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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Is There a Role for Surgery in Patients with Neuroendocrine Tumors of the Esophagus? A Contemporary View from the NCDB

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ABSTRACT

Background. Esophageal neuroendocrine tumors (eNETs) are exceedingly rare, aggressive and have a poor prognosis. Treatment guidelines are ill-defined and mainly based on evidence from case reports and analogous experiences drawn from similar disease sites.

Methods. The NCDB was reviewed for histologically confirmed stage I–III, primary eNETs from 2006 to 2014. Patients were grouped into whether or not they underwent primary tumor resection. Univariate, multivariable, and full bipartite propensity score (PS) adjusted Cox regression analyses were used to assess overall and relative survival differences.

Results. A total of 250 patients were identified. Mean age was 65.0 (standard deviation [SD] 11.9) years, and 174 (69.6%) patients were male. Most patients had stage III disease (n = 136, 54.4%), and the most common type of NET was small cell eNET (n = 111, 44.4%). Chemotherapy was used in 186 (74.4%), radiation therapy in 178 (71.2%), and oncological resection was performed in 69 (27.6%) patients. Crude 2-year survival rates were higher in the operated (57.3%) compared with the nonoperated group (35.2%; $p < 0.001$). The survival benefit held true after multivariable adjustment (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.32–0.69, $p < 0.001$). After full bipartite PS adjustment analysis, survival was longer for patients who received a surgical resection compared with those who did not (HR 0.48, 95% CI 0.31–0.75, $p = 0.003$) with a corresponding 2-year overall survival rate of 63.3% (95% CI 52.0–77.2) versus 38.8% (95% CI 30.9–48.8), respectively.

Conclusions. Multimodal treatment that includes surgery is associated with better overall survival for eNETs. Additional research is needed to more definitively identify patients who benefit from esophagectomy and to establish an appropriate treatment algorithm.

Esophageal neuroendocrine tumors (eNETs) are rare but with a rising incidence over the past few decades.[1] They are defined as epithelial neoplasms with predominantly neuroendocrine differentiation originating from the peripheral neuroendocrine cell system, mainly arising in the bronchopulmonary system and the gastrointestinal tract.[1–4]

Due to its rarity and due to the resulting lack of prospective data, no specific treatment algorithm for eNETs exists.[5] Most evidence originates from case reports or case series with very limited number of patients.[6,7] In addition, treatment recommendations are mirroring treatment guidelines of small-cell lung cancer, including surgery, chemo-, and radiotherapy.[8]

In general, neuroendocrine tumors (NETs) have the potential for early systemic dissemination with up to 70% of patients initially presenting with distant metastases.

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Given this high propensity for systemic spread, systemic therapy plays an important role in any multimodal treatment algorithm.[9,10] Adjuvant chemotherapy has proven to delay disease recurrence after surgery or radiation therapy.[11]

However, the role of surgical resection among patients with eNETs is still ill-defined. While it is increasingly accepted that cure can only be achieved surgical resection is performed, its specific role in a multimodal treatment algorithm needs further elaboration.[12–14] Despite major advancements in operative techniques and postoperative care, early postoperative mortality after esophagectomy still ranges from 1 to 13%.[15,16] In addition, quality of life even 12 months after esophagectomy is still impaired with reports of dysphagia reaching more than 50%.[17] These risks and ramifications need to be counterbalanced by the potential gain in survival.[18]

Using the National Cancer Database (NCDB), we tested the hypothesis that primary resection of localized esophageal NETs was associated with improved overall (OS) and relative survival (RS). Given the low prevalence of localized eNETs, prospective, randomized studies are very unlikely to be performed, and case reports and case series are limited in power. We therefore felt that advanced statistical modeling on high-quality nationwide data had the potential to provide high-level evidence to guide future therapy.

METHODS

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the deidentified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Ethical approval for this study was received from Duke University Medical Center.

NCDB was queried for histologically confirmed stage I–III, primary eNETs from 2006 to 2014 according to International Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography C15.0–9 and using the following histology codes 8041, 8246, 8013, 8240, 8243, and 8244. Patients were excluded if the disease was not confirmed by histology, if the eNET was not the primary tumor, or if surgical resection of the primary tumor was unknown.

Patient information was extracted and—given limited number of patients within the dataset—grouped as follows: age (< 64 years, > 65 years), gender (male, female), ethnicity (white, black, other, unknown), histology (small cell eNETs, large cell eNETs, eNETs not otherwise specified), tumor location in the esophagus (lower, middle, upper third, overlapping), tumor stage (I, II, III), chemotherapy performed (yes, no), radiation therapy performed (yes, no), and Charlson Deyo comorbidity index (0, 1 +). Tumor grade based on ICD-O-3 guidelines in NCDB is defined as grade 1: well differentiated, grade 2: moderately differentiated, grade 3: poorly differentiated, and grade 4: undifferentiated/anaplastic. NCDB does not contain information on the new WHO grading schema. To assess the impact of tumor resection on survival, patients were grouped into whether or not they underwent a primary tumor resection during their disease course.

Statistical Analysis

The statistical analyses were performed with the *R* statistical software version 3.4.1 (www.r-project.org). A p value of < 0.05 (two-sided) was considered to be statistically significant. Patient and tumor characteristics are presented as means (standard deviation, SD) for continuous and as counts (percentage, %) for categorical variables. Univariate comparisons between patients who underwent primary tumor resection and those who did not was performed using Chi square test for categorical variables. Spearman's rank correlation analyses were performed to assess time-trends. Results were reported using the non-parametric correlation coefficient R and p_{trend}. For regression analyses, the p-values were estimated by likelihood-ratio tests and the confidence intervals were estimated with the Wald method. To assess predictors of surgical resection of the primary tumor, univariate and multivariable-adjusted logistic regression analyses were performed with surgical resection as outcome and clinically relevant covariates as predictor variables. To assess OS, univariate, multivariable-adjusted, and stepwise Cox regressions were performed. In addition, full bipartite pairwise matching and weighting propensity score (PS)-adjusted Cox regression analyses were performed using the "MatchIt" and "optmatch" packages to further minimize inherent differences between the two groups.[19,20] The PS was calculated using all potential covariates such that no persisting bias remained (data not shown). To further account for unmeasured confounding, near/far matching with distance to the facility as the instrumental variable was used to perform causal inference analyses.[21–23] Given that NCDB has no information on cause of death, cancer-specific survival cannot be estimated. As an attempt to determine the impact of the eNET on cancer-related survival, RS analyses were performed using the Pohar-Perme estimator, which adjusts for population-based information on age, gender, ethnicity, and year of diagnosis (https://see

TABLE 1 Baseline patient characteristics with eNETs, treatment, and short-term outcome data

	Total (n = 250)	No resection (n = 181)	Resection (n = 69)	p value
Gender				
Male	174 (69.6%)	123 (68.0%)	51 (73.9%)	0.360
Female	76 (30.4%)	58 (32.0%)	18 (26.1%)	
Age				
Mean (SD)	65 (11.9)	66.6 (12.3)	61 (9.9)	0.001
< 64	120 (48.0%)	77 (42.5%)	43 (62.3%)	0.029
≥ 65	130 (52.0%)	104 (57.5%)	26 (37.7%)	
Race				
White	222 (88.8%)	157 (86.7%)	65 (94.2%)	0.094
Black/other	28 (11.2%)	24 (13.3%)	4 (5.8%)	
Charlson/Deyo				
Comorbidity score				
0	186 (74.4%)	133 (73.5%)	53 (76.8%)	0.590
1 +	64 (25.6%)	48 (26.5%)	16 (23.2%)	
Tumor stage				
Stage I	38 (15.2%)	21 (11.6%)	17 (24.6%)	0.002
Stage II	76 (30.4%)	50 (27.6%)	26 (37.7%)	
Stage III	136 (54.4%)	110 (60.8%)	26 (37.7%)	
Histology				
eNETs NOS	107 (42.8%)	66 (36.5%)	41 (59.4%)	< 0.001
Small cell eNETs	111 (44.4%)	96 (53.0%)	15 (21.7%)	
Large cell eNETs	32 (12.8%)	19 (10.5%)	13 (18.8%)	
Tumor localization				
Lower third	149 (59.6%)	100 (55.2%)	49 (71.0%)	0.090
Middle third	46 (18.4%)	36 (19.9%)	10 (14.5%)	
Upper third	14 (5.6%)	13 (7.2%)	1 (1.4%)	
Overlapping	41 (16.4%)	32 (17.7%)	9 (13.0%)	
Grading				
G4 (n = 39)	39 (15.6%)	31 (17.1%)	8 (11.6%)	< 0.001
G3 (n = 133)	133 (53.2%)	86 (47.5%)	47 (68.1%)	
G1–2 (n = 11)	11 (4.4%)	2 (1.1%)	9 (13.0%)	
GX (n = 67)	67 (26.8%)	62 (34.3%)	5 (7.2%)	
Chemotherapy				
No	64 (25.6%)	43 (23.8%)	21 (30.4%)	0.279
Yes	186 (74.4%)	138 (76.2%)	48 (69.6%)	
Chemotherapy				
No	59 (23.6%)	39 (21.5%)	20 (29.0%)	0.508
Single-agent	9 (3.6%)	5 (2.8%)	4 (5.8%)	
Multi-agent	156 (62.4%)	118 (65.2%)	38 (55.1%)	
Agent unknown	21 (8.4%)	15 (8.3%)	6 (8.7%)	
Unknown	5 (2.0)	4 (2.2%)	1 (1.4%)	
Radiotherapy				
No	72 (28.8%)	41 (22.7%)	31 (44.9%)	0.001
Yes	178 (71.2%)	140 (77.3%)	38 (55.1%)	
Surgical technique				
No resection	181 (72.4%)	181 (100%)	0	< 0.001

TABLE 1 continued

	Total (n = 250)	No resection (n = 181)	Resection (n = 69)	p value
Partial esophagectomy	12 (4.8%)	0	12 (17.4%)	
Total esophagectomy	9 (3.6%)	0	9 (13.0%)	
Esophagectomy +Gastrectomy	43 (17.2%)	0	43 (62.3%)	
Esophagectomy NOS	5 (2.0%)	0	5 (7.2%)	

eNETs esophageal neuroendocrine tumors; *NOS* not otherwise specified; *LOS* length of hospital stay; *NA* not applicable

r.cancer.gov/expsurvival/US.1970thru2015.individual.years.txt).[24]

RESULTS

Patient Characteristics

A total of 250 patients with primary eNETs were included in this study. Mean age of the patients was 65.0 (SD 11.9) years, and 174 (69.6%) patients were male (Table 1). The most common eNET was small cell eNET (n = 111, 44.4%) followed by eNETs not further classified/other (n = 107, 42.8%) and large cell eNETs (n = 32, 12.8%). Most tumors were located in the lower third of the esophagus (n = 149, 59.6%). Of the 250 included patients, 69 (27.6%) patients underwent surgical resection of the primary eNET. This rate did not change over time (R = 0.47, p_{trend} = 0.21). Chemotherapy was performed in 186 (74.4%) patients and increased from 52.0% in 2006 to 85.0% in 2014 (R = 0.83, p_{trend} = 0.006). Mean hospital stay for all patients was 12.0 (SD 10.1) days with a 30-day mortality rate of 2.9% and 90-day mortality rate of 4.3% in the operated group.

Predictors of Surgical Resection

The resection rate for small cell eNETs, large cell eNETs, and eNETs not other specified was 13.5%, 41% and 38%, respectively. In univariate analysis, the difference between patients with small cell eNETs and those with eNETs not otherwise specified is significant (Table 2). In addition, patients with lower esophageal tumors, stage I, and younger patients (< 64 years) were more likely to undergo surgical resection of the primary eNETs compared with their counterparts. These variables predicting a higher likelihood of undergoing primary tumor resection persisted in multivariable-adjusted analysis with the exception of tumor location.

Survival Analyses

Two-year OS rate of patients without surgical resection of the primary tumor was 35.2% (95% CI 28.7–43.1), whereas it was 57.3% (95% CI 46.4–70.7) for those who underwent a primary tumor resection (Fig. 1a). In multivariable-adjusted OS analyses, patients who underwent surgical resection of the eNET continued to have a better OS compared with those who did not undergo surgical resection (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.32–0.69, $p < 0.001$; Table 3). This also held true after stepwise adjustment (HR 0.46, 95% CI 0.32–0.66, $p < 0.001$). In multivariable-adjusted analysis, RS was better among resected patients compared with nonresected patients (HR 0.51, 95% CI 0.35–0.76, $p < 0.001$). After full bipartite PS adjustment on an analysis of 198 patients, there continued to be an improved OS for patients who underwent surgical resection (HR 0.48, 95% CI 0.31–0.75, p = 0.003), with a corresponding adjusted 2-year survival rate of 56.9% (95% CI 46.1–70.4%) for resected compared with 31.7% (95% CI 24.5–41.0%) for nonresected patients (Fig. 1b). The OS (HR 0.15, 95% CI 0.04–0.57, p = 0.003) and RS (HR 0.30, 95% CI 0.11–0.85, p = 0.046) advantages persisted after accounting for unmeasured bias in near/far-matched analyses for OS (HR 0.23, 95% CI 0.08–0.66, p = 0.009).

Survival benefit for resected patients also could be demonstrated in a subgroup analysis of patients limited to stage I/II disease. Of the overall cohort (n = 250 patients), 76 (30.4%) were diagnosed with stage I/II disease. In this subgroup, 31 (40.8%) patients were treated with primary oncologic resection, whereas 45 (59.2%) patients received systemic chemotherapy. The patients who underwent a primary oncologic resection had a longer overall survival compared with their counterparts, even after full bipartite propensity score adjustment (HR 0.38, 95% CI 0.18–0.81, p = 0.018).

In univariate OS analyses, large cell eNETs, thoracic (middle third of the esophagus) NETs, stage III disease, those without chemotherapy, nonwhites, and patients with a Charlson Comorbidity Index $\geq$ 1 had worse OS compared with their counterparts (Table 3). These differences

TABLE 2 Predictors of primary surgical resection among patients with esophageal NETs

	Unadjusted logistic regression		Multivariable adjusted logistic regression	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Gender				
Male	Reference	0.356	Reference	0.512
Female	0.75 (0.39–1.38)		0.74 (0.30–1.79)	
Age (yr)				
< 64	Reference	0.005	Reference	0.009
≥ 65	0.45 (0.25–0.79)		0.38 (0.18–0.79)	
Race				
White	Reference	0.076	Reference	0.457
Black/other	0.40 (0.11–1.09)		0.59 (0.13–2.23)	
Charlson/Deyo				
Comorbidity score				
0	Reference	0.587	Reference	0.665
1 +	0.84 (0.43–1.58)		0.84 (0.37–1.83)	
Tumor stage				
Stage I	Reference	0.003	Reference	0.016
Stage II	0.64 (0.29–1.43)		0.90 (0.33–2.52)	
Stage III	0.29 (0.13–0.63)		0.34 (0.12–0.94)	
Histology				
eNETs NOS	Reference	< 0.001	Reference	0.070
Small cell eNETs	0.25 (0.13–0.48)		0.42 (0.18–0.94)	
Large cell eNETs	1.10 (0.48–2.45)		1.09 (0.42–2.77)	
Localization				
Lower third	Reference	0.063	Reference	0.090
Middle third	0.57 (0.25–1.20)		1.27 (0.44–3.52)	
Upper third	0.16 (0.01–0.82)		0.22 (0.01–1.44)	
Overlapping	0.57 (0.24–1.25)		0.39 (0.14–1.04)	
Grading				
G4 (n = 39)	Reference	< 0.001	Reference	0.002
G3 (n = 133)	2.12 (0.94–5.28)		1.37 (0.55–3.72)	
G1–2 (n = 11)	17.44 (3.65–130.83)		10.37 (1.68–94.17)	
GX (n = 67)	0.31 (0.09–1.01)		0.32 (0.08–1.17)	
Chemotherapy				
No	Reference	0.285	Reference	0.660
Yes	0.71 (0.39–1.33)		1.23 (0.49–3.23)	
Radiotherapy		< 0.001		
No	Reference		Reference	0.005
Yes	0.36 (0.20–0.65)		0.31 (0.13–0.70)	

eNETs esophageal neuroendocrine tumors; *NOS* not otherwise specified; *NA* not applicable; *OR* odds ratio; *CI* confidence interval

held true even in multivariable-adjusted analysis with the exception of race.

DISCUSSION

To the best of our knowledge, this study on 250 patients with localized eNETs is the largest study assessing the impact of surgical resection of the primary tumor on OS and RS. Various advanced statistical modeling techniques used in this study consistently showed that patients who received a surgical resection of the primary tumor had a survival benefit compared with patients who did not receive a surgical resection.

While surgical resection of eNETs is associated with improved OS and RS compared to nonsurgical treatment regimens, it must be acknowledged that eNETs are a

TABLE 3 Univariate, multivariable adjusted, and stepwise adjusted overall and relative survival analyses for patients with eNETs

Overall survival						
	Unadjusted Cox regression		Multivariable adjusted Cox regression		Stepwise adjusted Cox regression	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Resection						
No	Reference	< 0.00	Reference	< 0.001	Reference	< 0.001
Yes	0.50 (0.36–0.69)	1	0.47 (0.32–0.69)		0.46 (0.32–0.66)	
Gender						
Male	Reference	0.566	Reference	0.576		
Female	1.10 (0.79–1.54)		1.11 (0.76–1.63)			
Age						
< 64	Reference	0.075	Reference	0.685		
> 65	1.30 (0.97–1.74)		0.93 (0.67–1.30)			
Race						
White	Reference	0.018	Reference	0.959		
Black/other	1.61 (1.09–2.37)		0.99 (0.64–1.53)			
Charlson/Deyo						
Comorbidity Score						
0	Reference	0.013	Reference	< 0.001	Reference	0.003
1 +	1.53 (1.09–2.14)		1.75 (1.26–2.44)		1.65 (1.18–2.30)	
Tumor stage						
Stage I	Reference	0.164	Reference	0.176	Reference	0.063
Stage II	1.40 (0.87–2.23)	0.015	1.45 (0.85–2.50)	0.051	1.64 (0.97–2.77)	0.012
Stage III	1.70 (1.11–2.59)		1.71 (1.00–2.92)		1.94 (1.16–3.26)	
Histology						
eNETs NOS	Reference	0.100	Reference	0.841	Reference	0.545
Small cell eNETs	1.30 (0.95–1.78)	0.006	1.04 (0.71–1.53)	0.002	1.12 (0.78–1.59)	< 0.001
Large cell eNETs	1.88 (1.20–2.94)		2.22 (1.35–3.66)		2.45 (1.49–4.03)	
Localization						
Lower third	Reference	0.012	Reference	0.039	Reference	0.004
Middle third	1.65 (1.12–2.44)	0.227	1.64 (1.03–2.63)	0.674	1.86 (1.22–2.84)	0.566
Upper third	1.38 (0.82–2.31)	0.967	1.14 (0.62–2.08)	0.828	1.20 (0.65–2.21)	0.775
Overlapping	1.01 (0.66–1.55)		1.05 (0.67–1.65)		1.07 (0.69–1.64)	
Grading						
G4 (n = 39)	Reference	0.009	Reference			
G3 (n = 133)	0.61 (0.42–0.88)	0.003	0.78 (0.49–1.25)	0.303		
G1–2 (n = 11)	0.27 (0.11–0.65)	0.079	0.32 (0.10–1.03)	0.057		
GX (n = 67)	0.67 (0.42–1.05)		0.73 (0.42–1.27)	0.268		
Chemotherapy						
No	Reference	0.004	Reference	< 0.001	Reference	< 0.001
Yes	0.60 (0.43–0.85)		0.44 (0.29–0.66)		0.45 (0.31–0.66)	
Radiotherapy						
No	Reference	0.839	Reference	0.805		
Yes	1.04 (0.73–1.46)		0.95 (0.63–1.43)			
Relative survival						
	Unadjusted Cox regression		Multivariable adjusted Cox regression		Stepwise adjusted Cox regression	
	HR (95% CI)		HR (95% CI)		HR (95% CI)	

TABLE 3 continued

Overall survival						
	Unadjusted Cox regression		Multivariable adjusted Cox regression		Stepwise adjusted Cox regression	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Surgical resection						
No	Reference	0.030	Reference	< 0.001	Reference	< 0.001
Yes	0.70 (0.50–0.97)		0.51 (0.35–0.76)		0.54 (0.38–0.78)	

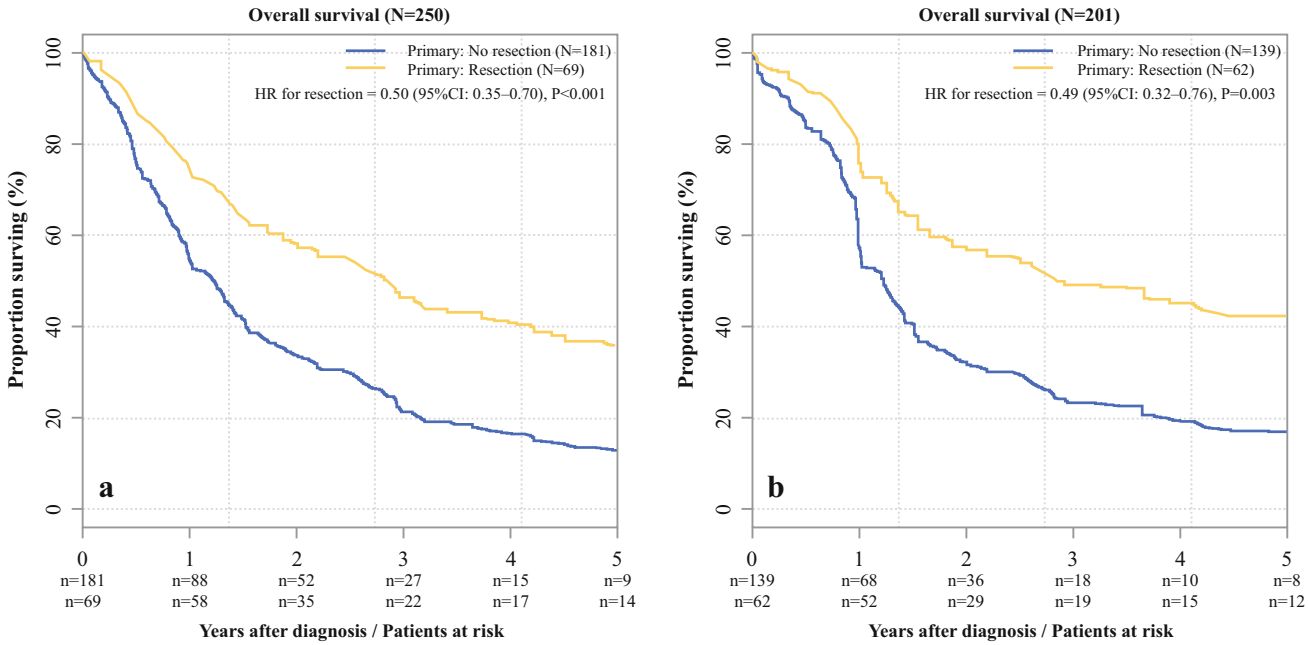

FIG. 1 **a** Overall survival curves, univariate. **b** Overall survival curves, after full bipartite propensity score adjustment

heterogenous group of tumors. Regarding grading of such tumors, there was significantly better OS and RS in patients with G1/2 eNETs compared with patients with G3 or G4 eNETs. G1/2 eNETs are associated with a reduced risk for lymph node metastases, and surgical resection is being increasingly recommended as evidenced by several studies.[13,14,25] Correspondingly, 9 of 11 (81%) of the G1/2 eNETs were resected. According to the currently used WHO classification for eNETs, G3 tumors are mainly composed of small cell NETs, which have high proliferative activity and a high risk of early lymph node and/or distant metastases and disease recurrence.[14,26,27] Based on retrospective data and drawing analogies from pulmonary small cell NETs, chemotherapy is still considered to be the cornerstone of any treatment algorithm. However, in small series a beneficial impact of surgical resection even among G3 NETs is acknowledged and is at least in part supported by our findings.[18,28] Yet, in our cohort over a 9-year time-period, surgical resection of the primary tumor was performed in only 32% of G3/4 tumors patients.

Aside from tumor grading, other tumor characteristics in our cohort were found to be associated with increased performance of surgical therapy, including stage I disease, lower eNETs, and younger patients (< 64 years). The importance of patient selection is supported by adjusted survival analyses where increased comorbidities, increasing tumor stage, underlying histology, and tumor localization were predictive for survival. Others have found that lower tumors, limited disease (T1/2, N0), and patients health status before operation were predictive factors whether or not a primary tumor resection was performed.[5] In our study, most of these characteristics are also associated with improved OS and RS compared with their counterparts, including underlying comorbidities, tumor histology, tumor localization, and tumor stage. Given limited power even in this cohort, any stratified analysis on

subgroups would even further limit the power and was therefore not performed. However, these characteristics should be considered as important factors when considering surgical resection of the primary eNET. Others have suggested that even patients with lower tumor stages (stage I/II), and no incidence of lymph node metastases might benefit from surgical treatment given their prolonged and nearly double OS.[13] In our subgroup analysis of patients limited to stage I/II disease, only 12 of 76 patients presented after a follow-up of 3 years for further analysis. Because of the limited number of patients, a statistically relevant conclusion between both groups concerning overall survival and/or disease-free survival should be made with caution.

However, most authors agree that surgery alone is rarely curative and that a survival benefit is mainly seen when combined with chemotherapy given the early risk of lymph node and other distant metastases if the tumor is in an advance staged (> IIa).[29–31] Surprisingly, the use of chemotherapy in addition to surgical resection of the primary tumor was found in only 52.2% of our patients. However, the use of chemotherapy significantly increased from 52.0% in 2006 to 85.0% in 2014, demonstrating the increasing acceptance of systemic therapy in the multimodal treatment approach of localized eNETs.

Given the limited number of patients with rare diseases, better survival rates after surgery are often criticized to be influenced by selection bias given that younger and fitter patients with lower tumor stage more often qualify for surgery.[32] While we cannot definitively eliminate selection bias despite including a total of 250 patients, we took any means to decrease its impact in our analysis. While propensity score matched analyses intend to achieve similar groups of patients based on measured covariates, near/far matching is even able to account for unmeasured bias. Even after applying these methods on the study population, an OS and RS benefit for patients undergoing primary tumor resection for eNETs persisted and indicates that surgical resection should be recommended as part of the treatment plan for suitable patients with eNETs.

To thoroughly counsel patients with eNETs regarding potential treatment options, aside from prolonging survival, short-term perioperative outcomes and expected quality of life are similarly important. As recently shown by an analysis from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP), rate of postoperative mortality in patients undergoing esophagectomy for various diseases is still between 2.7 and 9.8%.[33,34] We found a 30-day mortality rate of 2.9% and 90-day mortality rate of 4.3% in a cohort of eNETs, emphasizing that radical esophagectomy with extended lymphadenectomy is safe and feasible and can be performed with a comparable 30-day mortality risk to other more common indications for esophagectomy. In addition, as quality of life (QoL) is becoming an increasingly important outcome parameter in patients undergoing oncologic surgery, it is well known that postoperative complications after esophagectomy (i.e., anastomotic leakage, anastomotic stricture, reflux, and impairment of pulmonary function) affect QoL.[35] Given that the patients in this cohort had a median hospital stay of 12 days and a comparably low 30-day mortality rate of 2.9%, we conclude that they do not have a higher risk for surgical complications that could impact QoL compared with other patients undergoing esophagectomy. Still, while no explicit data exist on centralizing patients with eNETs to high-volume centers, it seems obvious that these patients should be referred to centers experienced not only in performing esophagectomy but also in treating NETs.[36–38]

LIMITATION OF THE STUDY

There are some inherent limitations in our study that need to be addressed. First, despite using one of the largest cancer registries worldwide, the number of patients is still limited, and advanced statistical modeling could only be applied to the overall cohort of patients but not to important subgroups of patients. Second, unmeasured bias and inherent selection bias cannot be fully excluded. However, given the large effect size, it is unlikely that hidden bias would explain all these findings. Furthermore, performing near/far matching is a novel way to overcome limitations of unmeasured bias. Third, inherent to any NCDB analyses, miscoding of variables cannot be excluded as a source of bias. However, this is generally considered to be nondifferential. Fourth, patients with a histology not other specified account for almost 43% of our sample, therefore leaving us somehow in the dark about which patients truly benefit from surgery. Given unavailable information in NCDB, a reclassification based on the WHO classification system cannot be performed. Fifth, information on tumor recurrence or tumor progression site is not available in NCDB. As such, differences in local versus systemic recurrence pattern cannot be assessed between groups. Despite these limitations and given that prospective randomized data will not be available in the near future, our results add to the current body of literature shedding some light on treatments for eNETs.

CONCLUSIONS

eNETs are a rare and aggressive disease with a poor prognosis that can be improved by resection of the primary tumor. We demonstrated that surgical resection of the primary tumor among patients with eNETs can prolong OS

and RS with limited postoperative mortality and acceptable length of hospital stay. The results of this study provide evidence that esophagectomy among selected patients with localized eNETs should be an integral part of the multimodal therapy algorithm.

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