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RESEARCH ARTICLE

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Timing of disease occurrence and hepatic resection on long-term outcome of patients with neuroendocrine liver metastasis

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Background and Objectives: The objective of the study was to evaluate the impact of timing of disease occurrence and hepatic resection on long-term outcome of neuroendocrine liver metastasis (NELM).

Methods: A total of 420 patients undergoing curative-intent resection for NELM were identified from a multi-institutional database. Date of primary resection, NELM detection and resection, intraoperative details, disease-specific (DSS), and recurrence-free survival (RFS) were obtained.

Results: A total of 243 (57.9%) patients had synchronous NELM, while 177 (42.1%) developed metachronous NELM. On propensity score matching (PSM), patients with synchronous versus metachronous NELM had comparable DSS (10-year DSS, 76.2% vs 85.9%, $P = 0.105$), yet a worse RFS (10-year RFS, 34.1% vs 59.8%, $P = 0.008$). DSS and RFS were comparable regardless of operative approach (simultaneous vs staged, both $P > 0.1$). Among patients who developed metachronous NELM, no difference in long-term outcomes were identified between early (≤ 2 years, $n = 102$, 57.6%) and late (> 2 years, $n = 68$, 42.4%) disease on PSM (both $P > 0.1$).

Conclusions: Patients with synchronous NELM had a higher risk of tumor recurrence after hepatic resection versus patients with metachronous disease. The time to development of metachronous NELM did not affect long-term outcome. Curative-intent hepatic resection should be considered for patients who develop NELM regardless of the timing of disease presentation.

KEYWORDS

metachronous, neuroendocrine liver metastasis, synchronous

1 | INTRODUCTION

Neuroendocrine tumors (NET) are a heterogeneous group of rare tumors mainly arising from the gastroenteropancreatic system.¹

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The liver is the most common site for the development of metastasis. In fact, approximately 60-90% of patients with NET develop synchronous or metachronous neuroendocrine liver metastasis (NELM) during the course of their disease.^{2,3} NELM can sometimes cause severe hormonal symptoms and dysfunction of the liver.⁴ As such, the presence of NELM can be associated with a poor quality of life and a worse long-term prognosis.^{4,5-7} While surgical resection is the main curative option for NELM, many patients will recur with either locally advanced or metastatic disease.¹

Even in the presence of extensive bilateral disease, hepatic resection offers the best therapeutic option for NELM, providing significant symptomatic relief and an improvement in survival.^{1,3,6,8,9} Similar to the surgical approach to colorectal liver metastasis (CRLM), the timing of NELM occurrence and hepatic resection may be determinants of long-term outcomes of patients. For example, among patients with CRLM, synchronous disease presentation has been associated with less favorable tumor biology and a shorter long-term survival compared with patients who had metachronous disease.¹⁰⁻¹³ Among patients who have synchronous CRLM, whether to perform a simultaneous or staged hepatic resection has also been a topic of debate.^{14,15} While simultaneous resection had traditionally been associated with higher morbidity and mortality,^{16,17} more recent studies have reported that simultaneous resection can be performed safely with comparable postoperative mortality, morbidity, and long-term outcomes, as well as a shorter hospital stay and lower health care costs.¹⁸⁻²⁰ Unlike CRLM, the impact of presentation (ie, synchronous vs metachronous), as well as operative approach of synchronous disease (ie, simultaneous vs stage), has not been well examined for patients with NELM. Therefore, the objective of the present study was to define the long-term outcomes of patients with synchronous versus metachronous NELM, assess the impact of simultaneous versus staged resection for synchronous NELM, as well as to investigate the long-term prognosis of early and late metachronous NELM using a large multi-institutional, international database.

2 | MATERIALS AND METHODS

2.1 | Patients

Between 1990 and 2015, a total of 547 patients undergoing curative-intent hepatectomy for NELM were identified from a multi-institutional database. Participating institutions included 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. All NELM diagnoses were confirmed histologically. Patients with unresectable primary NET ($n = 70$), macroscopic positive surgical margins (R2 resection, $n = 55$), and in-hospital death ($n = 2$) were excluded. A total of 420 patients who underwent a simultaneous or staged R0/R1 resection for NELM were included in the analytic cohort (Figure 1). The Institutional Review Boards of each participating institution approved the study.

2.1.1 | Data collection, definition, and follow up

Data on clinical, pathological, and operative details were collected for each patient pertaining to both the primary tumor and NELM. Synchronous NELM was defined as liver metastasis identified at or before the surgery for the patient's primary NET. Metachronous NELM was defined as detectable NELM following treatment of the primary NET.^{12,21} Simultaneous resection was defined as a concomitant resection of both the primary NET and NELM, while staged resection was defined as resection of the primary and NELM at separate operative times. Data regarding receipt of pre- and post-operative adjuvant octreotide treatment and chemotherapy were recorded. For all study groups, NELM disease-specific survival (DSS) and recurrence-free survival (RFS) were calculated from the date of hepatic resection for NELM. Recurrence was defined as suspicious imaging findings or a biopsy-proven intra- and/or extra-hepatic NET tumor.

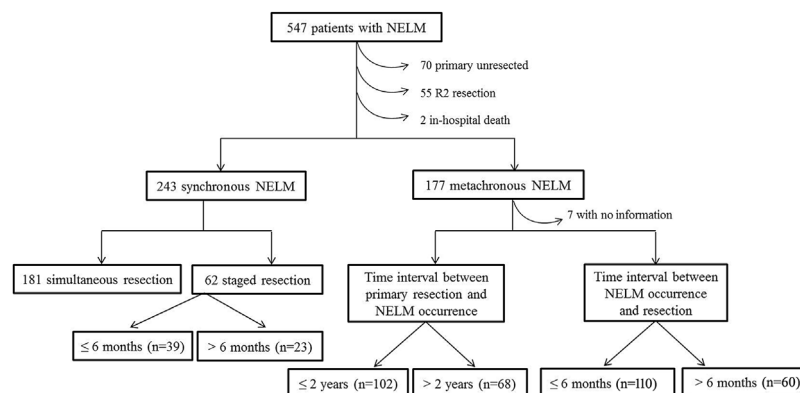


FIGURE 1 A diagram of patient inclusion and study scenario. NELM, neuroendocrine liver metastasis

2.1.2 | Statistical analysis

Continuous variables were expressed as medians with interquartile ranges (IQR), while categorical variables were expressed as numbers and percentages. Variables were compared between groups with the Mann-Whitney U test, Chi-squared test, or Fisher exact test, as appropriate. Survival was evaluated using Kaplan-Meier curves with log-rank tests. Odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI) were calculated as appropriate. Univariate and multivariable Cox regression models were used to determine factors associated with disease-specific and recurrence-free survival. Propensity score matching (PSM) was used to adjust for differences in baseline characteristics between groups. Specifically, variables potentially affecting long-term outcomes were derived from multivariable logistic regression analysis and propensity score matching was performed. In all analyses, a two-tailed P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 22.0 (Chicago, IL).

3 | RESULTS

3.1 | Synchronous versus metachronous NELM: Impact on long-term outcome

Among the 420 patients with NELM, 243 (57.9%) patients had synchronous disease, while 177 (42.1%) developed metachronous NELM. Patients with synchronous NELM were more likely to be male, have functional NETs and present with clinical symptoms (Table 1). Patients with synchronous NELM also had a higher incidence of primary NET lymph nodes metastasis (synchronous: 56.8% vs metachronous: 40.7%; $P = 0.007$; OR 1.8, 95%CI 1.2-2.7), and were more likely to have been treated with either a somatostatin analogue or cytotoxic chemotherapy (synchronous: 30.9% vs metachronous: 20.9%; $P = 0.023$; OR 1.7, 95%CI 1.2-2.7) prior to hepatic surgery. In contrast, extent of hepatic resection, surgical margin status, and receipt of adjuvant therapy were no different among patients who presented with synchronous versus metachronous disease (all $P > 0.05$) (Table 1).

Compared with patients who had metachronous disease, patients with synchronous NELM had a similar DSS (10-year DSS, synchronous: 70.8% vs metachronous: 77.1%, $P = 0.329$; HR 1.3, 95%CI 0.8-2.0; Figure 2A), yet a worse RFS (10-year RFS, synchronous: 33.6% vs metachronous: 46.8%, $P = 0.027$; HR 1.4, 95%CI 1.1-1.8; Figure 2B). On propensity score matching that accounted for primary and NELM tumor characteristics, nodal status, surgical procedure, and margin status (Supplementary Table S1), patients with synchronous versus metachronous NELM had comparable DSS (10-year DSS, synchronous: 76.2% vs metachronous: 85.9%, $P = 0.105$; HR 2.0, 95%CI 0.8-4.9; Figure 2C), yet a worse RFS (10-year RFS, synchronous: 34.1% vs metachronous: 59.8%, $P = 0.008$; HR 1.8, 95%CI 1.2-2.9; Figure 2D).

Factors associated with DSS among patients undergoing curative resection for NELM included characteristics of the primary NET (functional vs non-functional, HR 0.2, 95%CI 0.1-0.8, $P = 0.025$; poor

TABLE 1 Clinical and pathological characteristics of patients with synchronous and metachronous neuroendocrine liver metastasis (NELM) undergoing curative-intent surgery

	Synchronous (n = 243)	Metachronous (n = 177)	P value
Patient characteristics			
Age (years)	58 (49-67)	57 (48-66)	0.368
Male gender	137 (56.4%)	81 (45.8%)	0.032
Symptomatic	185 (76.1%)	102 (57.6%)	<0.001
Primary tumor characteristics			
Location of primary NET			0.171
Gastrointestinal	117 (48.1%)	79 (44.6%)	
Pancreas	113 (46.5%)	80 (45.2%)	
Other	13 (5.4%)	18 (10.2%)	
Functional status			0.027
Non-functional	201 (82.7%)	159 (89.8%)	
Functional	42 (17.3%)	17 (9.6%)	
Grade of differentiation			0.025
Well	130 (53.5%)	70 (39.6%)	
Moderate	53 (21.8%)	26 (14.7%)	
Poor	19 (7.8%)	24 (13.6%)	
Lymph node status			0.007
N0	89 (36.6%)	82 (46.3%)	
N1	138 (56.8%)	72 (40.7%)	
NELM characteristics			
Liver involvement			0.671
<50%	46 (18.9%)	35 (19.8%)	
≥50%	180 (74.1%)	123 (69.5%)	
Bilobar disease	133 (54.7%)	87 (49.2%)	0.258
Extrahepatic disease at diagnosis	22 (9.1%)	16 (9.0%)	1.000
Surgical procedures			
Types of hepatectomy			0.295
Parenchymal-sparing resection	131 (53.9%)	103 (58.2%)	
Major resection	107 (44.0%)	68 (38.4%)	
Pre-hepatectomy treatment			0.047
Octreotide	52 (21.4%)	29 (16.4%)	
Chemotherapy	23 (9.5%)	8 (4.5%)	
None	168 (69.1%)	140 (79.1%)	
Intraoperative ablation	39 (16.0%)	53 (29.9%)	0.956
Margin status			0.507

(Continues)

TABLE 1 (Continued)

	Synchronous (n = 243)	Metachronous (n = 177)	P value
RO	188 (77.4%)	132 (74.6%)	
R1	55 (22.6%)	45 (25.4%)	
Adjuvant therapy			0.066
Octreotide	74 (30.5%)	33 (18.6%)	
Chemotherapy	25 (10.3%)	18 (10.2%)	
None	125 (51.4%)	99 (55.9%)	

vs well differentiated, HR 3.1, 95%CI 1.3-7.3, $P = 0.009$) (Table 2). In addition, tumor recurrence was associated with characteristics of the primary NET (pancreatic vs gastrointestinal type, HR 1.7, 95%CI 1.1-2.5, $P = 0.010$; poor vs well differentiated, HR 1.6, 95%CI 1.0-2.6, $P = 0.050$; lymph nodes metastasis, HR 2.5, 95%CI 1.5-4.1, $P < 0.001$) and location of metastasis (extrahepatic disease, HR 2.6, 95%CI 1.4-4.5, $P = 0.001$). In multivariable analysis, after accounting for these factors, synchronous versus metachronous NELM was not associated with DSS (HR 1.3, 95%CI 0.8-2.0, $P = 0.331$) (Table 2), but synchronous disease presentation was independently associated with decreased RFS (HR 1.9, 95%CI 1.2-3.1, $P = 0.005$) (Table 3).

3.2 | Management of synchronous NELM: Simultaneous versus staged resection

Among the 243 patients with synchronous NELM, three quarters of patients ($n = 181$, 74.5%) underwent simultaneous resection, while one quarter ($n = 62$, 25.5%) underwent a staged resection. Most clinical and pathological characteristics of patients undergoing a simultaneous versus a staged resection were comparable (Table 4). Simultaneous resection of the primary NET and NELM was, however, more common

among patients with a pancreatic primary NET (OR 1.4, 95% 1.0-2.2) (Table 4). In addition, when a simultaneous resection was performed, the liver resection was more often a parenchymal-sparing/minor hepatectomy (simultaneous: 59.1% vs staged: 38.7%); in contrast, a major hepatectomy was more often performed in the setting of a staged resection (simultaneous: 39.8% vs staged: 56.5%; $P = 0.011$; OR 1.5, 95% 1.1-3.9) (Table 4).

A simultaneous versus staged approach for synchronous NELM had no effect on long-term outcomes. Specifically, DSS (10-year DSS, simultaneous: 72.8% vs staged: 66.2%, $P = 0.754$; HR 0.9, 95% CI 0.5-1.7) and RFS (10-year RFS, simultaneous: 34.6% vs staged: 32.8%, $P = 0.365$; HR 1.2, 95%CI 0.8-1.8) were comparable regardless of operative approach (Figures 3A and 3B). A subset of patients ($n = 23$) who underwent staged resection had the second procedure performed at 6 months or longer from the time of the first operation (median 4.3 months, IQR 2.1-10.5 months). There was no difference, however, in DSS (10-year DSS, <6 months: 61.0% vs ≥ 6 months: 71.8%, $P = 0.601$; HR 0.7, 95%CI 0.2-2.3) or RFS (10-year RFS, <6 months: 28.3% vs ≥ 6 months: 38.5%, $P = 0.624$; HR 0.8, 95%CI 0.4-1.7) among patients who underwent early versus delayed staged resection of simultaneous NELM (Figures 3C and 3D).

3.3 | Management of metachronous NELM: Early versus delayed resection

Among the 177 patients who developed metachronous NELM, more than half ($n = 102$, 57.6%) developed NELM within the first 2 years after resection of the primary NET (median time to metachronous NELM: 20 months, IQR [12-45.5 months]) (Figure 4A). On unmatched analyses, patients with early metachronous NELM had a similar DSS (10-year DSS, metachronous <2 years: 78.9% vs metachronous ≥ 2 years: 71.9%,

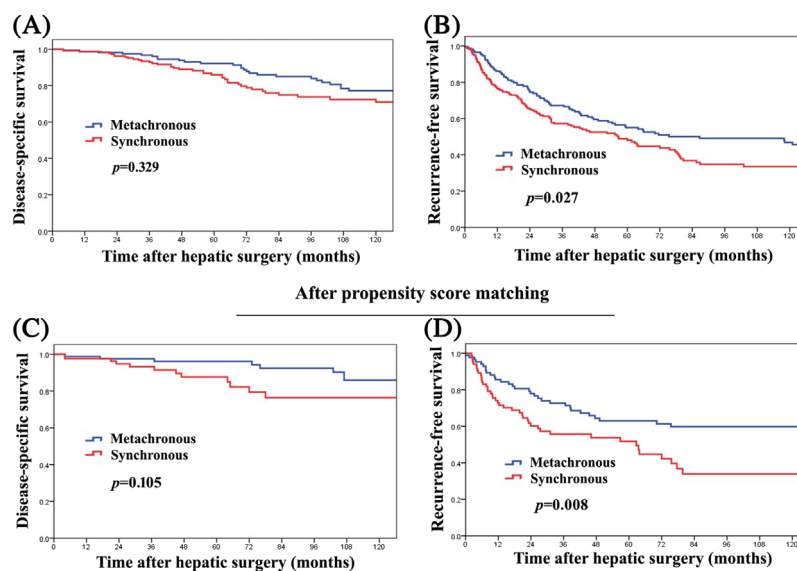


FIGURE 2 Disease-specific and recurrence-free survival after curative-intent hepatectomy for synchronous and metachronous neuroendocrine liver metastasis before (A,B) and after (C,D) propensity score matching

TABLE 2 Risk factors associated with disease-specific survival of neuroendocrine tumor liver metastasis after curative-intent surgery

Parameters	Univariate analysis		Multivariable analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Patient characteristics				
Age ($\leq 70 / > 70$)	0.9 (0.5-1.6)	0.615		
Gender (male/female)	0.7 (0.5-1.2)	0.218		
Primary tumor characteristics				
Location of primary NET				
Gastrointestinal	Ref.			
Pancreas	1.5 (0.9-2.4)	0.124		
Other	0.9 (0.4-2.2)	0.817		
Functional status				
Non-functional	Ref.		Ref.	
Functional	0.4 (0.2-0.9)		0.2 (0.1-0.8)	
Grade of differentiation				
Well	Ref.		Ref.	
Moderate	1.9 (0.9-4.1)	0.095	1.3 (0.6-3.2)	0.512
Poor	2.0 (1.0-3.9)	0.039	3.1 (1.3-7.3)	0.009
Lymph node status				
N0	Ref.		Ref.	
N1	2.5 (1.5-4.2)		1.8 (0.8-3.9)	
Liver metastases characteristics				
Synchronous vs metachronous	1.3 (0.8-2.0)	0.331		
Liver involvement				
<50%	Ref.		Ref.	
$\geq 50\%$	2.2 (1.2-4.2)		0.6 (0.2-1.5)	
Bilobar disease	0.6 (0.4-1.0)	0.052	0.8 (0.4-1.7)	0.592
Extrahepatic disease at diagnosis	2.4 (1.3-4.5)	0.005	1.5 (0.5-4.4)	0.425
Surgical procedures				
Types of hepatectomy				
Parenchymal-sparing resection	Ref.		Ref.	
Major resection	0.5 (0.3-0.7)		1.0 (0.4-2.4)	
Margin status				
R0	Ref.		Ref.	
R1	1.9 (1.2-3.1)		1.0 (0.5-2.3)	

$P = 0.188$; HR 0.6, 95%CI 0.3-1.3), yet a more favorable RFS (metachronous <2 years: 58.4% vs metachronous ≥ 2 years: 18.5%, $P = 0.003$; HR 0.5, 95%CI 0.3-0.8) (Figures 4A and 4B; Supplementary Table S2). On propensity score matching, there was no difference in long-term outcomes among patients with early versus late metachronous NELM (10-year DSS, metachronous <2 years: 60.8% vs metachronous ≥ 2 years: 77.0%, $P = 0.395$; HR 1.4, 95%CI 0.6-3.2) (10-year RFS, metachronous <2 years: 42.5% vs metachronous ≥ 2 years: 18.1%, $P = 0.632$; HR 0.9, 95%CI 0.5-1.5) (Figures 4D and 4E; Supplementary Table S3).

Of note, among patients with metachronous NELM, a delay in hepatic resection did not have an effect on long-term outcomes. Specifically, patients who had hepatic resection <6 months ($n = 110$)

following the diagnosis of metachronous disease had comparable long-term outcomes as patients with metachronous NELM who had a stage resection ≥ 6 months ($n = 60$) (10-year DSS, <6 months: 81.7% vs ≥ 6 months: 66.3%; $P = 0.219$; HR 0.8, 95%CI 0.3-1.9) (10-year RFS, <6 months: 50.1% vs ≥ 6 months: 38.5%, $P = 0.294$; HR 0.9, 95%CI 0.5-1.6) (Figures 4F and 4G).

4 | DISCUSSION

Timing of disease presentation and its impact on long-term outcomes, as well as the optimal timing of hepatic resection, remain poorly

TABLE 3 Risk factors associated with recurrence-free survival of neuroendocrine tumor liver metastasis after curative-intent surgery

Parameters	Univariate analysis		Multivariable analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Patient characteristics				
Age ($\leq 70 / > 70$)	1.9 (1.2-3.0)	0.006	1.6 (0.9-3.0)	0.115
Gender (male/female)	1.0 (0.7-1.3)	0.842		
Primary tumor characteristics				
Location of primary NET				
Gastrointestinal	Ref.		Ref.	
Pancreas	1.3 (1.0-1.8)	0.049	1.7 (1.1-2.5)	0.010
Other	0.5 (0.2-0.9)	0.032	0.5 (0.2-1.8)	0.297
Functional status				
Non-functional	Ref.	0.006	Ref.	0.317
Functional	0.5 (0.3-0.8)		0.7 (0.4-1.4)	
Grade of differentiation				
Well	Ref.		Ref.	
Moderate	1.5 (1.0-2.2)	0.062	1.4 (0.8-2.4)	0.234
Poor	1.6 (1.0-2.5)	0.040	1.6 (1.0-2.6)	0.050
Lymph node status				
N0	Ref.	<0.001	Ref.	<0.001
N1	3.1 (2.2-4.3)		2.5 (1.5-4.1)	
Liver metastases characteristics				
Synchronous vs metachronous	1.4 (1.0-1.8)	0.027	1.9 (1.2-3.1)	0.005
Liver involvement				
<50%	Ref.	<0.001	Ref.	0.986
$\geq 50\%$	3.0 (1.9-4.7)		1.0 (0.5-1.9)	
Bilobar disease	0.8 (0.6-1.1)	0.103		
Extrahepatic disease at diagnosis	1.7 (1.1-2.6)	0.012	2.6 (1.4-4.5)	0.001
Surgical procedures				
Types of hepatectomy				
Parenchymal-sparing resection	Ref.	<0.001	Ref.	0.006
Major resection	0.4 (0.3-0.5)		0.5 (0.3-0.8)	
Margin status				
R0	Ref.	<0.001	Ref.	0.077
R1	1.9 (1.4-2.6)		1.5 (1.0-2.2)	

defined in the treatment of NELM. The current study was important because it specifically defined outcomes among a large group of patients with NELM relative to disease presentation (synchronous vs metachronous) and operative approach (simultaneous vs staged). Using a multi-institutional cohort, we demonstrated that patients who presented with synchronous NELM had a worse post-surgical long-term RFS compared with patients with metachronous NELM. In contrast, the type of operative approach (simultaneous vs staged) was associated with similar long-term RFS and DSS for patients with synchronous NELM. Furthermore, a 6 month delay in performing hepatic resection appeared to have no detrimental effect on survival among patients with synchronous NELM. Among patients with

metachronous disease, although more than one half developed metastasis within the first 2 years, the survival of patients with early versus late metachronous disease was comparable.

Among patients with NET, approximately 50% of patients will present with synchronous NELM, while the other half develop metachronous NELM during the course of their disease.^{22,23} In the current study, there was a slightly higher predominance of patients who presented with synchronous disease (57.9%) versus metachronous disease (42.1%). The impact of disease presentation has been well studied in the setting of CRLM.^{12,24,25} Most surgeons agree that synchronous disease is an indicator of poor prognosis independent of treatment.^{12,24,26} Data from Adam et al from the LiverMetSurvey, an

TABLE 4 Clinical and pathological characteristics of patients undergoing simultaneous and staged hepatic resection for synchronous neuroendocrine liver metastasis (NELM)

	Simultaneous (n = 181)	Staged (n = 62)	P value
Patient characteristics			
Age (years)	58 (50-67)	58 (48-65)	0.564
Male gender	97 (53.6%)	40 (64.5%)	0.141
Symptomatic	142 (78.5%)	43 (69.4%)	0.147
Primary tumor characteristics			
Location of primary NET			0.017
Gastrointestinal	84 (46.4%)	33 (53.2%)	
Pancreas	91 (50.3%)	22 (35.5%)	
Other	6 (3.3%)	7 (11.3%)	
Functional status			0.565
Non-functional	148 (81.8%)	53 (85.5%)	
Functional	33 (18.2%)	9 (14.5%)	
Grade of differentiation			0.954
Well	99 (54.7%)	31 (50.0%)	
Moderate	40 (22.1%)	13 (21.0%)	
Poor	15 (8.3%)	4 (6.5%)	
Lymph node status			0.202
N0	63 (34.8%)	26 (41.9%)	
N1	108 (59.7%)	30 (48.4%)	
NELM characteristics			
Liver involvement			0.156
<50%	30 (16.6%)	16 (25.8%)	
≥50%	136 (75.1%)	44 (71.0%)	
Bilobar disease	103 (56.9%)	30 (48.4%)	0.355
Extrahepatic disease at diagnosis	16 (8.8%)	6 (9.7%)	0.802
Surgical procedures			
Types of hepatectomy			0.011
Parenchymal-sparing resection	107 (59.1%)	24 (38.7%)	
Major resection	72 (39.8%)	35 (56.5%)	
Pre-hepatectomy treatment			0.171
Octreotide	35 (19.3%)	17 (27.4%)	
Chemotherapy	15 (8.3%)	8 (12.9%)	
None	131 (72.4%)	37 (59.7%)	
Intraoperative ablation	39 (21.5%)	14 (22.6%)	0.865
Margin status			0.489
R0	142 (78.5%)	46 (74.2%)	
R1	39 (21.5%)	16 (25.8%)	
Adjuvant therapy			0.396
Octreotide	54 (29.8%)	20 (32.3%)	
Chemotherapy	16 (8.8%)	9 (14.5%)	
None	96 (53.0%)	29 (46.8%)	

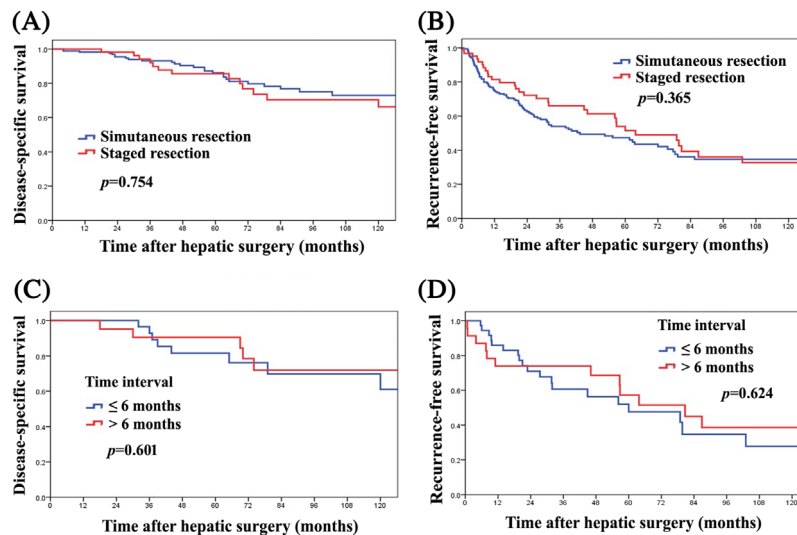


FIGURE 3 Outcome of patients after hepatic resection for synchronous neuroendocrine liver metastasis (NELM). A and B, Disease-specific and recurrence-free survival of synchronous NELM following simultaneous or staged hepatic resection. C and D, Disease-specific and recurrence-free survival of patients undergoing staged resection of NELM within or beyond 6 months after primary surgery

international registry of patients undergoing surgery for CRLM, demonstrated a significant difference in survival when CRLM were detected at or 1 month within diagnosis of the primary tumor versus >3 months after diagnosis.¹² In addition, in probably the most widely utilized prognostic scoring scheme for CRLM, the Clinical Risk Score (ie, “Fong” score) incorporates synchronous disease as one of the prognostic factors.¹⁰ In contrast, the impact of disease presentation (ie, synchronous vs metachronous) on the prognosis of patients with NELM has been less studied. While several studies have suggested that synchronous NELM may adversely impact outcomes, disease presentation was not the specific focus on these analyses.^{3,9,27,28} Unlike previous studies that did not utilize statistical techniques to control for potential biases affecting disease presentation, the current study employed both multivariable analyses and PSM to adjust for differences in baseline characteristics between groups. Specifically, by using PSM variables to balance factors potentially affecting long-term outcomes, we were able to create comparable groups of patients who had synchronous versus metachronous disease (Supplementary Table S1). These analyses demonstrated that synchronous NELM was associated with a worse RFS after curative-intent hepatic resection compared with patients who had metachronous disease. In fact, on PSM, patients who presented with synchronous disease had an 80% increased risk of having recurrence at 10 years versus individuals who developed metachronous disease (HR 1.8, 95%CI 1.2-2.9; Figure 2D).

Among patients with synchronous disease, the operative approach has also been a topic of much debate. For patients with CRLM, the classic approach to surgery of synchronous disease was to perform primary surgery of the primary colorectal tumor followed by resection of the CRLM after an interval of time.^{14,15,29} Some surgeons had traditionally recommended a delay in hepatic resection for 3-6 months as this “waiting time” might allow for occult hepatic disease to become

detectable, and thus avoid an “unnecessary” hepatic resection.^{16,17,29-32} Contemporary data and clinical thinking, however, has refuted this notion. In fact, multiple studies have demonstrated that simultaneous surgery of the primary and CRLM was safe and led to the same long-term survival outcomes.^{14,18-20,33} In fact, simultaneous surgery has been advocated as being the preferred approach for some patients with CRLM, as it eliminates the need for a second surgery and decreases both length of stay and health care costs.^{14,18-20,33} In the current study, a simultaneous versus staged approach for synchronous NELM had no effect on long-term outcomes. Specifically, DSS and RFS were comparable regardless of operative approach (Figures 3A and 3B). As such, similar to patients with CRLM, the data would suggest that a simultaneous approach to synchronous NELM may be preferable. For those patients with synchronous NELM who do undergo a staged approach, the timing of the second operation may not impact long-term outcomes. Specifically, the subset of patients who underwent staged resection at 6 months or longer from the time of the first operation had no difference in DSS or RFS versus patients who underwent an earlier resection of synchronous NELM (Figures 3C and 3D). Collectively, these data strongly suggest that, while synchronous NELM disease presentation is associated with long-term outcomes, operative strategy regarding the timing of surgical management (simultaneous vs staged) does not impact prognosis.

Almost one half of patients develop metachronous NELM after curative resection of primary NET,^{3,14,22,23} yet the clinical characteristics, treatment, and prognosis of metachronous NELM have not been specifically defined. Of note, based on a time course analysis, we noted that the majority (57.6%) of metachronous NELM was detected within the first 2 years following primary resection. On unadjusted analyses, patients who developed early metachronous NELM had a decreased incidence of recurrence, yet comparable DSS versus patients who had late NELM. However, in the matched cohort analysis, there was no

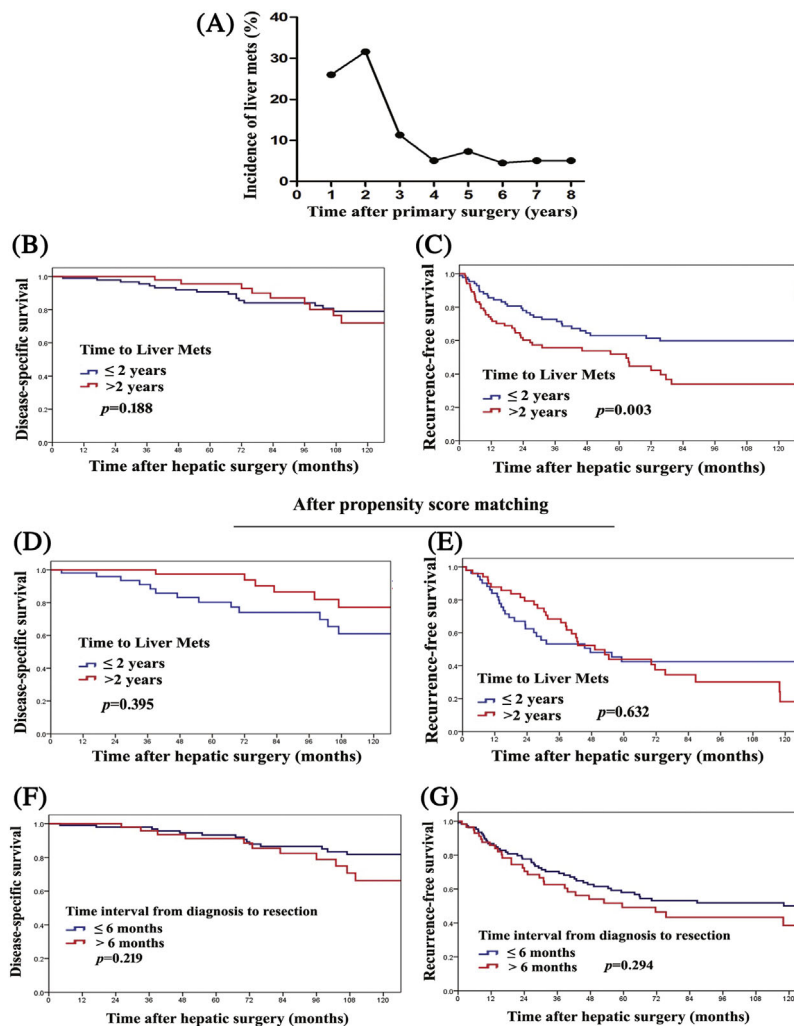


FIGURE 4 Outcome of patients undergoing hepatic resection for metachronous neuroendocrine liver metastasis (NELM). A, Timing and incidence of metachronous neuroendocrine liver metastasis (NELM). B and C, Disease-specific and recurrence-free survival of early (≤ 2 years after primary surgery) and late (> 2 years after primary surgery) metachronous NELM after hepatic resection. D and E, Disease-specific and recurrence-free survival of early and late metachronous NELM after hepatic resection in the propensity model. F and G, Outcome of patients after a delayed (> 6 months after diagnosis) and non-delayed (≤ 6 months after diagnosis) hepatic surgery

difference in RFS or DSS among patients who had early versus late metachronous NELM groups. Therefore, timing of disease occurrence itself did not influence the prognosis of patients with metachronous NELM. Similar to synchronous NELM, the operative management of metachronous disease has been debated.

To evaluate the assumption that occult liver metastasis might be found during a “waiting period,” Ueno et al evaluated a 3-months delay of hepatic resection on the long-term outcome of patients with metachronous CRLM.³⁴ In this study, the authors concluded that delayed liver resection for metachronous CRLM had no clinical benefit. Building on this work, we sought to examine whether a delayed approach to liver resection for patients with metachronous NELM would have clinical utility. Patients who underwent hepatic resection with a delay of more than 6 months after detection of metachronous NELM had comparable long-term survival as patients who received immediate hepatic resection within 6 months. These findings may be helpful to patients and providers as the data demonstrate that a delay

of resection for a moderate time period (~ 6 month) does not affect long-term survival—likely due to the slow-growing nature and long natural history of most NELM.^{34,35}

The present study had several limitations. Given the retrospective nature of the study, selection bias was likely. However, unlike many previous studies, we utilized propensity score matching to create groups that were well-matched on baseline characteristics to mitigate any selection bias. Moreover, “disease occurrence” was defined based on “disease detection;” therefore, a delayed or missed identification of liver metastasis due to technical problems, or lower patient compliance with regards to postoperative follow-up could not be completely excluded. Additionally, this multi-institutional database did not contain data on perioperative complications or socioeconomic status, and we were therefore unable to assess short-term outcomes or healthcare costs.

In conclusion, patients with synchronous NELM had a higher risk of tumor recurrence after hepatic resection versus patients with

metachronous disease. Simultaneous resection of synchronous disease may be preferred, as it results in equivalent long-term survival versus staged resection. The time to development of metachronous NELM did not affect long-term outcome, and therefore a curative-intent hepatic resection should be considered for patients who develop NELM at any time following resection of primary NET.

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AUTHORS' CONTRIBUTIONS

Study design, XF Zhang, TM Pawlik; Data collection and interpretation, EW Beal, Yi Lv, J Chakedis, F Bagante, D Moris, L Aldrighetti, GA Poultsides, TW Bauer, RC Fields, SK Maithel, HP Marques, M Weiss; Data analysis, XF Zhang, EW Beal, Y Lv, Chakedis, F Bagante; Drafting, XF Zhang, EW Beal; Revision of the draft: EW Beal, TM Pawlik.

CONFLICTS OF INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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