according to the consensus classification.[17] Major hepatectomy was defined as the resection of three or more segments (right hepatectomy, left hepatectomy, extended right hepatectomy, extended left hepatectomy, and any trisegmentectomy), whereas minor resection included resection of two or fewer segments and nonanatomic wedge resection according to the classification of Couinaud. Data regarding receipt of adjuvant octreotide treatment, chemo- and radiotherapy were recorded.

Recurrence was defined as suspicious imaging findings or a biopsy-proven tumor. Sites of recurrence were categorized as intrahepatic, extrahepatic, or both intra- and extrahepatic. Treatments of recurrent NELM were categorized as curative-intent surgery and non-curative therapies. Curative-intent surgery consisted of repeated resection, ablation, or both. Non-curative treatments were individualized for patients with advanced recurrent disease and included somatostatin analog therapy, systemic cytotoxic chemotherapy, and intra-arterial therapies (IAT).

Optimal Cutoff Value Between Early and Late Recurrence

Recurrence rate was evaluated at 1-year intervals to determine the optimal cutoff value to distinguish between early and late recurrence (Fig. 1). Recurrence was subsequently divided into two periods according to the slope of the curves identified with linear regression. The function of the two lines was $y = 22.433–5.75x$ and $y = 5.6214–0.55x$, respectively. The intercept value of the two lines was 3.2 years. Therefore, 3 years was defined as the optimal cutoff value to differentiate early and late recurrence of NELM in the current study (Fig. 1).

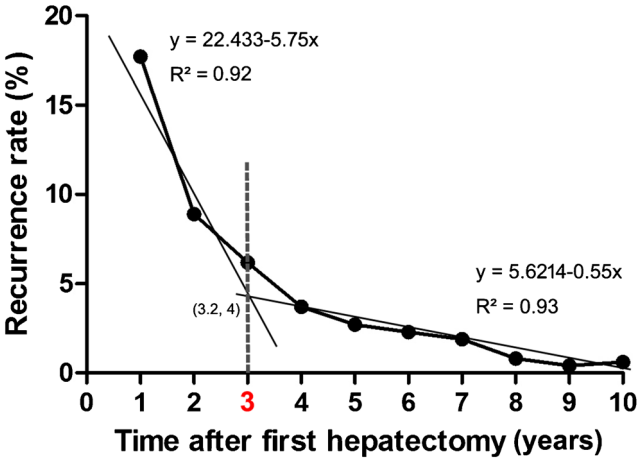

Fig. 1 Tumor recurrence after hepatic resection for NELM stratified at 1-year intervals. Recurrence was divided into two periods according to the slope of the curves identified with linear regression. Based on the intercept value of the two lines being 3.2 years, 3 years was utilized as the cutoff to differentiate early versus late recurrence

Statistical Analysis

NELM disease-specific survival and recurrence-free survival were calculated from the date of the initially curative-intent surgery for NELM. OS after the first recurrence was calculated from the date of recurrence after initial surgery for NELM. Continuous variables were expressed as medians with interquartile ranges (IQR) and compared with the Mann-Whitney *U* test. Categorical variables were expressed as number and percentages and compared with Chi-squared test or Fisher's exact test. Kaplan–Meier curves with log-rank tests were used to compare survival. Univariate and multivariable logistic regression models were used to determine factors associated with early recurrence following initial hepatic resection. Relative risks were expressed as hazard ratios (HR) and 95% confidence intervals (CI). Variables with a p value <0.1 by univariate analysis were entered into the multivariable model. Two-tailed p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 22.0 (Chicago, IL, USA).

Results

Patient Characteristics

Among the 481 patients, NELM was synchronous with the primary NET in 285 (59.3%) patients. The pancreas (n = 203, 42.2%) were the most common site of primary NET, followed by small bowel (n = 149, 31%), colon (n = 31, 6.4%), and lungs (n = 26, 5.4%). The majority of patients had more than 50% liver involvement (n = 347, 72.1%), and half of the patients had bilateral hepatic disease (n = 245, 50.9%). Extrahepatic disease was present in 46 (9.6%) patients at the time of NELM diagnosis. The proportion of patients with an R0 resection was 77.3% (n = 372). Major hepatectomy was performed in 213 (44.3%) patients. Although the majority of patients did not receive any preoperative treatment, a small number did receive octreotide (n = 90, 18.7%) or systemic chemotherapy (n = 36, n = 7.5%). After the initial hepatic resection, one third of patients received adjuvant therapy with either a somatostatin analog (n = 114, 23.7%) or systemic chemotherapy (n = 50, 10.4%).

Outcome and Recurrence

With a median follow-up time of 60 months, 89 (18.5%) patients died of disease progression; 161 (33.5%) patients were alive with disease; and 202 (42%) patients were alive with no evidence of disease. During follow-up, recurrence was noted in 223 (46.4%) patients, including 158 patients with an early (70.9% of recurrence, ≤3 years after hepatic resection) and 65 patients with a late recurrence (29.1% of recurrence, >3 years after hepatic resection). The cumulative incidence of recurrence at 1, 3, 5, and 10 years was 19.6, 38.0, 47.5, and 59.6%, respectively (Fig. 2a).

Compared with patients who were recurrence free for 3 years after curative-intent hepatic resection for NELM, early recurrence occurred more commonly in younger patients with pancreatic and a node positive primary tumor, as well as among patients with >50% liver involvement, an R1 resection and those patients who received pre- or post-operative chemotherapy (Table 1).

The 3-, 5-, and 10-year NELM-specific survival among the entire cohort was 93.9, 88.2, and 72.9%, respectively (Fig. 2a). Perhaps not surprising, survival was worse among patients with an early versus late recurrence (10-year NELM-specific survival rate, 44.5 vs 75.8%, p < 0.001, Fig. 2b). Of note, the recurrence pattern was, however, not different among patients who experienced an early versus late recurrence (Fig. 2c).

Risk Factors Associated with Early Recurrence

On multivariable analysis, pancreatic versus gastrointestinal NET (HR 2.1, 95% CI 1.4–4.0; p = 0.033), node positive primary NET (HR 5.1, 95% CI 2.5–10.3; p < 0.001), and extrahepatic disease at diagnosis of NELM (HR 3.1, 95% CI 1.1–8.6; p = 0.027) were independent risk factors associated with early "any-site" recurrence following curative-intent hepatic resection for NELM (Table 2). A separate multivariable analysis was then performed that included patients who experienced intrahepatic-only recurrence. In this analysis, pancreatic versus gastrointestinal NET (HR 2.9, 95% CI 1.5–5.8; p = 0.002), primary tumor lymph node metastasis (HR 3.3, 95% CI 1.7–6.4; p < 0.001), and a microscopic positive surgical margin (HR 2.0, 95% CI 1.0–3.9; p = 0.044) were

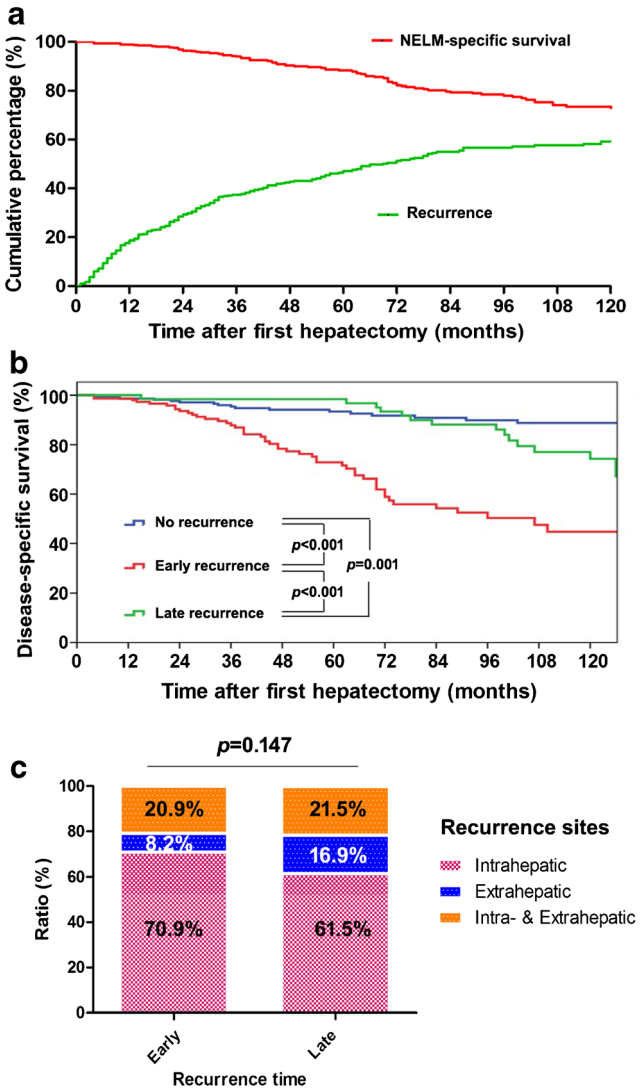

Fig. 2 **a** Cumulative disease-specific survival and recurrence from the time of first hepatic surgery for NELM. **b** NELM-specific survival of patients in no recurrence group, early recurrence group, and late recurrence group from the time of first hepatic surgery. **c** Sites of recurrence stratified by early versus late recurrence

independently associated with early intrahepatic recurrence following curative-intent hepatic resection (Table 3).

Outcome of Early Versus Late Recurrence

In total, 184 (82.5%) patients had available information on treatment of recurrence. Fifty-two (28.3%) patients underwent a curative-intent treatment for recurrence including re-resection and/or ablation. The median time from diagnosis of recurrence to curative retreatment was 103 days (IQR, 4–752 days). The majority (n = 48, 92.3%) of these patients developed intrahepatic-only recurrence at the time of retreatment, whereas 4 (7.7%) of them underwent curative resection/ablation for both intra- and extrahepatic recurrence. Specifically, 34 (21.5%) patients underwent curative treatment for early recurrence. Interestingly, the proportion of patients who were offered repeat curative-intent treatment with a late recurrence was comparable (n = 18, 27.7%). Disease-specific survival among patients with an early recurrence was improved following repeat curative versus non-curative treatment (10-year NELM-specific survival, 54.2 vs 26.3%, p = 0.028, Fig. 3a). Furthermore, curative treatment for recurrent NELM achieved similar disease-specific survival and recurrence-free survival among patients who had an early versus late recurrence (10-year NELM-specific survival, 54.2 vs 37.4%, p = 0.519, Fig. 3b; 5-year recurrence, 75.4 vs 49.7%, p = 0.305, Fig. 3c).

Overall, patients who experienced early recurrence had similar NELM-specific survival after the recurrence compared with patients who developed a late recurrence. NELM-specific survival remained comparable among patients who had early versus late recurrence when considering either intrahepatic-only recurrence (10-year NELM-specific survival, 50.3 vs 42.4%, p = 0.723, Fig. 4a) or extra- ± intrahepatic recurrence (10-year NELM-specific survival, 12.2 vs 37.5%, p = 0.189, Fig. 4b).

Discussion

Curative liver resection and debulking surgery are recommended for the treatment of many patients with NELM.[5, 18] Surgical extirpation of NELM can often lead to both symptomatic relief, as well as improved long-term survival. In fact, even the presence of extensive bilateral hepatic or extrahepatic disease are not absolute contraindications to liver resection, which is generally different from the treatment of other types of primary and secondary liver malignancies.[5] Although hepatic resection is the only curative treatment for NELM, the high incidence of recurrence has led some clinicians to question the benefit of surgery.[19–21] In the current study, the incidence of recurrence after curative hepatic resection of NELM was 46.4%. More specifically, the majority (70.9%) of recurrences occurred within the first 3 years (early recurrence), while only 29.1% of patients recurred beyond 3 years following hepatic surgery. Early intrahepatic recurrence was more common among patients with a pancreatic primary, nodal metastasis, as well as a microscopic positive hepatic resection margin at the time of NELM surgery. In turn, early recurrence was associated with worse overall disease-specific survival. Of note, curative surgery even for early recurrent tumor was associated with an improved post-recurrence survival, which was comparable to the outcomes achieved after curative treatment of late recurrences. These findings may have important implications, as the data highly suggest that repeat resection and/or ablation should be strongly considered in the treatment of early recurrent NELM, even in the presence of extrahepatic disease.

Table 1 Clinical and pathological characteristics of patients who developed recurrence within 3 years and who were 3-year recurrence free following curative-intent surgery for neuroendocrine liver metastasis (NELM)

	Early recurrence group (n = 158)	3-year recurrence-free group (n = 323)	P value
Patient characteristics			
Age (years)	56 (48–65)	59 (50–68)	0.022
Male gender	83 (52.5%)	164 (50.8%)	0.771
Race			0.980
White	137 (86.7%)	281 (87.0%)	
Black	11 (7.0%)	23 (7.1%)	
Other	10 (6.3%)	19 (5.9%)	
Symptomatic	112 (70.9%)	208 (64.4%)	0.181
Primary tumor characteristics			
Location of primary NET			0.024
Gastrointestinal	61 (38.6%)	147 (45.5%)	
Pancreas	80 (50.6%)	123 (38.1%)	
Other	17 (10.8%)	53 (16.4%)	
Functional status			0.255
Non-functional	137 (86.7%)	264 (81.7%)	
Functional	17 (10.8%)	48 (14.9%)	
Grade of differentiation			0.144
Well	59 (37.3%)	155 (48.0%)	
Moderate	33 (20.9%)	53 (16.4%)	
Poor	19 (12.0%)	34 (10.5%)	
Lymph node status			<0.001
N0	36 (22.8%)	149 (46.1%)	
N1	98 (62.0%)	130 (40.2%)	
Liver metastases characteristics			
Synchronous disease	102 (64.6%)	183 (56.7%)	0.137
Liver involvement			0.025
<50%	21 (13.3%)	75 (23.2%)	
≥50%	119 (75.3%)	228 (70.6%)	
Bilobar disease	86 (54.4%)	159 (49.2%)	0.929
Extrahepatic disease at diagnosis	21 (13.3%)	25 (7.7%)	0.068
Surgical procedures			
Types of hepatectomy			0.001
Minor resection	102 (64.5%)	154 (47.7%)	
Major resection	54 (34.2%)	159 (49.2%)	
Pre-hepatectomy treatment			0.031
Octreotide	23 (14.6%)	67 (20.7%)	
Chemotherapy	18 (11.4%)	18 (5.6%)	
None	117 (74.1%)	238 (73.7%)	
Intraoperative ablation	43 (27.2%)	56 (17.3%)	0.016
Margin status			<0.001
R0	104 (65.8%)	268 (83.0%)	
R1	54 (34.2%)	55 (17.0%)	
Adjuvant therapy			0.002
Octreotide	41 (25.9%)	73 (22.6%)	
Chemotherapy	27 (17.1%)	23 (7.1%)	
None	76 (48.1%)	190 (58.8%)	

The term "early recurrence" has been defined very differently in the literature for various hepatic tumors. For example, for patients with HCC, a cutoff of 6 months, 1 year, and 2 years has been proposed, [10–13, 22, 23] while 6 months, 8 months, 1 year, 1.5 years, and 2 years have been proposed as cutoff values to define "early recurrence" after curative resection of

Table 2 Risk factors for early "any-site" recurrence of neuroendocrine liver metastasis (NELM) after curative-intent surgery on univariate and multivariable analysis

Parameters	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Patient characteristics				
Age (≤70/>70)	2.3 (1.2–4.2)	0.010	1.7 (0.7–4.2)	0.219
Gender (male/female)	0.9 (0.6–1.4)	0.717		
Primary tumor characteristics				
Location of primary NET				
Gastrointestinal	Ref.		Ref.	
Pancreas	1.6 (1.0–2.4)	0.032	2.1 (1.1–4.0)	0.033
Other	0.8 (0.4–1.4)	0.418	0.7 (0.2–2.6)	0.609
Functional status		0.205		
Non-functional	Ref.			
Functional	0.7 (0.4–1.2)			
Grade of differentiation				
Well	Ref.		Ref.	
Moderate	1.5 (0.8–2.8)	0.237	0.9 (0.4–2.2)	0.862
Poor	1.6 (1.0–2.8)	0.068	1.7 (0.8–3.5)	0.169
Lymph node status		<0.001		<0.001
N0	Ref.		Ref.	
N1	3.1 (2.0–4.9)		5.1 (2.5–10.3)	
Liver metastases characteristics				
Synchronous metastases	1.4 (0.9–2.0)	0.123		
Liver involvement		0.022		0.208
<50%	Ref.		Ref.	
≥50%	1.9 (1.1–3.2)		0.6 (0.2–1.4)	
Bilobar disease	1.0 (0.7–1.5)	0.929		
Extrahepatic disease at diagnosis	1.8 (1.0–3.4)	0.055	3.1 (1.1–8.6)	0.027
Surgical procedures and perioperative treatments				
Pre-hepatectomy treatment				
None	Ref.		Ref.	
Octreotide	0.7 (0.4–1.2)	0.178	1.1 (0.5–2.4)	0.840
Chemotherapy	2.0 (1.0–4.1)	0.044	1.8 (0.6–5.1)	0.308
Types of hepatectomy		0.001		0.133
Minor resection	Ref.		Ref.	
Major resection	0.5 (0.3–0.8)		0.6 (0.3–1.2)	
Margin status		<0.001		0.107
R0	Ref.		Ref.	
R1	2.5 (1.6–3.9)		1.8 (0.9–3.6)	
Intraoperative ablation	1.8 (1.1–2.8)	0.012	1.8 (0.8–4.0)	0.160
Adjuvant therapy				
None	Ref.		Ref.	
Octreotide	1.4 (0.9–2.2)	0.153	1.0 (0.5–2.0)	0.908
Chemotherapy	2.9 (1.6–5.4)	0.001	2.0 (0.7–5.5)	0.197

CRLM.[14–16, 24–27] The optimal time point to differentiate between early and late recurrence after curative hepatic resection for NELM remains, however, undefined. In the current study, 3 years was proposed as the appropriate cutoff to categorize patients as early versus late recurrence. Unlike previous studies that utilized arbitrary cutoff values, we empirically defined the time course of recurrence using a mathematical model (Fig. 1). While the incidence of recurrence was highest in the first year after liver surgery (17.7%), the slope of the curves associated with the time to recurrence had an intercept

Table 3 Risk factors for early intrahepatic-only recurrence of neuroendocrine liver metastasis (NELM) after curative-intent surgery on univariate and multivariable analysis

Parameters	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Patient characteristics				
Age (≤70/>70)	2.3 (1.1–4.8)	0.019	1.7 (0.7–4.1)	0.201
Gender (male/female)	0.9 (0.6–1.5)	0.808		
Primary tumor characteristics				
Location of primary NET				
Gastrointestinal	Ref.		Ref.	
Pancreas	1.9 (1.2–3.0)	0.008	2.9 (1.5–5.8)	0.002
Other	0.8 (0.4–1.7)	0.493	1.0 (0.2–3.9)	0.964
Functional status		0.418		
Non-functional	Ref.			
Functional	0.8 (0.4–1.5)			
Grade of differentiation				
Well	Ref.			
Moderate	1.0 (0.5–2.4)	0.914		
Poor	1.4 (0.8–2.6)	0.274		
Lymph node status		<0.001		<0.001
N0	Ref.		Ref.	
N1	3.4 (2.0–5.7)		3.3 (1.7–6.4)	
Liver metastases characteristics				
Synchronous metastases	1.5 (0.9–2.4)	0.087	1.3 (0.7–2.5)	0.393
Liver involvement		0.029		0.956
<50%	Ref.		Ref.	
≥50%	2.0 (1.1–3.8)		1.0 (0.4–2.6)	
Bilobar disease	0.8 (0.5–1.3)	0.376		
Extrahepatic disease at diagnosis	1.2 (0.5–2.9)	0.668		
Surgical procedures and perioperative treatments				
Pre-hepatectomy treatment				
None	Ref.			
Octreotide	0.6 (0.3–1.1)	0.107		
Chemotherapy	1.7 (0.8–3.7)	0.172		
Types of hepatectomy		0.005		0.419
Minor resection	Ref.		Ref.	
Major resection	0.5 (0.3–0.8)		0.7 (0.4–1.5)	
Margin status		<0.001		0.044
R0	Ref.		Ref.	
R1	2.9 (1.8–4.8)		2.0 (1.0–3.9)	
Intraoperative ablation	1.9 (1.1–3.2)	0.013	1.9 (0.9–4.0)	0.121
Adjuvant therapy				
None	Ref.		Ref.	
Octreotide	1.8 (1.1–3.0)	0.032	1.1 (0.5–2.3)	0.811
Chemotherapy	2.9 (1.4–6.1)	0.004	1.8 (0.7–4.9)	0.258

value of 3.2 years based on linear regression. Specifically, we empirically demonstrated that the risk of recurrence precipitously dropped following year 3.

Interestingly, early recurrence was more likely to occur among younger patients. Age has been reported to be associated with outcomes among cancer patients. For example, Graff-Baker et al. reported that age less than 50 was the only independent risk factor associated with reduced progression-free and disease-free survival among patients undergoing partial hepatectomy for NELM.[18] Interestingly,

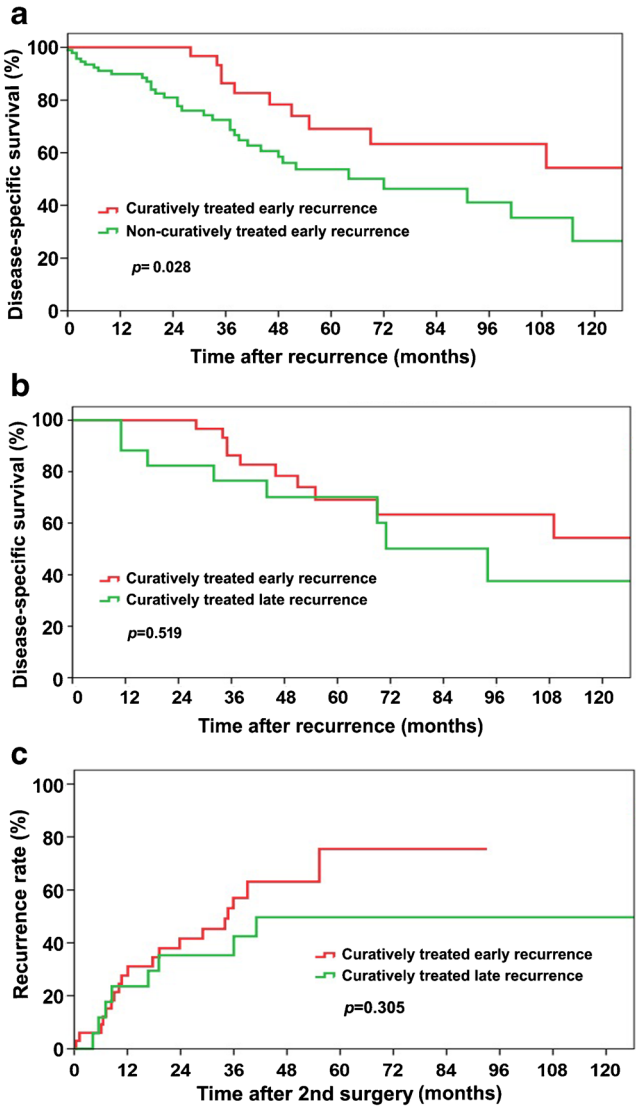

Fig. 3 **a** Disease-specific survival after tumor recurrence of patients after curatively and non-curatively treated early recurrence. **b** Disease-specific survival after tumor recurrence of patients with early and late recurrence after curative treatment. **c** Cumulative recurrence after second curative treatment stratified by early versus late recurrence

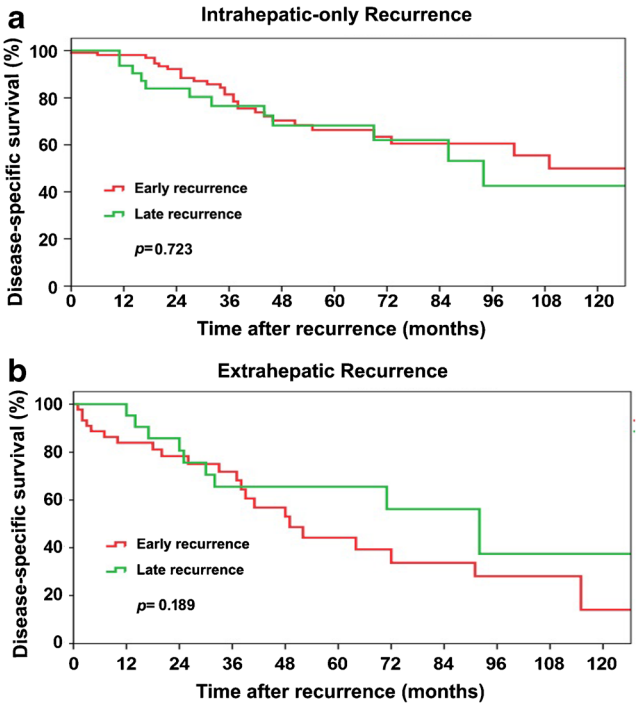

Fig. 4 **a** Disease-specific survival after tumor recurrence of patients with intrahepatic-only early versus late recurrence. **b** Disease-specific survival after tumor recurrence of patients with extra- ± intrahepatic stratified by early versus late recurrence

younger patient age has similarly been associated with a more aggressive tumor phenotype and worse prognosis for other cancers including colorectal cancer.[28, 29] The reason for a worse prognosis is undoubtedly multifactorial and related, in part, to worse tumor biology. To this point, early recurrence was also more common among patients with aggressive primary NET features, such as a pancreatic primary tumor site as well as primary NET lymph node metastasis. On univariate analysis, receipt of pre- and postoperative chemotherapy was similarly associated with early recurrence. This association may have been confounded, as patients who received systemic therapy were more likely to have advanced disease. In fact, receipt of systemic chemotherapy was not associated with early recurrence on multivariate analysis. Rather, consist with previous studies,[6, 7, 30, 31] primary NET characteristics including pancreatic NET, primary NET nodal metastasis, and the presence of extrahepatic disease at NELM diagnosis were independently associated with early recurrence. For patients with early intrahepatic-only recurrence, R1 resection was also an important risk factor. Unlike primary and other secondary liver cancers, NELM tends to grow expansively by pushing the surrounding liver parenchyma aside rather than invading it.[5] Despite this, an R1 resection should still be the goal of resection of NELM, as a microscopic positive margin was associated with an increased risk of intrahepatic recurrence and may be associated with worse outcome.[31].

While early recurrence is often considered a marker of "bad biology," repeat curative-intent therapy may still be warranted in certain circumstances. In the present study, among all patients who recurred, individuals who developed an early recurrence were treated with curative and non-curative approaches at similar frequency compared with patients who developed a late recurrence. Of note, curative treatments for early recurrent NELM improved survival and achieved comparable post-recurrence survival versus patients with a late recurrence. In fact, post-recurrence disease-specific survival was comparable among patients with early versus late recurrences when considering either intrahepatic-only recurrence or extra- ± intrahepatic recurrence. Therefore, surgery should be considered for the treatment of recurrent NELM, even in the setting of early recurrence.

The current study had several limitations. Given the retrospective nature of the study, residual confounding and selection bias were possible. In particular, the selection of patients for repeat curative-intent surgery following recurrence likely was affected by selection bias. Surgeons undoubtedly chose patients for repeat curative-intent surgery based on a number of features that were both measured and unmeasured in the current study. Notwithstanding this limitation, the data still strongly suggest that repeat curative-intent surgery for patient with early recurrence may be both feasible and effective in a subset of patients. The lack of data collection on perioperative complications was another limitation of the current study that did not permit us to assess the safety of initial or repeat NELM surgery.

In conclusion, recurrence following curative-intent surgery for NELM occurred in almost half of patients (~46.4%), with predominantly early recurrence within the first 3 years (70.9%). Early recurrence at any site after hepatic resection was strongly associated with the characteristics of the primary NET (pancreatic type, primary lymph node metastasis, and extrahepatic disease at presentation). In addition to these factors, an R1 surgical margin was associated with an increased risk factor of intrahepatic recurrence. Although early recurrence diminished overall survival, re-treatment with curative intent prolonged survival after recurrence and therefore operative intervention even for early recurrences of NELM should be considered.

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