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RESEARCH ARTICLE

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The impact of extrahepatic disease among patients undergoing liver-directed therapy for neuroendocrine liver metastasis

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Introduction: Management of neuroendocrine liver metastasis (NELM) in the presence of extrahepatic disease (EHD) is controversial. We sought to examine outcomes of patients undergoing liver-directed therapy (resection, ablation, or both) for NELM in the presence of EHD using a large international cohort of patients.

Methods: 612 patients who underwent liver-directed therapy were identified from eight institutions. Postoperative outcomes, as well as and overall (OS) were compared among patients with and without EHD.

Results: Most primary tumors were located in the pancreas (*N* = 254;41.8%) or the small bowel (*N* = 188;30.9%). Patients underwent surgery alone (*N* = 471;77.0%), ablation alone (*N* = 15;2.5%), or a combined approach (*N* = 126;20.6%). Patients with EHD had more high-grade tumors (EHD: 44.4% vs no EHD: 16.1%; *P* < 0.001). EHD was often the peritoneum (*N* = 29;41.4%) or lung (*N* = 19;27.1%). Among 70 patients with EHD, 20.0% (*N* = 14) underwent concurrent resection for EHD. After median follow-up of 51 months, 174 (28.4%) patients died with a median OS of 140.4 months. Patients with EHD had a shorter median OS versus patients who did not have EHD (EHD: 87 months vs no EHD: not reached; *P* = 0.002). EHD was independently associated with an increased risk of death (HR: 2.56, 95%CI 1.16-5.62; *P* = 0.02).

This study was presented at the 2017 Society of Surgical Oncology annual cancer symposium.

Conclusion: Patients with NELM and EHD had more aggressive tumors, conferring a twofold increased risk of death. Surgical treatment of NELM among patients with EHD should be individualized.

KEYWORDS
extrahepatic, liver, metastasis, neuroendocrine

1 | INTRODUCTION

Neuroendocrine tumors (NET) are a mixed group of epithelial neoplasms that can arise in a variety of organs. While several staging and classification systems exist, most systems classify neuroendocrine tumors based on the site of origin as well as the aggressiveness of the tumor. The World Health Organization classifies neuroendocrine tumors based on degree of differentiation (well vs poorly), tumor grade, mitotic count, and Ki-67 index. Although the majority of neuroendocrine tumors exhibit a slow-growing indolent behavior, up to 60-90% of NET metastasize to the liver during the course of the disease.[1] Patients with untreated neuroendocrine liver metastasis (NELM) have a worse overall survival compared with patients without NELM.[2] Previous work from our group has demonstrated that liver-directed therapy for NELM can provide an overall survival benefit, particularly among patients with functioning tumors or those with synchronous disease.[3]

Similar to other malignancies, the presence of extrahepatic disease (EHD) has been identified as a poor prognostic factor among patients with NELM.[3–5] Among patients with colorectal liver metastasis, several studies have reported that liver-directed therapy can still provide an overall survival benefit even in the presence of EHD.[6,7] Despite a high likelihood of recurrence, treatment of liver metastasis and extrahepatic disease in patients with colorectal liver metastasis resulted in long-term survival in a select group of patients.[8] Data regarding liver-directed therapy (surgical resection, operative ablation, or a combined approach) among patients with NELM and EHD has not been well studied, however. As such, the management of NELM in the presence of synchronous EHD remains controversial. Given this, we sought to examine the outcomes of patients undergoing liver-directed therapy for NELM in the presence of EHD using a large multicenter international cohort of patients.

2 | METHODS

2.1 | Patient selection and data collection

All patients who underwent liver-directed therapy for NELM between January 1990 to December 2014 were identified from a multi-institutional database. This multi-institutional database included patients treated at eight major hepatobiliary institutions (Johns Hopkins Hospital, Baltimore, MD; Stanford University, Stanford, CA; The Ohio State University Comprehensive Cancer Center, Columbus, OH; Washington University School of Medicine, St Louis, MO; University of Virginia, Charlottesville, VA; Scientific Institute San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; Curry Cabral Hospital, Lisbon, Portugal; Winship Cancer Institute, Emory University, Atlanta, GA). The Institutional Review Board of the participating institutions approved the study.

Standard demographic and clinicopathologic data were collected including age, gender, race, type of surgery, and tumor-specific characteristics of both the primary NET and the liver metastases. Tumor-specific characteristics of the primary NET included location, histology, functional status, grade of differentiation, and presence or absence of lymph node metastases. Grade of tumor differentiation was defined according to the 2010 WHO grading system.[9] Data on treatment-related variables, such as type of liver surgery and receipt of intraoperative ablation of unresected tumors, resection margin and estimated volume of liver involvement (intraoperative estimation: 0-25%, 25-50%, 50-75%, >75%) were collected. Outcomes were stratified according to the presence of EHD either preoperatively or at the time of liver-directed therapy. Liver-directed therapy is defined as surgical resection, ablation (most commonly radiofrequency ablation, 81.3%), or a combined approach. Ablation was performed on small lesions distant from major vascular structures at the discretion of the surgeon. Most patients who underwent ablation were treated for 4 or less lesions (71.1%). The primary outcome of interest was overall survival (OS) defined as the time interval between the date of first liver-directed therapy and the date of death.

2.2 | Statistical analysis

Discrete variables were described as medians with interquartile range (IQR) and categorical variables were described as totals and frequencies. Univariable comparisons were assessed using the chi-squared or Wilcoxon-rank sum test as appropriate. Univariable and multivariable logistic regression models were utilized to determine the association of relevant clinicopathological factors with the development of EHD. Variables of statistical significance on univariable analysis and factors of clinical significance or potential confounders were included in the multivariable model. Overall survival time was calculated from the date of initial liver-directed therapy. Survival adjusted for censoring was calculated using the Kaplan-Meier method and medians compared using the log-rank test. The impact of various clinicopathological

factors on OS was assessed using a Cox proportional hazards model. All analyses were carried out with STATA version 13.0 (StataCorp, College Station, TX) and a *P*-value of <0.05 (two-tailed) was considered statistically significant.

3 | RESULTS

A 612 patients who underwent liver-directed therapy for NELM and met the inclusion criteria were included in the current study. Median patient age was 57 years (IQR: 49, 65) (Table 1). Most patients were Caucasian (*n* = 538, 87.9%) and male (*n* = 326, 53.3%). Among the patients with a known primary tumor location, most tumors originated in the pancreas (*n* = 256, 41.6%), with the small (*n* = 188, 30.8%) and large (*n* = 42, 6.9%) intestine being other common primary tumor locations. At the time of liver-directed therapy, patients underwent either liver resection alone (*n* = 471, 77.0%), ablation alone (*n* = 15, 2.4%), or combined resection/ablation (*n* = 126, 20.6%). Bilateral liver disease was present in a slight majority of patients (*n* = 329, 59.9%), however, most patients had an estimated <50% liver involvement (*n* = 440, 79.4%).

Extrahepatic disease was present in 11.4% (*n* = 70) of patients who underwent liver-directed therapy. The most common sites of EHD were peritoneum (*n* = 27, 38.6%) and bone (*n* = 13, 18.6%). Several clinicopathologic characteristics differed among patients with and without EHD. Patients who had EHD were more commonly Caucasian (EHD: *n* = 68, 97.1% vs no EHD: *n* = 470, 86.7%; *P* = 0.04) and had primary tumors more often located in the small (EHD: *n* = 28, 40.0% vs no EHD: *n* = 160, 29.5%) or large (EHD: *n* = 11, 15.7% vs no EHD: *n* = 31, 5.7%) intestine (both *P* < 0.001). Patients with EHD also more

TABLE 1 Clinicopathological characteristics of patients who underwent resection for neuroendocrine liver metastasis

	All patients (*N* = 612)	No extrahepatic disease (*n* = 542)	Extrahepatic disease (*n* = 70)	*P*-value
Age, years (IQR)	57 (49, 65)	57 (48, 65)	57 (52, 65)	0.93
Male sex	326 (53.3)	290 (53.5)	36 (51.4)	0.74
Ethnicity				0.04
Caucasian	538 (87.9)	470 (86.7)	68 (97.1)	
Black	38 (6.2)	37 (6.8)	1 (1.4)	
Other	36 (5.9)	35 (6.5)	1 (1.4)	
Location of primary tumor				<0.001
Pancreas	256 (41.6)	351 (64.8)	31 (44.3)	
Small intestine	188 (30.7)	160 (29.5)	28 (40.0)	
Large intestine	42 (6.9)	31 (5.7)	11 (15.7)	
Symptomatic disease	356 (65.7)	356 (65.7)	52 (74.3)	0.15
Primary tumor grade (*N* = 406)				<0.001
Low	227 (55.9)	209 (57.9)	18 (40.0)	
Intermediate	101 (24.9)	94 (26.0)	7 (15.6)	
High	78 (19.2)	58 (16.1)	20 (44.4)	
Lymph node metastasis (*N* = 518)	301 (58.1)	255 (55.6)	46 (78.0)	0.001
Synchronous liver metastasis	379 (61.9)	336 (62.0)	43 (61.4)	0.93
Bilateral liver metastases	329 (59.9)	287 (59.1)	42 (66.7)	0.25
Estimated liver involvement				0.48
<50%	440 (79.4)	387 (79.0)	53 (82.8)	
≥50%	114 (20.6)	103 (21.0)	11 (17.2)	
Type of liver operation				0.01
Resection	471 (77.0)	426 (78.6)	45 (64.3)	
Ablation	15 (2.5)	14 (2.6)	1 (1.4)	
Resection + Ablation	126 (20.6)	102 (18.8)	24 (34.3)	
Location of EHD				
Peritoneum	27 (38.6)	—	27 (38.6)	
Lung	9 (12.9)	—	9 (12.9)	
Bone	13 (18.6)	—	13 (18.6)	
Other	21 (30.0)	—	21 (30.0)	

commonly had high-grade tumors (EHD: $n = 20$, 44.4% vs no EHD: $n = 58$, 16.1%; $P = 0 < 0.001$) and evidence of lymph node metastasis (EHD: $n = 46$ 78.0% vs no EHD: $n = 255$, 55.6%; $P = 0.001$). After controlling for all measurable factors, patients with high-grade tumors (OR: 4.19, 95%CI 1.95-8.99; $P < 0.001$) and patients with lymph node metastasis (OR: 5.31, 95%CI 1.98-14.24; $P = 0.001$) were more likely to develop EHD (Table 2).

3.1 | Overall survival

After a median follow-up of 51 months, 173 patients died during the follow-up period for a median overall survival of 140 months. Overall 1-, 3-, and 5-year survival for the entire cohort was 96.3%, 87.0%, and 78.2% respectively. Several factors were associated with worse median OS (Table 3). Patient factors associated with worse median OS included age over 65 years (age <65 years: 138 months vs age ≥65 years: 89 months; $P < 0.007$). Pathologic factors associated with worse OS include high-grade tumors (low grade: not reached vs high grade: 71 months; $P < 0.001$), islet cell histology (carcinoid: 123 months vs islet cell: 71 months; $P = 0.003$) and lymph node metastasis (no lymph node metastasis: not reached vs lymph node metastasis: 91 months; $P < 0.001$). Patients with evidence of EHD had nearly one-half the median OS compared with patients who did not have EHD (no EHD: 138 months vs EHD: 70 months: $P < 0.001$) (Fig. 1). On cox proportional hazard regression analysis, patients with islet cell histology (HR: 1.91, 95%CI 1.02-3.58; $P = 0.04$), synchronous disease (HR 1.89, 95%CI 1.04-3.43; $P = 0.04$) and EHD (HR: 2.18, 95%CI 1.05-4.53; $P = 0.04$) remained the only factors independently associated with an increased risk of death (HR: 2.18, 95%CI 1.05-4.53; $P = 0.04$). In a subset analysis of only patients with EHD, patients with lymph node metastasis and those with synchronous disease were at higher risk of death (both $P < 0.05$).

Patients with EHD were stratified based on extent of liver involvement. Among patients with EHD who underwent liver-directed therapy, over four out of every five patients had <50% of estimated hepatic involvement ($n = 53$, 82.8%). Median survival among patients with EHD was higher among patients with <50% hepatic involvement versus patients with ≥50% hepatic involvement (<50%: 93 months vs ≥50%: 63 months; $P = 0.0003$) (Fig. 2). Five-year OS among patients with EHD was higher among patients with limited hepatic involvement versus patients with ≥50% hepatic involvement (<50%: 76.9% vs ≥50%: 54.6%; $P < 0.001$).

4 | DISCUSSION

The presentation and aggressiveness of neuroendocrine tumors vary greatly. Because of this heterogeneity, treatment guidelines for patients with this type of rare tumor are not uniform. For patients with NELM, our group previously reported that surgical resection provided an overall survival benefit, particularly among patients with functioning tumors or synchronous disease.[3] Outcomes following liver-directed therapy among patients with NELM in the presence of EHD have not been well-studied. As such, liver-directed therapy in the presence of EHD remains controversial. In the current study, we analyzed the largest cohort of patients to date who underwent liver-directed therapy for NELM in the presence of EHD. Of note, the overall incidence of EHD was 11.4% among patients who underwent

TABLE 2 Univariable and multivariable regression analysis of factors associated with the development of extrahepatic disease

	Univariable analysis			Multivariable analysis		
	OR	95%CI	*P*-value	OR	95%CI	*P*-value
Age	1.01	0.98-1.03	0.46	—	—	—
Male Sex	0.92	0.56-1.51	0.74	—	—	—
Race						
White	Ref	—	—	—	—	—
Black	0.19	0.03-1.38	0.10	—	—	—
Other	0.20	0.03-1.46	0.11			
Primary tumor location						
Pancreas	Ref	—	—	Ref	—	—
Small intestine	1.98	1.15-3.41	0.01	1.21	0.57-2.56	0.63
Large intestine	4.02	1.84-8.76	<0.001	1.63	0.50-5.34	0.42
Synchronous disease	0.98	0.59-1.63	0.93	—	—	—
Grade						
Low	Ref	—	—	Ref	—	—
Intermediate	0.86	0.35-2.14	0.75	0.99	0.36-2.69	0.99
High	4.00	1.99-8.06	<0.001	4.19	1.95-8.99	<0.001
Lymph node metastasis	2.83	1.49-5.38	0.002	5.31	1.98-14.24	0.001

TABLE 3 Hazard regression analysis of factors associated with overall survival

			Multivariate survival analysis		
Variables	**Median survival (months)**	***P*-value**	**Hazard ratio**	**95%CI**	***P*-value**
Age		0.007			
<65 years	138		Ref	–	
≥65 years	89		1.31	0.86-2.57	1.41
Histology		0.003			
Carcinoid	123		Ref	–	
Non-functioning islet cell	71		1.91	1.02-3.58	0.04
Primary tumor grade		<0.001			
Low	Not Reached		Ref	–	
High	71		11.75	0.88-3.50	0.11
Lymph node status		<0.001			
No lymph node metastasis	Not Reached		Ref	–	
Lymph node metastasis	91		1.54	0.88-2.71	0.13
Liver disease presentation		<0.001			
No synchronous disease	138		Ref	–	
Synchronous disease	99		1.89	1.04-3.43	0.04
Functioning tumor		<0.001			
Functional	140		Ref	–	
Non-functional	88		0.59	0.28-1.23	0.16
Extrahepatic disease		<0.001			
No extrahepatic disease	138		Ref	–	
Extrahepatic disease	70		2.18	1.05-4.53	0.04

liver-directed therapy. Patients with high tumor grade and primary tumor lymph node metastasis were more likely to develop EHD. Furthermore, the presence of EHD was strongly associated with an increased risk of death compared with patients without EHD. Perhaps more importantly, we noted that that long-term survival could be achieved with liver-directed therapy in the presence of EHD, particularly among patients with <50% of estimated NET hepatic involvement.

When confined to the liver, liver-directed therapy can provide long-term survival for patients with neuroendocrine tumors.[3] In fact, our group recently published results using cure fraction models among 376 patients who underwent hepatectomy for NELM and reported

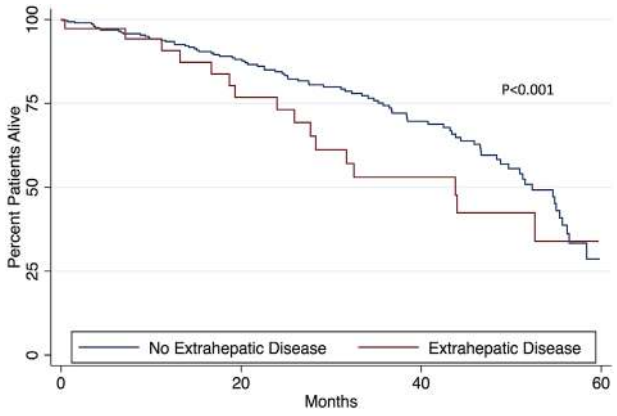

FIGURE 1 Kaplan-Meier overall survival curve among patients who underwent liver-directed therapy as stratified by the presence of extrahepatic disease (KM graph truncated at 60 months)

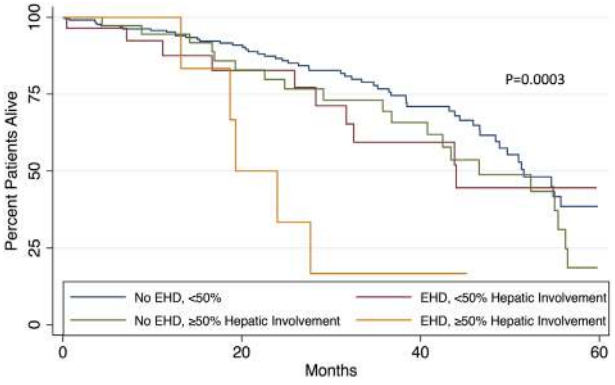

FIGURE 2 Kaplan-Meier overall survival curve among patients who underwent liver-directed therapy as stratified by the presence of extrahepatic disease and estimated hepatic involvement (KM graph truncated at 60 months)

that statistical cure after surgery is possible.[10] Similar to patients with colorectal metastasis, EHD in the presence of NELM was previously considered to be an absolute contraindication to curative-intent surgery. Several groups, however, have reported that liver-directed therapy among patients with colorectal liver metastasis and concurrent EHD may provide a survival benefit.[6,7] Consistent with the typical indolent nature of some NET, we noted that long-term survival was feasible after resection of NELM and EHD in a subset of patients. Though EHD was an independent poor prognostic factor, conferring an over twofold increased risk of death compared with patients without EHD, 5-year survival among patients with EHD was still 72.2%. This is likely due to a combination of the surgical treatment undertaken in these patients to eradicate all visible areas of disease as well as the natural history of these typically slow-growing tumors. Perhaps not surprisingly, the survival benefit of liver-directed therapy for patients with EHD was associated with the extent of intrahepatic disease. Specifically, the 5-year survival of patients with a large volume of hepatic burden (≥50%) was only 54.6% versus 76.9% among patients with <50% hepatic involvement. Taken together, resection of NELM even in the setting of EHD should be considered, especially among patients who have a low-burden of intrahepatic disease.

In the current study, patients with more aggressive tumors were at higher risk of developing EHD. Specifically, patients with high-grade tumors and patients with lymph node metastasis were at a 4-5 times increased risk of developing EHD. These factors, however, were not independently associated with worse OS after controlling for the development of EHD (both $P > 0.05$). These data suggest that patients with aggressive microscopic NET features may warrant closer follow-up for the early detection of both intrahepatic and extrahepatic spread of disease. Though not reported in the current cohort, patients with increased Ki-67 indices are also at higher risk for the development of metastases and recurrence and should be considered for closer surveillance.[11] In one of the only other studies to examine treatment of NELM in the setting of EHD, Arrese et al reported on 192 patients who underwent transarterial chemoembolization (TACE) for NELM in the presence of EHD.[12] Similar to the current study, patients with EHD had a worse OS versus patients without EHD. In this study, the authors noted that TACE treatment was associated with symptomatic relief and biochemical response, especially among patients with carcinoid syndrome. Given these data, the presence of EHD should not be considered a contraindication to liver-directed therapy. Liver directed therapy including surgical resection/debulking or chemoembolization may provide not only a survival benefit, but also a quality of life benefit for those patients with symptomatic disease. In turn, asymptomatic patients with a large burden of liver disease benefited least from surgical management and chemoembolization may be a more appropriate treatment strategy. As such, particularly in patients with relatively indolent disease (low tumor grade, low Ki-67 level etc.), active surveillance with cross-sectional imaging in these patients could be considered. Surgical management of NELM may particularly benefit patients with lower-volume intra- and extra-hepatic disease, especially those patients with symptomatic disease.[4]

The current study had several limitations that need to be considered when interpreting the data. As with all the retrospective studies, selection bias was a possibility, particularly among patients with known EHD preoperatively. Secondly, patients in the current cohort were treated at high-volume international hepatobiliary centers, which may limit the generalizability of the results. In addition, our cohort includes patients treated over the past 25 years who may have not benefited from modern surgical and ablative techniques. We believe, however, that the inclusion of all these patients is important due to the relatively low incidence and rarity of NELM. Furthermore, less than 15% of our cohort ($n = 86$) were treated prior to 2000 and represent a relatively small portion of the cohort. Finally, certain clinicopathologic data (eg, Ki67) and post-operative data (eg, complications) were not ascertained, which has been previously demonstrated to affect overall survival among patients undergoing liver-directed therapies.[13]

In conclusion, patients with NELM and EHD had more aggressive tumors, which conferred over a twofold increased risk of death compared with patients who did not have EHD. Liver-directed therapy for patients with NELM may provide a survival benefit for patients even in the presence of EHD, particularly among patients with limited <50% hepatic involvement.

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