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Original Article

Survival According to Primary Tumor Location, Stage, and Treatment Patterns in Locoregional Gastroenteropancreatic High-grade Neuroendocrine Carcinomas

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Abstract

Background: Although the gastrointestinal tract (including the pancreas, gastroenteropancreatic (GEP) is the most common site for extrapulmonary neuroendocrine carcinoma (NEC), the current treatment patterns of locoregional GEP NEC and in particular, the role of surgical resection is unclear.

Methods: Data from the National Cancer Database between 2004 and 2016 were used for this study.

Results: Of 2314 GEP NEC cases (stages I–III), 52.5% were stage III. Colon was the most common site (30%); 30.9% of all cases were small cell morphology. Age, morphology, stage, and primary site were associated with significant differences in treatment patterns. Management of NEC mimicked that of adenocarcinomas arising at the respective sites: colon NEC most likely to be treated with surgery and chemotherapy; anal and esophageal NEC was primarily likely to receive chemotherapy and radiation, and rectal NEC mostly likely to receive trimodality therapy. However, 25%-40% of patients did not undergo surgical resection even at sites typically managed with curative resection, and there was a trend toward lesser resection over time. The prognostic impact of surgical resection was significant across all stages and correlated with variations in survival across primary sites. Even in patients undergoing chemoradiation, surgery was the only prognostic variable that significantly affected survival in stages I–II patients (HR 0.63) and showed a strong trend in stage III (HR 0.77) patients.

Conclusions: Treatment patterns in GEP NEC vary considerably according to stage and primary tumor site. Surgery significantly improved survival in stages I–II patients and showed a strong trend in stage III patients regardless of primary tumor location and other perioperative therapies.

Key words: small cell; large cell; neuroendocrine carcinoma; poorly differentiated; NCDB.

Implications for Practice

In this first large observational study, we found that 25%–40% of locoregional gastrointestinal neuroendocrine carcinoma patients did not undergo resection even though surgical resection was significantly associated with improved survival. Such findings suggest that careful consideration should be made for surgical resection as this may be associated with improved survival among patients without progression.

Introduction

Poorly differentiated neuroendocrine carcinomas (NEC) are an aggressive subgroup of neuroendocrine neoplasms defined based on morphology (small cell, large cell, and other mixed histologies) and markers of proliferation Ki-67 and/or mitotic index) most commonly arising in the lung.[1-3] A recent, large US-based population study showed that the gastrointestinal tract was the most common extrapulmonary site for NECs, accounting for over a third of all such cases.[4] Multiple studies have documented the grim prognosis of these patients, especially in those with metastatic disease with a median overall survival (OS) of less than a year for gastroenteropancreatic (GEP) NEC.[4-6] However, such studies have shown that nearly 40% of GEP NEC patients have localized or regional disease at the time of diagnosis. Furthermore, in contrast to patients with metastatic disease, these patients diagnosed at an earlier stage appear to have a much better prognosis, with a significant proportion having a relatively good 5-year survival rate.

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For instance, in GEP NECs, the 5-year survival rate for patients with local/regional disease ranged from 40% to 50% for those with gastric, pancreatic, and colorectal NECs and 25% for esophageal NECs.[4,5,7-11] Given the rare incidence of this tumor type, there are no prospective studies or a comprehensive evaluation of current practice patterns of locoregional NEC.

The aim of the current study was to evaluate the impact of surgery on the survival of locoregional GEP NEC patients, especially in those undergoing multimodality perioperative management with radiation and chemotherapy.

Methods

Data were retrieved from the National Cancer Database Participant Use File (NCDB-PUF) for GEP NECs registered from January 1, 2014, to December 31, 2016. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Poorly differentiated neuroendocrine carcinomas were identified with the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) morphology codes and primary sites with ICD-O-3 topography codes as described previously by our group.[4,12] We excluded small bowel primaries because they are rare and often well-differentiated high-grade neuroendocrine tumors likely miscoded as high-grade poorly differentiated neuroendocrine carcinomas under the prior WHO classification of neuroendocrine malignancies.[13,14] In line with this, a prior SEER study, showed that median survival of small bowel NEC is much higher compared with other sites.[4] The detailed cohort creation steps are provided in Supplementary Table S1. The staging was done according to AJCC 7th edition as provided in the NCDB-PUF. Variables including patient factors, clinicopathological features, treatment details, and OS were evaluated. Patient factors included sex, race, age, and Charlson-Deyo Comorbidity Index (CCI). Clinicopathological features included the year of diagnosis, stage, primary site, and morphological subtype (small cell versus large cell and others). Treatment details included receipt of surgery, radiation, and/or chemotherapy. Statistical calculations were performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA) or SAS (version 9·4, SAS Institute, Cary, NC).

Demographic and tumor characteristics were expressed as frequencies (percentages) for categorical variables and compared using Pearson's χ^2 test. Treatment patterns were

Table 1. Patient and treatment characteristics according to primary site

	Anal canal	Colon	Esophagus	Pancreas	Gastric	Gallbladder	Rectum	*P*
Number	133	696	314	423	286	89	373	
Age, years								
<65	104 (78.2%)	249 (35.8%)	153 (48.7%)	231 (54.6%)	121 (42.3%)	42 (47.2%)	227 (60.9%)	
65-74	15 (11.3%)	173 (24.9%)	84 (26.8%)	103 (24.3%)	79 (27.6%)	23 (25.8%)	73 (19.6%)	
75+	14 (10.5%)	274 (39.4%)	77 (24.5%)	89 (21%)	86 (30.1%)	24 (27%)	73 (19.6%)	
Sex								<.001
Male	35 (26.3%)	321 (46.1%)	215 (68.5%)	249 (58.9%)	195 (68.2%)	34 (38.2%)	179 (48%)	
Female	98 (73.7%)	375 (53.9%)	99 (31.5%)	174 (41.1%)	91 (31.8%)	55 (61.8%)	194 (52%)	
Race								<.001
White	108 (81.2%)	620 (89.1%)	275 (87.6%)	353 (83.5%)	200 (69.9%)	64 (71.9%)	314 (84.2%)	
Other	25 (18.8%)	76 (10.9%)	39 (12.4%)	70 (16.5%)	86 (30.1%)	25 (28.1%)	59 (15.8%)	
Year of diagnosis								.001
2004-2008	54 (40.6%)	246 (35.3%)	99 (31.5%)	106 (25.1%)	73 (25.5%)	37 (41.6%)	119 (31.9%)	
2009-2012	40 (30.1%)	224 (32.2%)	104 (33.1%)	143 (33.8%)	104 (36.4%)	24 (27%)	138 (37%)	
2013-2016	39 (29.3%)	226 (32.5%)	111 (35.4%)	174 (41.1%)	109 (38.1%)	28 (31.5%)	116 (31.1%)	
Stage								<.001
I-II	54 (40.6%)	219 (31.5%)	154 (49%)	352 (83.2%)	128 (44.8%)	52 (58.4%)	139 (37.3%)	
III	79 (59.4%)	477 (68.5%)	160 (51%)	71 (16.8%)	158 (55.2%)	37 (41.6%)	234 (62.7%)	
Morphology								<.001
Large cell and others	27 (20.3%)	606 (87.1%)	132 (42%)	347 (82%)	226 (79%)	28 (31.5%)	234 (62.7%)	
Small cell	106 (79.7%)	90 (12.9%)	182 (58%)	76 (18%)	60 (21%)	61 (68.5%)	139 (37.3%)	
Surgery								<.001
Yes	46 (34.6%)	676 (97.1%)	78 (24.8%)	260 (61.5%)	180 (62.9%)	66 (74.2%)	238 (63.8%)	
No	87 (65.4%)	20 (2.9%)	236 (75.2%)	163 (38.5%)	106 (37.1%)	23 (25.8%)	135 (36.2%)	
Radiation								<.001
Yes	110 (82.7%)	29 (4.2%)	231 (73.6%)	86 (20.3%)	90 (31.5%)	27 (30.3%)	226 (60.6%)	
No	23 (17.3%)	667 (95.8%)	83 (26.4%)	337 (79.7%)	196 (68.5%)	62 (69.7%)	147 (39.4%)	
Chemotherapy								<.001
Yes	111 (83.5%)	340 (48.9%)	247 (78.7%)	205 (48.5%)	163 (57%)	54 (60.7%)	281 (75.3%)	
No	22 (16.5%)	356 (51.1%)	67 (21.3%)	218 (51.5%)	123 (43%)	35 (39.3%)	92 (24.7%)	

compared using logistic regression; univariate OS was measured using the Kaplan-Meier method and compared using the log-rank test. The Cox-proportional hazards model was used for multivariate OS analyses with the variables discussed above that were identified as significant from published literature. All differences were considered statistically significant if the 2-sided *P* was <0.05.

Approval by an Institutional Review Board was not required for the study as the data used were derived from a de-identified NCDB file.

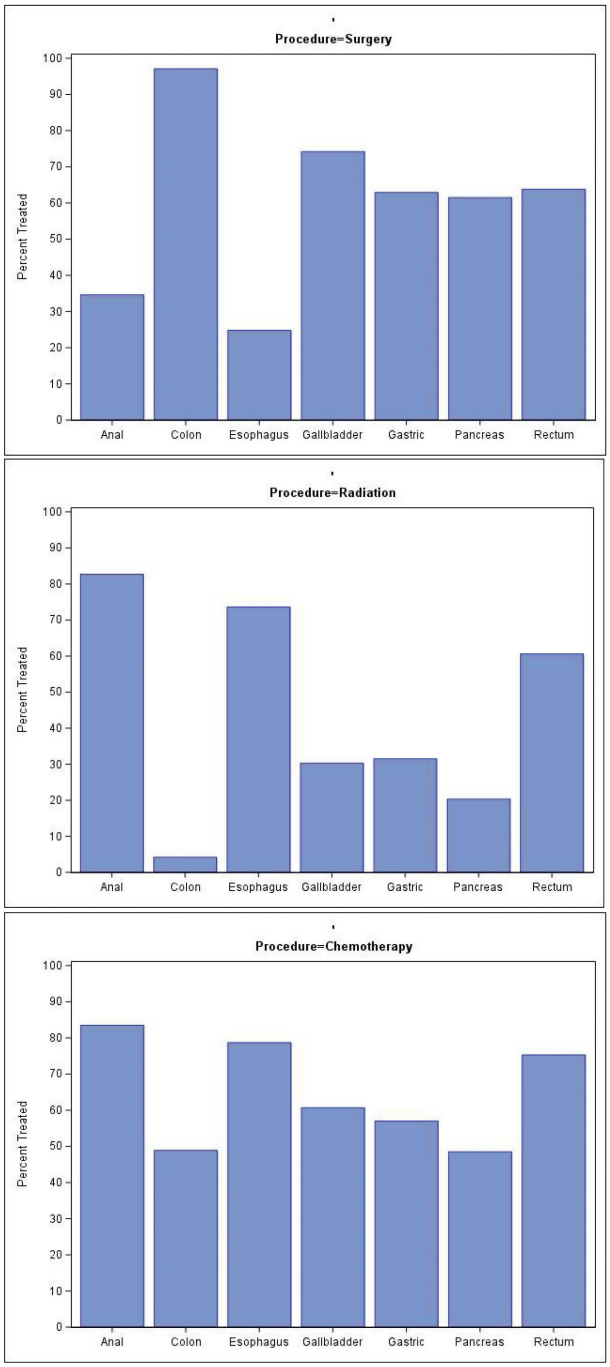

Fig. 1. Treatment patterns according to the primary site.

Results

Clinical and Pathologic Characteristics

Of 2314 identified GEP NEC cases, 1228 (53.1%) were men. Eighty-four percent (83.6%) were white, and the rest were of other races. Fifty-three percent (52.5%) were stage III, and the rest were stages II or I; small cell morphology accounted for 30.9%, with the rest being large cells and other histologies. The luminal gastrointestinal tract accounted for the majority of the patients with the lower GI sites (colon, rectum, anal canal), accounting for over half the patients (51.9%), followed by upper GI sites (gastric + esophageal, 25.9%) and pancreatic NEC (18.3%). Colon was the most common single primary site accounting for 30.1% of all cases. Significant demographic differences were noted across sites for all evaluated variables as detailed in Table 1. Anal canal and gallbladder NEC were most likely to be younger females with small cell morphology.

In contrast, upper GI sites, including (esophagus and gastric) along with pancreas, were more likely to be male, with a larger proportion of esophageal being small cell carcinoma. Gastric, colorectal, and pancreatic NEC predominantly had large cell and other histology. Almost all sites were more likely to be diagnosed at stage III except pancreatic NEC that was more likely to be diagnosed at stages II or I.

Treatment Patterns

The percentages of patients who received surgery, chemotherapy, and radiation are provided in Fig. 1. Using logistic regression, age, primary site (using a colon as the reference group), stage at diagnosis, and morphology were shown to be associated with significant differences in treatment patterns with surgery, radiation, and chemotherapy (Table 2). Younger patients (<65 years) were more likely to receive all of the treatment modalities as compared to older patients, with the most impact being noted in the use of chemotherapy (odds ratio, OR 0.23 for 75+ years and 0.67 for 65-74 years). Colon NEC patients were most likely to receive surgery, with almost all patients undergoing surgery and least likely to receive radiation or chemotherapy amongst all sites. More specifically, all ORs of other sites receiving surgery were significantly lower than 1 with $P < .001$ compared with colon; all ORs of other sites receiving radiation were significantly higher than 1 with $P < .001$ compared with colon; while most ORs of other sites receiving chemotherapy were higher than 1 with $P < .05$ compared with colon except pancreas ($P = .299$) and gallbladder ($P = .093$). Radiation was most likely to be used for the anal canal (OR 71.26), esophageal (OR 55.25), and rectal NEC (OR 11.69). These sites were also most likely to receive chemotherapy compared with the colon (OR 3.31 for the anal canal, 3.51 for esophageal, and 2.55 for rectal NEC), suggesting that perioperative chemoradiation was most often used at these sites. More advanced stage (stage III) NEC patients were less likely to undergo surgery (OR 0.40) and more likely to undergo chemoradiation (radiation (OR 1.69) and chemotherapy (OR 2.57) compared with earlier stages (stages I, II). Large cell and other histology NEC were more likely to undergo surgery (OR 0.40) instead of chemoradiation (radiation (OR 0.52) and chemotherapy (OR 0.62) compared with small cell NEC. Patients belonging to races other than white had less likelihood of receiving either radiation or chemotherapy, and

Table 2. Logistic regression to evaluate treatment patterns.

	Surgery			Radiation			Chemotherapy		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age, years									
75+ versus <65	0.51	[0.39,0.67]	<.001	0.51	[0.39,0.68]	<.001	0.23	[0.19,0.29]	<.001
65-74 versus <65	0.62	[0.47,0.81]	<.001	0.70	[0.53,0.92]	.009	0.67	[0.53,0.85]	<.001
Sex									
Female versus male	1.14	[0.91,1.43]	.249	0.94	[0.75,1.18]	.582	0.81	[0.67,0.98]	.034
Race									
Other versus white	0.88	[0.66,1.16]	.360	0.64	[0.48,0.86]	.003	0.74	[0.58,0.96]	.022
Diagnosis year									
2013-2016 versus 2004-2008	0.72	[0.55,0.94]	.015	0.96	[0.73,1.26]	.779	1.25	[0.99,1.58]	.057
2009-2012 versus 2004-2008	0.92	[0.70,1.21]	.557	1.00	[0.77,1.32]	.976	1.14	[0.90,1.43]	.275
Site									
Gastric versus colon	0.04	[0.03,0.07]	<.001	11.69	[7.35,18.5]	<.001	1.42	[1.04,1.94]	.027
Rectum versus colon	0.05	[0.03,0.08]	<.001	30.60	[19.7,47.3]	<.001	2.55	[1.88,3.47]	<.001
Pancreas versus colon	0.02	[0.01,0.04]	<.001	7.00	[4.38,11.1]	<.001	1.16	[0.87,1.55]	.299
Gallbladder versus colon	0.12	[0.06,0.23]	<.001	8.43	[4.55,15.6]	<.001	1.54	[0.93,2.56]	.093
Esophagus versus colon	0.01	[0.01,0.02]	<.001	55.25	[34.5,88.3]	<.001	3.51	[2.46,4.99]	<.001
Anus versus colon	0.02	[0.01,0.04]	<.001	71.26	[38.5,131.]	<.001	3.31	[1.94,5.66]	<.001
Stage									
III versus I–II	0.40	[0.32,0.51]	<.001	1.69	[1.34,2.13]	<.001	2.57	[2.09,3.16]	<.001
Histology									
Large cell and others versus small cell	3.32	[2.61,4.24]	<.001	0.52	[0.41,0.67]	<.001	0.62	[0.49,0.79]	<.001
Charlson Comorbidity									
2+ versus none	1.05	[0.70,1.55]	.822	0.66	[0.43,1.02]	.059	0.76	[0.54,1.07]	.111
1 versus none	1.36	[1.03,1.80]	.032	0.80	[0.61,1.06]	.127	0.80	[0.63,1.01]	.056

a trend was noted in the same direction for surgery. Surgical resection for NEC decreased over time (OR 0.72 for 2013-2016 versus 2004-2008) while an opposite trend for the use of systemic therapy was noted over the same time.

Survival

The median survival of all cases was 20.7 months (m), and the 5-year survival rate was 29.2%. Significant differences in survival were noted according to site and morphology (all $P < .0001$) (Supplementary Fig. S1). Colon NEC had the longest median survival (28.5 m with 39.7% 5-year survival), while gallbladder and biliary NEC (14.8 m with 20.9% 5-year survival) had the shortest median survival. Small cell morphology was associated with worse median survival compared with large cells and other histologies (17.7 versus 22.3 m). We first performed multivariate analyses stratified by stage to evaluate the impact of treatment on OS in all patients (Table 3) while adjusting for prognostic factors influencing survival of NEC patients using the Cox proportional hazards model. The prognostic parameters were identified from prior studies and included age, gender, race, year of diagnosis (2004-2008, 2009-2012, and 2013-2016), primary site, morphological subtype, comorbidities (Charlson Comorbidity Index), and treatment modalities.

This multivariate model confirmed the prognostic importance of age and primary site when stratified according to the stage (stages I/II versus III; Table 3). Older patients had worse survival; for instance, patients over 75 compared with <65 had a hazard ratio, HR 1.72 for stage I-II and HR 1.59 for stage III. Prognostic implications of the primary site on OS noted with univariate (Kaplan–Meier) analyses were similarly confirmed in this multivariate model with the colon having the best survival amongst all sites, as almost all HRs were above 1 for other sites compared with colon with $P < .05$ except gastric ($P = .139$). The gallbladder (HR 3.23 in stages I-II) and anal canal (HR 2.11 in stage III) had the worst survival compared with the colon. Surgical resection was associated with significantly better survival across all stages (HR 0.37 and 0.60 for stages I & II and stage III, respectively), as was radiation therapy, although the impact appeared to be lower compared with surgery (0.74 and 0.70 for stages I & II and stage III respectively). Chemotherapy was associated with better survival only for stage III (HR 0.64).

To address confounding by indication, we first evaluated the entire cohort using the same multivariate model stratified according to surgical resection (Table 4). The prognostic effects of the primary site were only noted in patients undergoing surgical resection and were no longer significant in those who did not undergo surgery. In the latter group, chemotherapy (HR 0.62, P <.001 in the non-surgery group compared with HR 0.79, P =.002 in the surgery group) and radiation (HR 0.57, P <.001 in the non-surgery group compared with HR 0.97, P = .761 in the surgery group) appeared to have a larger benefit on survival compared with those receiving surgery. Similar trends were noted with stage, age, and time period of diagnosis with attenuation of the prognostic impact of these variables in those without surgery.

Table 3. Multivariate analysis of overall survival with Cox proportional hazard model stratified by stage at diagnosis.

	Stages I-II				Stage III			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value
Age, years								
65-74 versus <65	1.39	1.13	1.70	.002	1.20	1.01	1.43	.040
75+ versus <65	1.72	1.40	2.11	<.001	1.59	1.34	1.89	<.001
Sex								
Female versus male	0.91	0.77	1.07	.246	0.91	0.79	1.05	.176
Race								
Other versus white	1.09	0.87	1.37	.446	1.02	0.85	1.22	.837
Diagnosis year								
2013-2016 versus 2004-2008	0.93	0.77	1.12	.422	0.95	0.80	1.11	.498
2009-2012 versus 2004-2008	0.70	0.57	0.87	.001	0.81	0.68	0.96	.015
Primary site								
Anus versus colon	1.65	1.07	2.55	.025	2.11	1.50	2.97	<.001
Esophagus versus colon	1.65	1.19	2.28	.002	1.67	1.25	2.23	.001
Gallbladder versus colon	3.23	2.17	4.82	<.001	1.53	0.99	2.37	.054
Pancreas versus colon	1.75	1.35	2.27	<.001	1.60	1.17	2.20	.003
Rectum versus colon	1.48	1.07	2.06	.017	1.53	1.22	1.92	<.001
Gastric versus colon	1.28	0.92	1.76	.139	1.39	1.10	1.76	.007
Morphology								
Large cell and others versus small cell	1.19	0.98	1.46	.086	1.04	0.88	1.24	.654
Charlson Comorbidity								
1 versus none	1.01	0.82	1.25	.944	1.21	1.03	1.44	.025
2+ versus none	1.63	1.24	2.13	.001	1.35	1.07	1.71	.013
Surgery								
Yes versus no	0.37	0.30	0.45	<.001	0.60	0.49	0.73	<.001
Radiation								
Yes versus no	0.74	0.59	0.91	.005	0.70	0.57	0.85	<.001
Chemotherapy								
Yes versus no	0.89	0.73	1.08	.230	0.64	0.54	0.75	<.001

Next, the analysis was repeated in a subcohort of 719 patients (stages I/II = 302; stage III = 417) who received both chemotherapy and radiation (Table 5). This analysis revealed that the only variable with prognostic effects was surgery with a significant HR of 0.63 in stages I–II patients and a strong trend toward improvement in stage III patients (HR 0.77; 95% CI, 0.59-1.01).

Discussion

High-quality data regarding the management of stages I-III poorly differentiated GEP NEC are lacking due to their rare incidence. In this study, we attempted to evaluate the current trends in the management of this rare cohort and evaluate patient and treatment factors affecting survival.

The role of surgical resection for patients with GEP NEC who have apparently localized and locoregional disease is unclear although some retrospective studies have suggested benefit[4,10,11,15] In a population-based study of high-grade colorectal NEC, surgery was associated with improved survival for localized NEC with non–small cell morphology. However, data on chemotherapy and comorbidities were unavailable in this study.[10] In a study of 51 cases of gastric NEC, multivariate analysis identified curative surgery as the sole independent prognostic factor.[16] In a Nordic multicenter study of 119 pancreatic NEC, resection was associated with improved survival.[9] Similar findings were reported for NEC arising from these sites by other studies as well.[8,11,17] In 2 recent studies of surgery in stages I-III GEP NEN G3 patients, 65% were alive after 2 years in one study, and 5-year survival was 42% in another study[18,19] In contrast, some experts have questioned the role of surgery in this setting extrapolating data from limited-stage small cell lung cancer where surgery is typically not recommended except for very early-stage disease.[20] For instance, in a study of 199 patients with esophageal NEC of small cell type, survival was better in those who had systemic therapy in addition to local management.[21] In another study, of 127 patients with esophageal NEC, survival was better for patients with radiation plus chemotherapy as compared to those treated with surgery and chemotherapy.[22] Similarly, in the above-mentioned population study of colorectal NEC, small cell NEC did not appear to have a benefit with surgical resection, and such lack of benefit with surgical resection was confirmed by another single-institution study of colorectal NEC.[10,23]

This uncertainty around the role of surgical resection is also reflected in consensus guidelines. Given the high propensity for metastatic spread, there is general agreement amongst guidelines regarding multimodality therapy incorporating

Table 4. Multivariate analysis of overall survival with Cox proportional hazard model stratified by surgery.

	Received surgery				No surgery			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value
Age, years								
65-74 versus <50	1.33	1.12	1.58	.001	1.16	0.94	1.42	.160
75+ versus <50	1.86	1.57	2.19	<.001	1.32	1.06	1.64	.015
Sex								
Female versus male	0.91	0.80	1.05	.198	0.94	0.78	1.12	.475
Race								
Other versus white	1.13	0.93	1.36	.216	0.95	0.76	1.18	.618
Diagnosis Year								
2009-2012 versus 2004-2008	0.90	0.77	1.04	.156	0.98	0.80	1.21	.857
2013-2016 versus 2004-2008	0.69	0.58	0.82	<.001	0.86	0.70	1.06	.160
Primary site								
Anus versus colon	2.23	1.50	3.34	<.001	1.31	0.75	2.30	.348
Esophagus versus colon	2.00	1.46	2.73	<.001	1.15	0.68	1.93	.608
Gallbladder versus colon	1.89	1.34	2.67	<.001	1.86	0.93	3.72	.080
Pancreas versus colon	1.46	1.16	1.84	.001	1.19	0.71	1.99	.507
Rectum versus colon	1.35	1.09	1.67	.006	1.06	0.62	1.82	.833
Gastric versus colon	1.27	1.02	1.59	.036	0.96	0.56	1.65	.873
Morphology								
Large cell and others versus small cell	1.00	0.83	1.20	1.000	1.19	0.99	1.43	.062
Charlson Comorbidity								
1 versus none	1.09	0.93	1.28	.289	1.28	1.02	1.61	.030
2+ versus none	1.37	1.09	1.71	.006	1.60	1.19	2.16	.002
Stage								
Stage III versus stages I-II	2.01	1.72	2.34	<.001	1.27	1.06	1.51	.008
Radiation								
Yes versus no	0.97	0.80	1.18	.761	0.57	0.46	0.69	<.001
Chemotherapy								
Yes versus no	0.79	0.67	0.92	.002	0.62	0.50	0.77	<.001

chemotherapy and/or radiation to reduce the risk of distant and locoregional recurrence, respectively, for patients with GEP NEC. However, whereas the NANETS guidelines only recommend resection of a primary locoregional GEP NEC in carefully selected cases, ENETS guidelines generally recommend surgery of the primary tumor (except stage III oesophageal)[24,25]

In the current study, almost all patients with colon and the majority of patients with gallbladder NEC were treated with surgery. In contrast, patients requiring surgery at sites that may entail higher morbidity, such as the anal canal, esophagus were less likely to undergo surgical resection and were treated with chemoradiation instead. Trimodality therapy was most often used to treat patients with rectal NEC. Thus, trends in NEC management in the current study appeared to mimic that of the more common adenocarcinomas arising in those sites. However, it is essential to note that despite being diagnosed at the locoregional stage, 25%-40% of patients did not undergo resection even at sites typically managed with curative resection for adenocarcinomas. It is possible that patient and physician preferences played an important role. A systematic survey of such preferences would be an important next step to identify potential biases in making decisions about treatment choices, especially around surgical resection.

Primary site and surgical resection were the strongest prognostic factors determining survival irrespective of stage in the current study, as revealed by Table 3. However, the prognostic implications of the primary site were no longer significant when stratified by surgery, suggesting that treatment modality rather than primary site may determine the prognosis for these patients. Of note, in patients undergoing surgery, this analysis suggested that additional perioperative chemotherapy provided survival benefit—this is not surprising given the high propensity of these cancers to develop metastatic spread during their clinical course. The benefit from radiation, however, was limited only to later-stage tumors. We also evaluated the benefit of surgery in patients who had received both chemotherapy and radiation and found that surgery still had prognostic effects, as detailed in Table 5.

Together, these data strongly suggest that there is a role for surgery in the management of locoregional GEP NEC. This is especially important given the trend of decreasing surgery rates noted over time. We propose that patients with locoregional NEC undergo comprehensive staging with FDG-PET/CT to rule out occult metastatic disease before surgery. Subsequently, these patients must be initiated on therapy immediately. For primary sites such as the colon, where the primary modality of local management is surgery, it would be

Table 5. Multivariate analysis of overall survival with Cox proportional hazard model stratified by stage in patients receiving chemotherapy and radiation.

	Stages I–II (*N* = 302)				Stage III (*N* = 417)			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value
Age, years								
65-74 versus <65	1.28	0.88	1.88	.196	1.08	0.81	1.44	.612
75+ versus <65	1.32	0.86	2.02	.209	1.12	0.79	1.58	.534
Sex								
Female versus male	1.07	0.78	1.48	.665	0.98	0.76	1.26	.862
Race								
Other versus white	0.99	0.64	1.51	.951	1.05	0.75	1.47	.783
Diagnosis year								
2013-2016 versus 2004-2008	0.79	0.56	1.12	.181	0.91	0.69	1.21	.529
2009-2012 versus 2004-2008	0.74	0.49	1.10	.130	0.87	0.65	1.18	.368
Site								
Anus versus colon	1.81	0.52	6.27	.348	1.24	0.62	2.51	.543
Esophagus versus colon	2.20	0.67	7.21	.195	0.88	0.45	1.74	.713
Gallbladder versus colon	1.61	0.41	6.25	.496	0.42	0.14	1.26	.120
Pancreas versus colon	2.28	0.69	7.55	.176	1.06	0.46	2.46	.887
Rectum versus colon	1.24	0.38	4.10	.724	0.70	0.37	1.35	.286
Gastric versus colon	1.57	0.44	5.58	.485	0.63	0.31	1.26	.190
Morphology								
Large cell and others versus small cell	1.13	0.81	1.57	.476	1.34	1.04	1.74	.027
Charlson Comorbidity								
1 versus none	0.99	0.65	1.50	.949	1.40	1.02	1.93	.035
2+ versus none	1.44	0.81	2.57	.215	1.53	0.92	2.53	.100
Surgery								
Yes versus no	0.63	0.44	0.91	.012	0.77	0.59	1.01	.058

reasonable to start with chemotherapy. However, frequently a diagnosis of NEC is first found after pathological examination of the surgical specimen. For other primary sites, patients may be evaluated for chemoradiation unless for very early-stage tumors or if dictated otherwise by tumor location. At most institutions, these patients are started on therapy along these lines in concordance with expert guidelines. After a period of such therapy, based on the findings of the current study, we propose that patients who have not developed metastatic spread should be evaluated for surgical resection. During this evaluation, the primary site, patient and other factors determining surgical outcomes should be weighed in. As discussed above, some retrospective data suggest that perhaps esophageal NEC stage III are best treated with definitive chemoradiation similar to esophageal squamous cell carcinoma. Chemoradiation was in our study frequently used for rectal NEC, however study data are lacking. Patients with primary sites in the lower rectum and anal canal may be hesitant to consider surgery as it may entail a lifelong colostomy.

Although NCDB is not a population-based data set, significant differences in demographics, stage at diagnosis, morphological subtype, and treatment patterns were noted based on the primary site worthy of discussion. Anal and rectal NEC were most likely to be noted in younger patients, with the former most likely to be of small cell types and females. A recent study reported the association of a proportion of NEC sites with high-risk HPV infections allowing for classification into distinct genomic subtypes of NECs of these sites. Given the higher prevalence of HPV infections in younger patients and the association of anal squamous cell cancers with HPV infections, more extensive studies must evaluate these genetic subtypes more robustly and attempt to link to the demographic trends noted here. Such studies may have implications for the screening, prevention, and treatment of NECs of these sites. In addition to the anal canal, NEC arising in the esophagus and gallbladder were more likely to be small cell carcinoma. Whether these sites have separate carcinogenic pathways compared with the anal canal, such as related to smoking, will also need to be evaluated.

Our study has several limitations. The NCDB does not classify NEC according to the WHO classification, nor does it have Ki-67 proliferation data. Given the small numbers, the sequencing of therapies was not discerned. Additionally, the NCDB does not capture information on specific chemotherapy regimens or dose intensity. Since the NCDB also does not capture disease-free survival, whether it may have been impacted without affecting OS is unknown. Since NCDB does not code chemotherapy delivered as part of chemoradiation separately, we were unable to discern this; furthermore, given issues with sample sizes at some sites, evaluating whether these therapies were delivered neoadjuvantly or adjuvantly was not performed and such therapies were considered perioperative. Finally, confounding factors not captured in the NCDB may have impacted the results.

Despite these limitations, our study has important implications. We had previously shown that a curative approach is possible for a substantial proportion of patients with locoregional NEC. In the current study, we show the key role of surgical resection in improving outcomes for these patients.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/design: A.D., C.S., H.S. Provision of study material or patients: C.S. Collection and/or assembly of data: C.S. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared at reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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