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Resection of primary tumor may prolong survival in metastatic gastroenteropancreatic neuroendocrine tumors ☆

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ABSTRACT

Background: Patients with gastroenteropancreatic neuroendocrine tumors often present with stage IV disease. Primary tumor resection in these patients remains controversial. Herein, we studied the impact of primary tumor removal, identified variables associated with prolonged survival for each neuroendocrine tumor subtype, and determined factors that influence surgeons to perform primary tumor resection.

Methods: Patients with metastatic gastroenteropancreatic neuroendocrine tumors diagnosed from 2004 to 2014 were identified from the National Cancer Database. Nested Cox proportional hazards and logistic regression models were used to assess variables associated with survival and primary resection.

Results: A total of 14,510 patients met inclusion criteria. On multivariable analysis, resection of the primary tumor and grade 1 or 2 tumors was associated with prolonged survival in all subtypes ($P < .001$). Organ-specific variables associated with prolonged survival in patients undergoing primary tumor resection included the following: low grade for all organs; young age for pancreatic, small intestinal, colonic, and rectal neuroendocrine tumor; tumor size for colonic and rectal neuroendocrine tumor; and tumor location for colonic neuroendocrine tumor. Low tumor grade was found to be significantly associated with removal of the primary tumor across all organs.

Conclusion: This study is the first suggesting that primary tumor resection is associated with prolonged survival for all gastro-entero-pancreatic NETs. Additional variables related to survival for each NET subtype were identified and might help select patients who benefit from primary tumor removal.

Introduction

Neuroendocrine tumors were first described in 1907 by the German pathologist Siegfried Oberndorfer in the small intestines of seven patients, and named “carcinoid” tumors because of their small size and apparent indolent nature.[1] Since then, gastroenteropancreatic neuroendocrine tumors (GEP-NETs) have been better characterized and are now known to present with distant metastases in up to 50% of patients.[2,3] The incidence of GEP-NETs in the United States is increasing in all primary tumor sites.[4–6] NETs are one of the few tumor types in which debulking operations are recommended for patients with metastatic disease, because debulking improves symptomatic control of hormone hypersecretion and survival.[7–10]

Despite robust evidence for resection of metastases, the role of removing the primary tumor in patients with stage IV GEP-NETs remains unclear.[8,9] A recent study using the California Cancer Registry demonstrated that primary tumor resection was associated with prolonged survival among patients with stage IV gastrointestinal NETs and untreated liver metastases, but that study had a relatively small sample size, which limited its ability to identify variables that might help select patients which patients might benefit most from primary tumor removal.[11]

We therefore used the National Cancer Database (NCDB) to determine whether primary tumor resection is associated with prolonged survival in patients with stage IV GEP-NETs and unresected metastases, to identify variables associated with prolonged survival for each NET subtype, and to report factors that influence surgeons to resect primary tumors.

Methods

The NCDB, a joint project of the Commission on Cancer of the American College of Surgeons (Chicago, IL) and the American

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Cancer Society (Atlanta, GA), represents the largest database of cancer patients in the United States, including about 70% of all patients diagnosed with cancer.[12] The NCDB and its participating hospitals are the source of the deidentified data used; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. This study was exempt from institutional review board review because it uses public data that do not contain identifiable patient information.

Information was obtained on all patients diagnosed with GEP-NETs from 2004 to 2014. Patients with metastases at the time of diagnosis were selected, using the "CS_METS_AT_DX" variable. Patients who underwent operations on metastatic sites (as identified by the "RX_SUMM_SURG_OTH_REGDIS" variable) and those whose record contained insufficient information for survival analysis were excluded.

For each organ of origin, the following variables were examined to determine whether they were associated with survival: age, sex, race, ethnicity, insurance status, hospital type, Charlson comorbidity index (CCI), tumor grade, tumor location within the organ (except for small intestine and rectum), primary tumor resection (as identified by the "RX_SUMM_SURG_PRIM_SITE" variable), chemotherapy status, and radiation therapy status. Treatments listed in the NCDB occurred within 6 months of diagnosis. Grade for gastrointestinal NETs was determined by histology codes 8240 and 8249 (well-differentiated or moderately differentiated tumors) were defined as grade 1 or 2 tumors and 8013, 8041, and 8246 (poorly differentiated tumors), as grade 3 tumors. Grade for pancreatic NETs was determined by the "GRADE" variable and was classified as grade 1 and 2, grade 3, and missing. Proximal colon was defined as cecum, appendix, ascending colon, and hepatic flexure; distal colon was defined as transverse colon, splenic flexure, descending colon, and sigmoid. Proximal stomach was defined as cardia, fundus, and lesser curvature; distal stomach was defined as as body, pylorus, antrum, and greater curvature. Differences in survival curves were compared with Mantel-Haenszel tests.

Nested Cox proportional hazard models were created using the significant variables for each organ, tested for proportionality, and compared. Likelihood ratio tests were performed to determine factors significant in multivariable analysis. Initial models for all organs failed the proportionality hazards assumption, which indicates that one or more of the variables have a significant interaction with time. Data were therefore split at 6 months for colon; 30 months for small intestine; and 9 months for pancreas, rectum, and stomach to incorporate these interactions with time effects. These new models passed the test of proportionality.

Patients whose primary tumor was resected were examined separately to identify factors associated with prolonged survival. Kaplan-Meier survival curves were created for age (divided at the median for each organ), grade (grade 1 or 2 versus grade 3), tumor location, and tumor size (divided at the median) and compared with Mantel-Haenszel tests. Median survival in months was calculated for each group.

The following variables were analyzed to determine whether they were associated with a patient having undergone primary tumor resection: age, sex, race, ethnicity, insurance status, CCI, tumor grade, and tumor location. Comparisons were made using Fisher exact tests, Welch t tests, and Wilcoxon rank sum tests, depending on the measurement scale of the variable. Variables significant in univariate analyses were included in nested linear models, which were compared using likelihood ratio tests.

Two-tailed P values $\leq .05$ were considered significant. P values within organs were adjusted to control for familywise error rates. All analyses were conducted in R, 3.3.2.[13]

Results

Pancreas

A total of 6,088 patients with stage IV pancreatic NETs who did not undergo an operation on a metastatic site were included. Overall median survival was 16.4 months. Primary site tumors were resected in 460 patients (7.6%) (Fig 1). Patients who underwent primary tumor resection had prolonged overall survival (63.6 months versus 14.2 months, $P < .001$; Fig 2, *A*). Additional factors associated with prolonged survival on univariate analysis included treatment at an academic or research hospital, younger age, low CCI, tumor grade 1 or 2, and tumor location in the body or tail. On multivariable analysis, primary tumor removal remained significantly associated with prolonged survival (hazard ratio [HR] 0.30–0.53, $P < .001$). Additional factors significant on multivariable analysis included treatment at an academic or research program, grade 1 or 2 tumors, and tumor location in the pancreatic body/tail (Table 1).

Among patients who underwent primary tumor resection, patients with grade 1 or 2 tumors or younger than the median age of 57 years had significantly longer survival than those with grade 3 tumors or older age ($P \leq .006$; Table 2, Supplemental Fig 1). There was no difference in survival between patients with tumors in the head of the pancreas and those with tumors in the body or tail ($P = .11$).

Patients with younger age, grade 1 or 2 tumors, and body or tail tumors were more likely to undergo primary tumor resection on univariate analysis. On multivariable analysis, younger age and having a grade 1 or 2 tumor were associated with increased odds of undergoing resection (Table 3).

Small intestine

A total of 4,252 patients with stage IV small intestinal NETs who did not undergo a metastatic site operation were included. Overall median survival was 72.4 months. Primary tumors were resected in 2526 patients (59.4%; Fig 1). Patients who underwent primary tumor resection had prolonged overall survival compared with those who did not have surgery (91.3 months versus 44.2 months, $P < .001$; Fig 2, *B*). Additional factors associated with prolonged survival included younger age, low CCI, tumor grade 1 or 2, and absence of chemotherapy. On multivariable analysis, primary tumor resection (HR 0.55), absence of chemotherapy, younger age, grade 1 or 2 tumor, and CCI of 0 were independently associated with prolonged survival ($P < .001$; Table 1).

Among patients who underwent primary tumor resection, patients younger than the median age (64 years) or those with grade 1 or 2 tumors had prolonged survival compared with older patients or those with grade 3 tumors ($P \leq .009$; Table 2, Supplemental Fig 1).

Age, sex, and tumor grade were associated with patients' undergoing primary tumor removal on univariate analysis. On multivariable analysis, females, younger patients, and those with grade 1 or 2 tumors were more likely to undergo an operation (Table 3).

Colon

A total of 2,326 patients with stage IV colon NETs who did not undergo an operation on a metastasis were identified. Median survival for all patients was 8.2 months. Primary tumors were resected in 1,170 patients (50.3%) (Fig 1). Patients who underwent primary tumor resection had prolonged overall survival (12.9 months versus 4.8 months, $P < .001$; Fig 2, *C*). Additional factors associated with prolonged survival included hospital type (academic or research centers), younger age, low CCI, tumor grade

Table 1
Factors associated with prolonged survival in stage IV GEP-NETs.

Organ	Interaction with time	Variable (*n*)	Hazard ratio	95% Confidence interval	*P* value
Pancreas		Community cancer program (429)	1.55	1.36–1.79	< .001
		Comprehensive community cancer program (1,917)	1.35	1.23–1.48	< .001
		Integrated network cancer program (507)	1.22	1.05–1.40	.007
		Academic/research program (2,150)	1		
	Within 9 months of diagnosis	Primary tumor resection (4,882)	0.30	0.24–0.28	< .001
		Grade 1 (912)	0.26	0.22–0.30	< .001
		Grade 2 (342)	0.45	0.37–0.55	< .001
		Grade: missing (3,284)	0.53	0.48–0.60	< .001
		Grade 3 (804)	1		
		Location: head (1,890)	1.26	1.14–1.39	< .001
		Location: body/tail (1,673)	1		
	After 9 months	Primary tumor resection	0.53	0.44–0.64	< .001
		Grade 1	0.43	0.35–0.52	< .001
		Grade 2	0.51	0.39–0.67	< .001
		Grade: missing	0.53	0.44–0.63	< .001
		Grade 3	1		
		Location: head	0.98	0.86–1.12	.77
		Location: body/tail			
Small intestine		Age ≥ median (64 years) (1,953)	2.04	1.84–2.27	<0.001
		Age < median (64 years) (1,788)	1		
		Did not get chemotherapy (623)	0.75	0.67–0.85	<0.001
		Received chemotherapy (2,949)	1		
		Primary tumor resection (2,526)	0.55	0.49–0.60	< .001
	Within 30 months of diagnosis	CCI = 0 (2,971)	1		
		CCI = 1 (596)	1.59	1.36–1.87	< .001
		CCI ≥ 2 (174)	2.31	1.82–2.93	< .001
		Grade 1 or 2 (2,282)	0.75	0.66–0.85	< .001
		Grade 3 (1,459)	1		
	After 30 months	CCI = 0	1		
		CCI = 1	1.06	0.85–1.34	.59
		CCI ≥ 2	1.83	1.24–2.71	.002
		Grade 1 or 2	0.95	0.79–1.13	.56
Colon		Comprehensive community cancer program (926)	1.27	1.13–1.43	< .001
		Integrated network cancer program (217)	1.25	1.05–1.49	.01
		Community cancer program (276)	1.15	0.98–1.35	.09
		Academic/research program (633)	1		
		Age ≥ median (65 y) (1,079)	1.58	1.43–1.76	< .001
		Age < median (65 y) (1,038)	1		
		Grade 1 or 2 (620)	0.33	0.27–0.40	< .001
		Grade 3 (1,497)	1		
		Primary tumor resection (1,170)	0.59	0.54–0.66	< .001
	Within 6 months of diagnosis	CCI = 0 (1,608)	1		
		CCI = 1 (362)	1.39	1.18–1.65	< .001
		CCI ≥ 2 (147)	2.34	1.89–2.89	< .001
	After 6 months	CCI = 0	1		
		CCI = 1	1.10	0.89–1.35	.39
		CCI ≥ 2	1.09	0.74–1.59	.67
Rectum		Primary tumor resection (176)	0.48	0.35–0.65	< .001
		Race–Asian/other/unknown (29)	0.49	0.35–0.70	< .001
		Race–black (180)	0.82	0.67–1.00	.05
		Race–white (542)	1		
		CCI = 0 (591)	1		
		CCI = 1 (122)	1.23	1.00–1.51	.05
		CCI ≥ 2 (59)	1.88	1.41–2.51	< .001
		Grade 1 or 2 (167)	0.43	0.34–0.53	< .001
		Grade 3 (605)	1		
	Within 9 months of diagnosis	Age ≥ median (60 y) (380)	1.99	1.61–2.47	< .001
		Age < median (60 y) (392)	1		
	After 9 months	Age ≥ median (60 y)	1.22	0.97–1.54	.10
		Age < median (60 y)	1		
Stomach		Age ≥ median (65 y) (439)	1.45	1.19–1.76	< .001
		Age < median (65 y) (404)	1		
		CCI ≥ 2 (73)	1.58	1.21–2.06	< .001
		CCI = 1 (186)	1.09	0.91–1.32	.31
		CCI = 0 (584)	1		
		Grade 1 or 2 (191)	0.46	0.37–0.56	< .001
		Grade 3 (652)	1		
	Within 9 months of diagnosis	Primary tumor resection (114)	0.34	0.22–0.51	< .001
	After 9 months	Primary tumor resection	0.66	0.48–0.91	.01
		Distal stomach (182)	0.62	0.44–0.87	.006
		Location: NOS (302)	0.50	0.38–0.66	< .001
		Proximal stomach (359)	1		

Reference groups: Primary tumor resection – did not have primary tumor resection.

Table 2
Median survival by patient/tumor characteristics in patients who underwent primary tumor resection.

Primary Site	Variable (*n*)		Median survival in months (*n*)	*P* value
Pancreas				
	Location	Head (133)	68.6 (133)	.11
		Body/tail (205)	60.5 (205)	
		NOS (122)	71.3 (122)	
	Grade	1 or 2 (253)	74.0 (253)	< .001
		3 (79)	18.5 (79)	
		Missing (128)	62.9 (128)	
	Size	> median (4.5cm) (204)	63.8 (204)	.97
		≤ median (204)	66.8 (204)	
	Age	≤ 57 y (220)	68.6 (220)	.006
		> 57 y (240)	57.0 (240)	
Small intestine				
	Grade	1 or 2 (1,612)	96.4 (1,612)	.009
		3 (914)	84.0 (914)	
	Size	> median (2.2cm) (1,098)	95.3 (1,098)	.41
		≤ median (1,109)	96.1 (1,109)	
	Age	≤ 64 y (1,307)	118.5 (1307)	< .001
		> 64 y (1,219)	57.7 (1219)	
Colon				
	Location	Proximal (880)	15.9 (880)	< .001
		Distal (176)	6.7 (176)	
		NOS (114)	22.1 (114)	
	Grade	1 or 2 (396)	77.6 (396)	< .001
		3 (227)	7.4 (774)	
	Size	> median (4cm) (509)	6.6 (509)	< .001
		≤ median (512)	33.9 (512)	
	Age	≤ 63 y (594)	20.3 (594)	< .001
		> 63 y (576)	7.8 (576)	
Rectum				
	Grade	1 or 2 (70)	54.8 (70)	< .001
		3 (106)	12.2 (106)	
	Size	> median (3.9cm) (77)	12.2 (77)	.01
		≤ median (75)	32.9 (75)	
	Age	≤ 60 y (87)	32.9 (87)	< .001
		> 60 y (89)	12.3 (89)	
Stomach				
	Location	Proximal (32)	18.6 (32)	.41
		Distal (38)	21.2 (38)	
		NOS (44)	26.9 (44)	
	Grade	1 or 2 (43)	47.3 (43)	< .001
		3 (71)	17.4 (71)	
	Size	> median (4 cm) (44)	17.8 (44)	.23
		≤ median (52)	32.1 (52)	
	Age	≤ 59 y (62)	29.6 (62)	.10
		> 59 y (52)	17.9 (52)	

NOS, not otherwise specified.

Table 3
Multivariable analysis of variables associated with whether patients underwent primary tumor resection.

Organ	Variable	Odds ratio	95% Confidence interval	*P* value
Pancreas	Age	0.97	0.965–0.98	< .001
	Grade 1	2.31	1.76–3.03	< .001
	Grade 2	2.29	1.63–3.20	< .001
	Grade: missing	0.36	0.28–0.48	< .001
	Location: head	0.82	0.66–1.03	.09
	Location: NOS	0.66	0.52–0.83	< .001
Small intestine	Age	0.99	0.987–1.00	.005
	Sex: female	1.20	1.06–1.37	.005
	Grade 1 or 2	1.34	1.18–1.53	< .001
Colon	Age	0.99	0.98–1.00	.001
	Grade 1 or 2	1.80	1.48–2.18	< .001
	Location: proximal	1.42	1.14–1.78	.002
	Location: NOS	0.45	0.33–0.60	< .001
Rectum	Insured	7.31	2.22–24.1	.001
	Grade 1 or 2	3.59	2.45–5.27	< .001
Stomach	Age	0.97	0.96–0.98	< .001
	Grade 1 or 2	1.79	1.19–2.70	.006
	Location: distal	3.03	1.86–4.92	< .001
	Location: NOS	1.64	1.02–2.62	.04

Reference groups: grade–3; location–pancreatic body/tail, distal colon, proximal stomach; sex – male; insurance status uninsured. Age is represented per year, increasing.

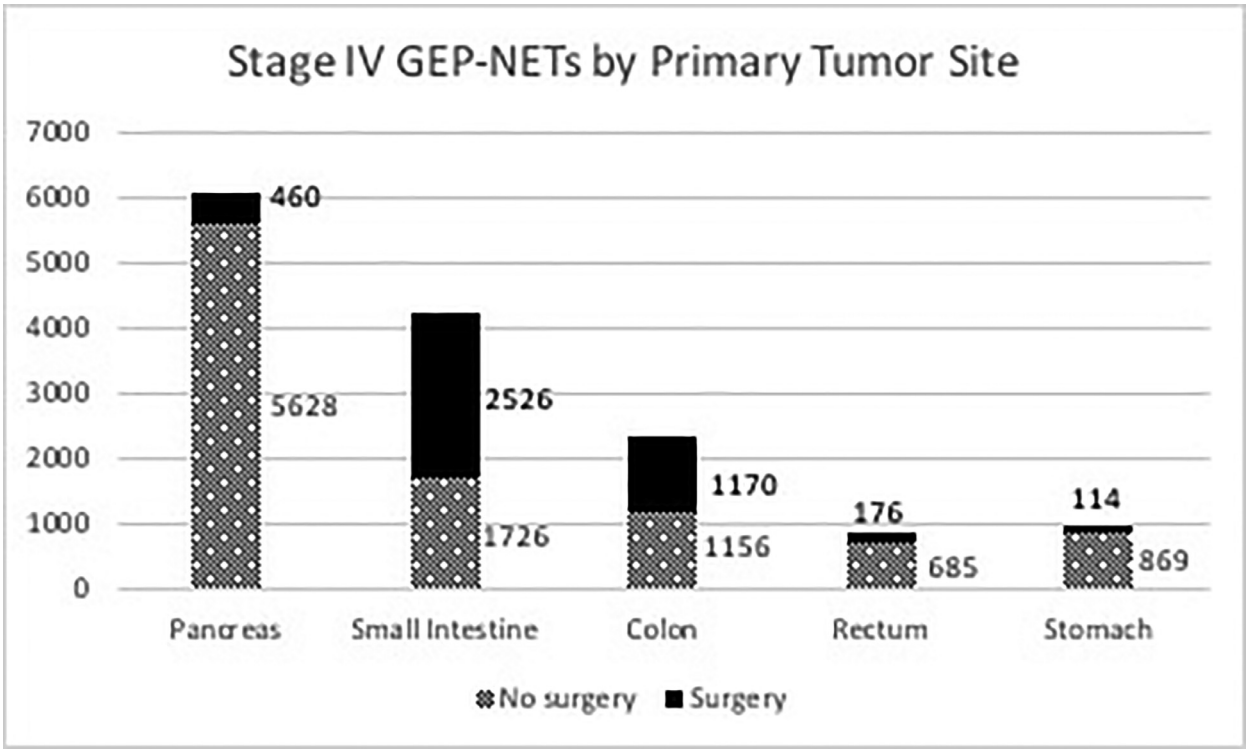

Fig 1. Proportion of GEP-NETs that underwent primary tumor resection by organ site.

1 or 2, and tumor location in the proximal colon. On multivariable analysis, primary tumor resection (HR 0.59, $P < .001$), treatment at an academic or research hospital, younger patient age, grade 1 or 2 tumors, and CCI of 0 were associated with prolonged survival (Table 1).

Prolonged survival among patients who underwent primary tumor resection was observed in those with tumors which were grade 1 or 2, located in the proximal colon, smaller than the median size (4 cm), or in patients younger than the median age (63 years; $P < .001$; Table 2, Supplemental Fig 1).

Younger age, lower tumor grade, and tumor location in the proximal colon were associated with an increased chance of undergoing primary tumor resection on univariate analysis and remained significant on multivariable analysis (Table 3).

Rectum

A total of 861 patients with stage IV rectal NETs who did not undergo a metastatic site operation were included. Median survival for all patients was 9.7 months. Primary tumors were resected in 176 patients (20.4%; Fig 1). Patients who underwent primary tumor resection had prolonged overall median survival compared with those who did not have surgery (20.7 months vs 8.2 months, $P < .001$; Fig 2, *D*). Additional factors associated with prolonged survival on univariate analysis were younger age, race (Asian, other, or unknown), low CCI, and tumor grade 1 or 2. On multivariable analysis, primary tumor resection, Asian/other/unknown race, a CCI of 0, a grade 1 or 2 tumor, and younger age were each associated with prolonged survival ($P < .001$; Table 1).

Prolonged survival among patients who underwent primary tumor resection was observed in those with tumors that were grade 1 or 2 or smaller than the median size (3.9 cm) and in patients younger than the median age (60 years; $P \leq .01$; Table 2, Supplemental Fig 1).

Insurance status and tumor grade were associated with patients having undergone an operation on the primary tumor on univariate analysis. When controlling for other variables, insured patients and those with grade 1 or 2 tumors were significantly more likely to undergo primary tumor resection (Table 3).

Stomach

A total of 983 patients with stage IV gastric NETs who did not undergo an operation on a metastatic site were identified. Median survival for all patients was 8.3 months. Primary tumors were resected in 114 patients (11.6%; Fig 1). Patients who underwent primary tumor resection had prolonged overall survival (21.2 months vs 7.0 months, $P < .001$; Fig 2, *E*). Additional factors associated with prolonged survival included younger age, low CCI, tumor grade 1 or 2, and tumor location in the distal stomach. On multivariable analysis, primary tumor resection was associated with significantly prolonged survival (HR 0.34–0.66, $P \leq .01$). Additional factors significant on multivariable analysis included younger age, CCI of 0, and grade 1 or 2. Tumor location was not significant on multivariable analysis within 9 months of diagnosis, but location in the distal stomach was associated with prolonged survival beyond nine months (HR 0.62, $P = .006$) (Table 1).

Among patients who underwent primary tumor resection, those with grade 1 or 2 tumors had prolonged survival compared with those with grade 3 tumors ($P < .001$; Table 2, Supplemental Fig 1).

Age, grade, and location were associated with an increased chance of undergoing an operation on the primary tumor on univariate analysis. Younger age, location in the distal stomach, and grade 1 or 2 differentiation were associated with having primary tumor resection on multivariable analysis (Table 3).

Discussion

This study suggests that primary tumor resection is associated with prolonged survival for patients with stage IV GEP-NETs, even when metastatic disease was not removed, and is the first to show

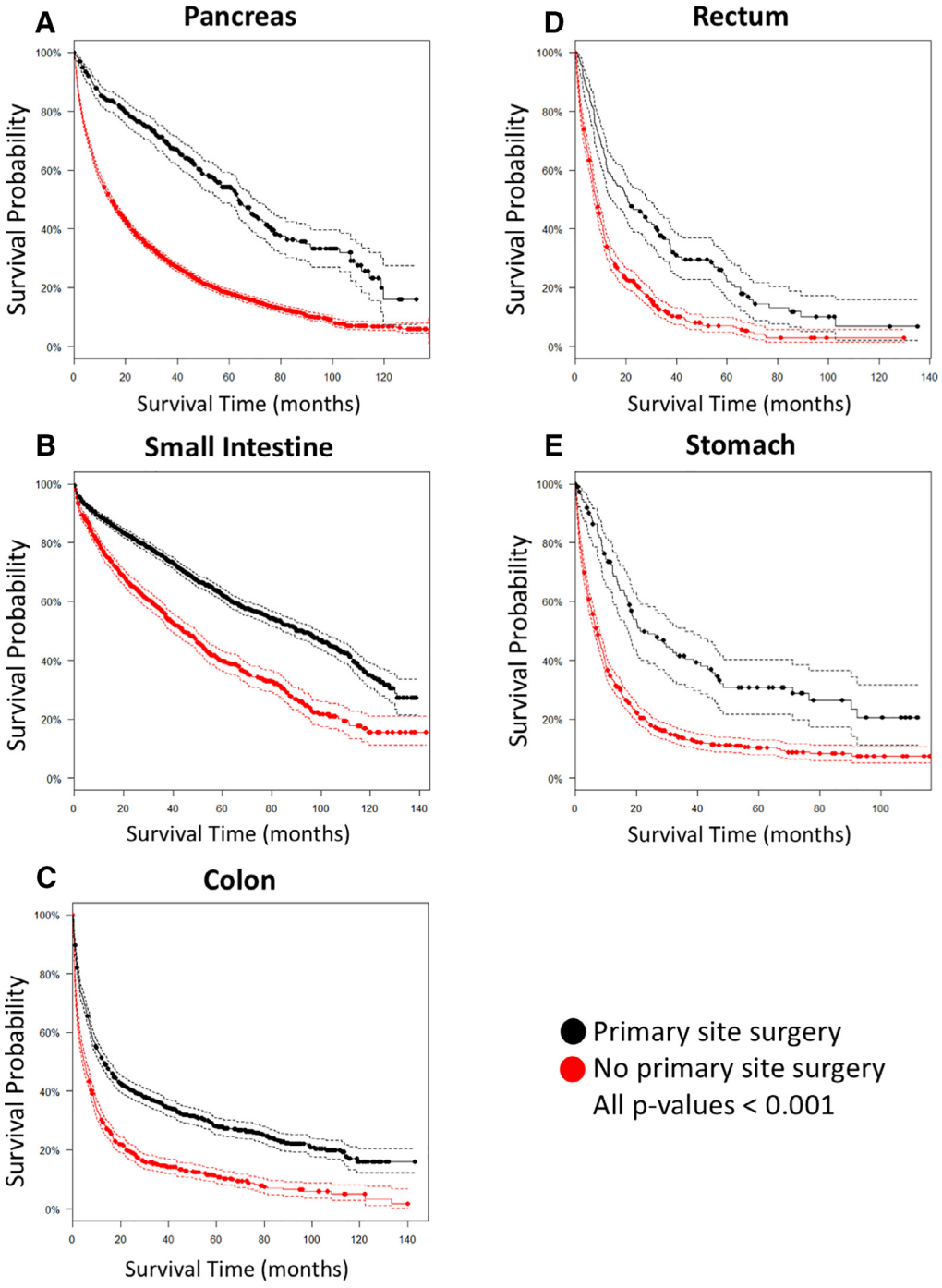

Fig 2. Kaplan-Meier survival curves demonstrating improved survival after primary tumor resection for each organ. (*A*) Pancreas. (*B*) Small intestine. (*C*) Colon. (*D*) Rectum. (E) Stomach.

a survival benefit for all GEP-NET subtypes. Earlier single-center studies, a series of reports using the SEER database, and a review of the California Cancer Registry previously established similar findings in more limited patient populations, but this is the largest study on this topic to date and the first to show a survival benefit for all GEP-NET subtypes.[11,14–18]

Earlier studies have consistently found a survival benefit with primary tumor resection of metastatic pancreatic NETs. The 49.4 month median survival benefit seen in this study is consistent with previous studies from the Surveillance, Epidemiology, End Results (SEER) database, which have found survival benefits ranging from 16 months to 55 months.[14,16,17] Our finding that younger patients and those with low-grade pancreatic NETs have prolonged survival after an operation is consistent with an earlier study using the SEER database.[14] Furthermore we found that survival of patients with resected pancreatic head NETs was not significantly different than those with pancreatic body or tail tumors, perhaps implying that a pancreatic head tumor resection or enucleation may not necessarily be contraindicated if technically feasible. This finding, however, should be taken with caution because of the high proportion of missing data on pancreatic NET tumor location. Finally, our finding of prolonged survival being associated with treatment at an academic institution suggests that management of patients with advanced pancreatic NETs should perhaps be concentrated at

Table 4
Recommended criteria for resection of primary tumor.

Organ	Criteria
Pancreas	Grade 1 or 2
Small intestine	All patients*
Colon	Proximal location
	Grade 1 or 2
	Size < 4 cm
Rectum	Grade 1 or 2
	Size < 3.9 cm
Stomach	Grade 1 or 2

* Although patients with grade 1 or 2 tumors lived significantly longer after resection than those with grade 3 tumors, median survival for those with grade 3 tumors was 84 months, long enough to justify resection.

high-volume centers, similar to the management of pancreatic adenocarcinoma.[19]

A total of 59 % of patients with small intestinal NETs underwent primary tumor resection, which is the highest percentage of all tumor sites studied herein. Although the NCDB does not record the indication for operation, this higher rate of primary site resection is likely because small intestinal NETs more frequently present with obstructive or hormonal symptoms. A retrospective review of patients who underwent operations for gastrointestinal NETs with liver metastases at the time of diagnosis found that 32 of 84 patients had surgery after presenting with an acute abdomen.[15] That study also found that resected patients survived longer than unresected patients, even in the subgroup without an acute abdomen; the authors concluded that the benefit from resection was likely oncologic in nature.[15]

Patients with metastatic colonic NETs had the lowest overall median survival of any patients in this study. Tumor grade appears to drive this short overall survival for both colonic and rectal NETs. An earlier study using the SEER database found a median survival of 4 months among patients with stage IV, poorly differentiated colorectal NETs, consistent with the data reported herein.[20] Although colonic NETs are more likely to be poorly differentiated than most other NET subtypes, low-grade and moderate-grade colonic NETs have previously been reported to be more common than high-grade tumors among patients with all disease stages.[21] According to the data reported here, however, high-grade tumors are more common among patients with stage IV disease. The difference in survival and in response to primary tumor resection by tumor grade in colorectal NETs is more pronounced than in other organs studied here and suggests that poorly differentiated colorectal NETs perhaps have a distinct, more aggressive biology.

This is the first study, to our knowledge, to demonstrate that patients with metastatic gastric NETs experience prolonged survival with primary tumor resection without undergoing metastasectomy. The type of gastric NET (type 1, 2, or 3), which determines the tumor's aggressiveness and impacts prognosis, is not available in the NCDB. Further investigation should include the effect of gastric NET type on the response to primary tumor resection in stage IV patients.[22,23]

Primary tumor resection should, in our opinion, be considered in the carefully selected patient with a stage IV GEP-NET because it is associated with prolonged survival as shown herein (Table 4). Based on findings of the subgroup analysis shown in Table 2, we recommend that patients with low tumor grade should be considered for resection of pancreatic, colorectal, and gastric NETs, and small tumor size should be considered for resection of colorectal NETs. Surgeons should perhaps refrain from resecting the primary tumor in patients with stage IV GEP-NETs and unresectable metastases who do not meet these criteria. Although younger patients and those with grade 1 and 2 tumors also had prolonged survival after resection of small intestinal NETs, relatively long survival was observed among all subgroups, suggesting that all patients with metastatic small intestinal NETs should be evaluated for an operation. The low morbidity of a small bowel resection, the potential for prolonged survival, and the possibility that an unresected tumor could cause an obstruction support this recommendation.

In addition to confirming a previous study's report that grade 1 or 2 tumors and younger age were associated with increased rates of primary tumor removal, we demonstrate that tumor location in the proximal colon, body or tail of the pancreas, and distal stomach were associated with resection, likely because surgeries in these locations are considered easier to perform and carry less morbidity.[24]

This study has several limitations, in addition to the inherent data entry errors associated with all large database studies. First, this analysis is retrospective and subject to selection bias. It is possible that patients who underwent primary tumor resection had less metastatic disease burden than patients who did not undergo an operation. Although the NCDB does not report metastatic disease burden, we attempted to mitigate this potential source of bias by excluding patients who underwent resection of metastases, thereby limiting the comparisons in this study to patients with unresectable metastatic disease. Moreover, a retrospective two-institution study that included liver tumor burden confirmed our findings that primary tumor resection in patients with unresectable liver disease was an independent predictor of prolonged survival.[18] Second, the NCDB records whether a patient received chemotherapy, but does not provide information about specific drugs. The recent emergence of new systemic and targeted therapies could have influenced survival rates in either group. Third, we do not have information on hormones or symptoms produced by these tumors. Fourth, the study includes patients diagnosed from 2004 to 2014, so many patients were diagnosed before the implementation of the 2010 North American Neuroendocrine Tumor Society guidelines that recommended using Ki-67 and mitotic index to determine tumor grade.[25,26] Last, patients with significant medical comorbidities are less likely to undergo resection and also will likely have shorter survival, regardless of their neuroendocrine tumor diagnosis. We attempted to mitigate the effect of comorbidities by including CCI and patient age in our multivariable analysis.

Despite these limitations, using the NCDB we found that resection of primary tumor in patients with metastatic GAP-NETs is associated with prolonged survival in a large cohort of patients. Primary tumor resection should therefore be considered by clinicians treating patients with stage IV GEP-NETs and be could be based on individual patient and tumor characteristics identified in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.09.006.

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