Research article

Extrahepatic biliary neuroendocrine tumors: A national cancer database analysis

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A B S T R A C T

Background: Extrahepatic biliary neuroendocrine tumors (EBNETs) are rare. We aimed to characterize EBNETs including factors associated with survival.
Methods: The National Cancer Database was queried for patients with EBNETs from 2004 to 2016. Patients who underwent resection were examined using Cox proportional hazards regression and the Kaplan-Meier method. We compared overall survival (OS) among patients with EBNETs to those with NETs from other primary sites.
Results: Overall, 223 patients with EBNETs were identified. Patients were predominantly male (n = 113, 50.7 %), white (n = 177, 79.4 %) and presented without distant metastasis (n = 182, 81.6 %). The majority underwent operation (n = 127, 57.9 %) with resection of the primary tumor (n = 89, 70 %). Among patients who underwent resection (n = 71), multivariable regression demonstrated older age (HR 1.11, 95 % C.I. 1.04–1.17), lymph node metastases (HR 1.19, 95 % C.I. 1.02–1.38) and poorly/undifferentiated tumors [HR 22.3, 95 % C.I. 3.78–131]) were associated with worse overall survival. Patients with EBNETs experienced abbreviated OS compared to patients with small bowel or pancreas NETs (p < 0.001), but improved OS when compared to patients with gallbladder NETs (p = 0.001).
Conclusions: Tumor differentiation and lymph node status significantly impact overall survival.

1. Introduction

With less than 200 cases reported in the literature, extrahepatic bile duct neuroendocrine tumors (EBNETs) are an exceedingly rare subtype of cancer arising from the proximal or distal biliary tree [1–3]. Distinguishing these lesions from adenocarcinoma can be challenging clinically, as EBNETs are predominantly non-functioning tumors that commonly present with signs and symptoms of biliary obstruction, much like classical extrahepatic cholangiocarcinoma [3,4]. However, in contrast to patients who typically develop biliary tree adenocarcinoma in the Western world, those who develop EBNETs are more likely to be younger, female, and to have a familial syndrome [1,3,5].

Due to the rarity of EBNETs, there are limited data for prognostication and defining best practices [1–3,6–12]. For instance, tumor differentiation has a significant impact on survival in patients with NETs that originate from other anatomic sites whereas little is known of the importance of tumor differentiation on survival in patients with EBNETs [3]. Treatment patterns for patients with EBNETs appear to parallel those with distal bile duct adenocarcinoma and often involve extirpation of the primary tumor by

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extrahepatic bile duct resection and regional lymphadenectomy, with the occasional use of adjuvant therapy [6–13]. Although patients with EBNETs collectively seem to fare better than their counterparts with classical distal cholangiocarcinoma, these outcomes are poorly defined and are derived mostly from heterogeneous historical cohorts [3].

Due to the limited prognostic and treatment-specific data alongside the lack of defined guidelines for EBNETs, we aimed to characterize EBNETs using a large national database, identify national practice patterns, and determine factors associated with overall survival.

2. Methods

2.1. Data source

The National Cancer Database (NCDB) participant user files were the source of all data in our study. The NCDB is a nationwide repository of de-identified patient data related to cancer metrics and outcomes in the United States derived from the submissions of over 1500 Commission on Cancer (CoC)-accredited programs. The NCDB captures over 70 % of new cancer diagnoses in the United States per year. The CoC is a multidisciplinary association maintained by the American College of Surgeons and the American Cancer Society that accredits US hospitals based on various aspects of cancer care. Due to our study's inclusion of only de-identified data, it was exempt from institutional review board review.

2.2. Cohort selection

We selected patients diagnosed with EBNETs from the NCDB from 2004 to 2016. Patients were identified using the International Classification of Disease for Oncology, 3rd edition (ICD-*O*-3) topography code for the extrahepatic bile duct (C24.0), overlapping biliary tract (C24.8) and biliary tract not otherwise specified (NOS) (C24.9). ICD-*O*-3 morphology codes for neuroendocrine histology (8013, 8041, 8240, 8246) were used to select patients. Individual patients with more than one primary cancer were excluded, as were patients with intrahepatic (C22.1) and periampullary tumors (C24.1). The elimination of intrahepatic and periampullary tumors served to remove the ambiguity associated with evaluating potentially metastatic lesions or pancreatic NETs (Fig. 1).

2.3. Survival analysis

In order to determine factors associated with survival in patients who underwent resection of EBNETs (n = 71), we first excluded patients with missing information regarding tumor differentiation (n = 92) and then excluded those whose data suggested the presence of distant metastasis, including those with clinical M1 disease, grossly positive resection margins, documentation of having undergone a debulking surgical procedure, or documentation of not having undergone any surgical procedure (n = 60, Fig. 1). Unadjusted OS was estimated using the Kaplan-Meier method, and comparisons between groups were made using the log-rank test. Additionally, using the same selection criteria and time frame, we compared unadjusted survival of patients with EBNETs to those with NETs from primary sites in the small bowel, pancreas, and gallbladder. Covariate effects on OS were estimated in an adjusted model using bivariable and multivariable Cox proportional hazards regression.
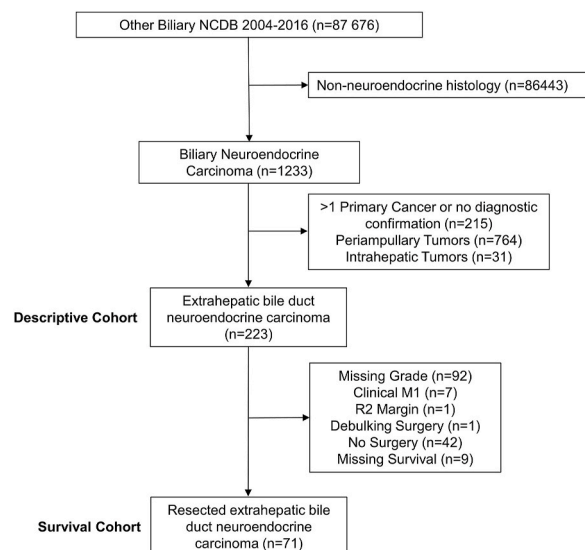

Fig. 1. Selection of the study cohort. *NCDB* National Cancer Database, *NET* neuroendocrine tumor.

2.4. Statistical analysis

Univariable and bivariable descriptive statistics were calculated for variables of interest. Continuous variables were reported as medians and interquartile range (IQR). Categorical variables were described using frequencies and percentages. Comparisons between groups were performed using chi-squared or Fisher's exact test for categorical variables and Mann Whitney-U test for continuous variables, as appropriate. A multivariable Cox proportional hazards model including all variables with $p < 0.10$ on bivariable analysis was used to determine adjusted covariate effects on OS. Statistical significance was defined as a two-tailed *p*-value <0.05. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA).

3. Results

3.1. Characteristics of extrahepatic biliary neuroendocrine tumors

We identified 223 patients with EBNETs who met inclusion for this analysis. Patients had a median age of 61 years (IQR 51–71) and were mostly male (n = 113, 50.7 %), white (n = 177, 79.4 %) and had Charlson-Deyo Comorbidity Score of zero (n = 170, 76.2 %). Forty-one (18.3 %) patients presented with synchronous distant metastases, and the most common metastatic site was the liver (n = 29, 13.0 %). Median tumor size was 17.5 mm (IQR 6.5–30) and 40 patients (17.9 %) presented with at least one pathologically positive lymph node. Most tumors did not have a specified location of origin within the extrahepatic biliary tree (n = 113, 50.7 %), but 53 (23.8 %) were located in the distal bile duct, and the remaining tumors originated in the proximal/perihilar region or cystic ducts (n = 29, 13 % and n = 28, 13 %, respectively). While most patients had neuroendocrine histology (n = 177, 73.6 %), other represented subtypes included small and large cell carcinoma (n = 42, 19 % and n = 8, 4 %, respectively). Additionally, although many patients were missing information regarding tumor differentiation (n = 92, 41 %), most were well (n = 62, 27.8 %) or poorly differentiated (n = 56, 25 %) (Table 1).

Table 1
Patient and disease characteristics.

n = 223	N	%
Age at Diagnosis (median, IQR)	61	(51,71)
Sex		
Male	113	50.7 %
Female	110	49.3 %
Race		
White	177	79.4 %
African-American	30	13.5 %
Asian	7	3.1 %
Other/Unknown	9	4.0 %
Charlson-Deyo Score		
0	170	76.2 %
1	38	17.0 %
≥2	15	6.7 %
Positive Lymph Node(s)		
No Positive Lymph Nodes	54	24.2 %
≥1 Positive Lymph Node	40	17.9 %
No Nodes Examined	129	57.8 %
Tumor Size (mm), (median, IQR)	17.5	(6.5,30)
Number of Positive Lymph Nodes, (median, IQR)	0	(0,1)
Tumor Location		
Distal Bile Duct	53	23.8 %
Proximal Bile Duct/Perihilar	29	13.0 %
Cystic Duct	28	12.6 %
Other NOS	113	50.7 %
Histology		
Neuroendocrine Tumor	173	77.6 %
Small Cell Carcinoma	42	18.8 %
Large Cell Carcinoma	8	3.6 %
Tumor Morphology		
Well Differentiated	62	27.8 %
Moderately Differentiated	13	5.8 %
Poorly Differentiated/Undifferentiated	56	25.1 %
Unknown	92	41.3 %
Bone Metastasis at Diagnosis	2	0.9 %
Brain Metastasis at Diagnosis	1	0.4 %
Liver Metastasis at Diagnosis	29	13.0 %
Lung Metastasis at Diagnosis	7	3.1 %
Other Metastasis at Diagnosis	2	0.9 %

4. Treatment of extrahepatic biliary neuroendocrine tumors

There were 127 patients (57.9 %) who underwent resection. Among these patients, most underwent removal of the primary tumor (n = 89, 70 %), while 23 (18 %) had a radical resection that included part of an adjacent organ. Most patients (n = 88, 69 %) who underwent surgical resection had specimens with negative margins. Overall, the use of chemotherapy or radiation was more common in patients who did not undergo operative intervention (Table 2).

5. Factors associated with survival

Among patients who underwent resection, multivariable regression demonstrated that older age (HR 1.11, 95 % C.I. 1.04–1.17) and lymph node metastasis (HR 1.19, 95 % C.I. 1.02–1.38) were associated with worse survival on a per-unit basis. Additionally, in this model, tumor differentiation was the strongest independent predictor of decreased survival (moderately-differentiated [HR 38.8, 95 % C.I. 4.11–367] and poorly/undifferentiated [HR 22.3, 95 % C.I. 3.78–131]). Notably, tumor location within the bile duct, receipt of chemotherapy, small or large cell histology, and tumor size were not associated with survival (Table 3). Median survival was not reached for all resected EBNETs, but mean survival was 93.1 months (95 % C.I. 76.1–110.0). The differences in survival stratified by degree of tumor differentiation that were seen in the Cox model were also demonstrated in the unadjusted model (Fig. 2), which demonstrates that median overall survival is reached only in patients with poorly/undifferentiated histology (16.6 months, 95 % C.I. 10.4–22.7) (Fig. 2). Furthermore, when compared to those with NETs originating from other primary sites, survival among patients with EBNETs who undergo resection is worse than those with NET originating from the pancreas or small bowel (p < 0.001), but better than those with NET arising from the gallbladder (p = 0.001, Fig. 3).

6. Discussion

Here we report a large cohort of patients with EBNETs using a national database. Our findings demonstrate survival stratification is governed by tumor differentiation, akin to NETs arising from other primary sites. Most patients in this study were treated with resection alone for this rare tumor. Our findings suggest that EBNETs generally carry a better prognosis than the classical adenocarcinoma subtype of bile duct cancer, however poorly differentiated EBNETs portend a substantially worse overall survival than more differentiated variants. Interestingly, while prognosis for patients with EBNETs is generally worse than that of pancreatic or small bowel NET, it appears to be better than that of gallbladder NETs.

Cancer prognostication and the formulation of consensus recommendations must involve the consideration of the best available evidence. Thus, while prior data consisted of case reports and small series, we believe that our study offers the largest and most comprehensive cohort to evaluate the importance of tumor differentiation and lymph node metastasis on long-term survival, as well as highlights modern, national treatment trends for EBNETs [3]. Our data demonstrate that EBNET survival clearly stratifies based on the degree of tumor differentiation, even when including only a modest sample size. It is important to recognize that while we do not have these tumors' complete grade-specific data, which would include a mitotic count and Ki-67 proliferative index in addition to each tumor's degree of differentiation, our findings are largely consistent with those of other visceral NETs [14–17]. Specifically, while well-differentiated NETs can be associated with a spectrum of low-to high-grade histopathologic features, poorly-differentiated NETs are uniformly high-grade and aggressive cancers that draw morphologic and survival comparisons to small cell lung carcinoma [14, 18]. Our data also suggest that the presence of metastases in lymph nodes does carry prognostic significance, but the effect size is lower than that of poorer tumor differentiation. Once again, this finding is consistent with suggested conventions for poorly-differentiated

Table 2
Type(s) of treatment received.

n = 223	Surgical Management				
	Yes (n = 127)		No (n = 96)		
Received Chemotherapy	N	%	N	%	
No	98	77.20 %	57	59.40 %	
Yes	29	22.80 %	39	40.60 %	
Received Radiation					
No	117	92.10 %	92	95.80 %	
Yes	10	7.90 %	4	4.20 %	
Surgical Procedure					
Local Therapy Only	11	8.70 %			
Removal of Primary Site	89	70.10 %			
Debulking	1	0.80 %			
Radical Resection	23	18.10 %			
Surgery, NOS	3	2.40 %			
Margin Status					
R0	88	69.30 %			
R1/R2	27	21.30 %			
Unknown	12	9.40 %			

Table 3
Cox proportional hazards regression.

| n = 71	N	Univariable			Multivariable		
		HR	95 % C.I.	p-value	HR	95 % C.I.	p-value
Age at Diagnosis	71	1.06	(1.03–1.09)	<0.001	1.11	(1.04–1.17)	0.001
Sex							
Male	38	ref	–	–	ref	–	–
Female	33	0.44	(0.19–1.01)	0.051	0.31	(0.07–1.27)	0.102
Race							
White	59	ref		–			
African-American	8	0.23	(0.03–1.71)	0.152			
Other/Unknown	4	1.29	(0.30–5.52)	0.729			
Charlson-Deyo Score							
0	57	ref	–	–			
1	11	0.62	(0.19–2.08)	0.442			
≥2	3	1.05	(0.14–7.90)	0.963			
Lymphovascular Invasion							
Absent	19	ref	–	–	Excluded from MVA due to missing values		
Present	14	4.88	(1.24–19.24)	0.023			
Unknown	12	0.97	(0.16–5.83)	0.974			
Tumor Size (mm), (median, IQR)	62	1.02	(1.00–1.05)	0.040	0.98	(0.92–1.04)	0.495
Number of Positive Lymph Nodes	51	1.19	(1.09–1.30)	<0.001	1.19	(1.02–1.38)	0.025
Tumor Location							
Distal Bile Duct	20	ref	–	–			
Proximal Bile Duct/Perihilar	10	1.50	(0.42–5.33)	0.528			
Cystic Duct	12	0.48	(0.10–2.38)	0.369			
Other NOS	29	1.44	(0.55–3.79)	0.463			
Histology							
Neuroendocrine Tumor	62	ref	–	–	ref	–	–
Small/Large Cell Tumor	9	4.76	(1.97–11.47)	0.001	1.32	(0.35–4.97)	0.683
Tumor Morphology							
Well Differentiated	39	ref	–	–	ref	–	–
Moderately Differentiated	9	4.52	(1.07–19.10)	0.040	38.84	(4.11–366.99)	0.001
Poorly Differentiated/Undifferentiated	23	15.58	(5.66–42.91)	<0.001	22.30	(3.78–131.49)	0.001
Chemotherapy							
No	53	ref	–	–	ref	–	–
Yes	12	2.66	(1.14–6.17)	0.023	0.32	(0.05–2.13)	0.236
Unknown	6	0.67	(0.09–5.04)	0.696	1.69	(0.16–17.60)	0.661
Radiation							
No	63	ref	–	–			
Yes	8	2.27	(0.85–6.02)	0.101			
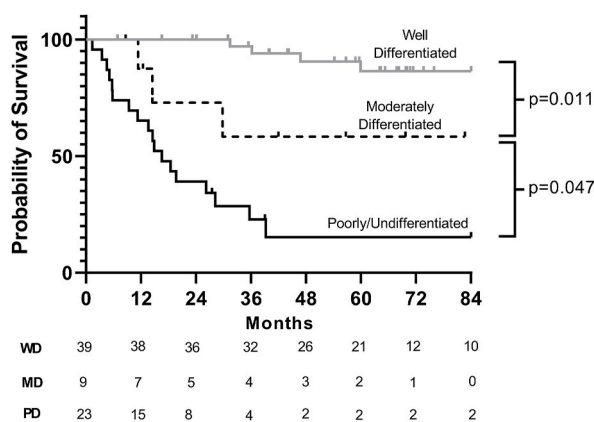
Fig. 2. Survival in resected patients stratified by degree of tumor differentiation (n = 71). Median overall survival is reached only in patients with poorly/undifferentiated histology (16.6 months, 95 % C.I. 10.4–22.7).

(and thus, high-grade) bronchopulmonary and gastroenteropancreatic NETs, for which the conventional TNM staging systems have been called into question [18]. Overall, we believe that while lymph node positivity is important in EBNET staging, tumor differentiation should hold more weight in an optimal system, as it does for poorly-differentiated NETs from other primary sites.

Additionally, this study re-emphasizes the utility of large national databases in studying rare tumors. The NCDB has been used to evaluate prognosis and treatment patterns for patients with NETs of various primary sites, and we demonstrate that these insights can
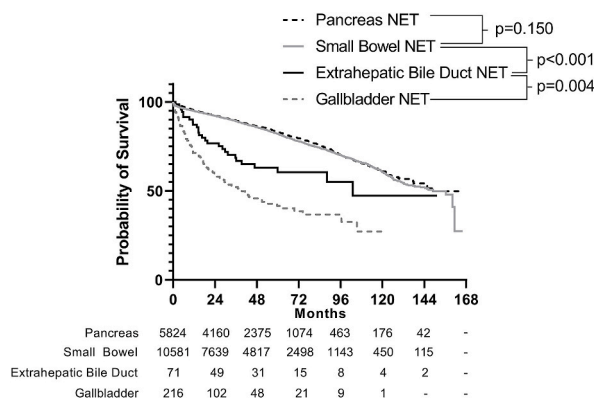
Fig. 3. When comparing survival in patients with NETs from different primary sites, survival is worse in patients with EBNETs than in patients with NETs originating from the pancreas or small bowel (p < 0.001), but better than those with NETs arising from the gallbladder (p = 0.001).

now be extended to patients with EBNETs [19–21]. Accurately evaluating national trends in treatment strategies is challenging when using the aggregation of case series and reports due to the heterogeneity of patients, tumors, and reporting quality of historical cohorts. While not without flaws, the NCDB provides a more uniform survey of this and other tumor subtypes and allows for a broad evaluation of a modern cohort of EBNET patients. While we concede that a dedicated, multi-institutional collaborative likely would have the potential to generate more granular and potentially more reliable data, the overall challenges that would be associated with such an endeavor are perhaps the reason why such an enterprise has not been undertaken to date.

Despite the strengths that we believe our analysis offers, it is not without limitations. The retrospective nature of our study renders it susceptible to selection bias, potential effects on survival from unmeasured confounders, shortcomings related to non-standardized follow-up, inconsistent recording of data, and a lack of granularity among histopathologic characteristics. Specifically, the NCDB lacks details regarding mitotic count and proliferative index, subsequently preventing tumor grade designation. Interestingly, although conventional staging of NETs strongly considers grade in prognostication, studies aimed specifically at delineating the importance of this finding have shown that even high-grade well-differentiated pancreatic NETs seem to have considerably better survival than poorly differentiated tumors [14,18]. Furthermore, the NCDB does not report data on recurrence, and we are also not able to ascertain the details of the respective surgical operation or systemic therapy regimen that each patient underwent. Another limitation of the study is exclusion of lymphovascular invasion. With respect to the multivariable Cox model, there was a high proportion of patients (35, 43.8 %) with missing values among other covariates in patients with available lymphovascular invasion status (LVI). The inclusion of only patients with documented LVI status in this model would have excluded many patients who were missing values of several other covariates, therefore, in order to preserve the maximum number of patients, LVI was excluded from the model. Additionally, survival analysis is limited to patients with available follow up. A significant number of patients are lost to follow up and censored in the survival analysis during the longer study period times, therefore the far right of the curves must be interpreted with caution. Nevertheless, the use of this large database offers insight into a rare tumor subtype that otherwise is difficult to evaluate even when approaching this uncommon entity through single-institution experiences or even a large, multi-institutional collaborative.

In conclusion, EBNETs are a rare variant of extrahepatic bile duct tumors associated with worse overall survival than pancreatic and small bowel NETs. Older age, lymph node positivity, and poor tumor differentiation were independent predictors of abbreviated survival in patients who underwent surgical intervention. These findings suggest that patients with locoregional EBNETs may benefit from resection of their primary tumors and regional lymphadenectomy for local tumor control and adequate staging. Advances in systemic options for patients with NETs from all primary sites may augment the benefit of primary tumor resection in EBNETs.

CRediT authorship contribution statement

Dominguez Da: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Eade Av:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis. **Aversa Jg:** Writing – original draft, Formal analysis, Conceptualization. **Hagerty Bl:** Writing – original draft, Methodology, Conceptualization. **A.M. Blakely:** Writing – review & editing, Supervision, Conceptualization. **Davis Jl:** Writing – review & editing, Supervision, Conceptualization. **Melstrom Lg:** Writing – review & editing, Supervision, Conceptualization. **Hernandez Jm:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34714.

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