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REVIEW ARTICLE

One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States

James C. Yao, Manal Hassan, Alexandria Phan, Cecile Dagohoy, Colleen Leary, Jeannette E. Mares, Eddie K. Abdalla, Jason B. Fleming, Jean-Nicolas Vauthey, Asif Rashid, and Douglas B. Evans

From the Departments of Gastrointestinal Medical Oncology, Surgical Oncology, and Pathology, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

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Corresponding author: James C. Yao, MD, Department of Gastrointestinal Medical Oncology, Unit 426, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; e-mail: jyao@mdanderson.org.

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ABSTRACT

Purpose
Neuroendocrine tumors (NETs) are considered rare tumors and can produce a variety of hormones. In this study, we examined the epidemiology of and prognostic factors for NETs, because a thorough examination of neither had previously been performed.

Methods
The Surveillance, Epidemiology, and End Results (SEER) Program registries were searched to identify NET cases from 1973 to 2004. Associated population data were used for incidence and prevalence analyses.

Results
We identified 35,618 patients with NETs. We observed a significant increase in the reported annual age-adjusted incidence of NETs from 1973 (1.09/100,000) to 2004 (5.25/100,000). Using the SEER 9 registry data, we estimated the 29-year limited-duration prevalence of NETs on January 1, 2004, to be 9,263. Also, the estimated 29-year limited-duration prevalence in the United States on that date was 103,312 cases (35/100,000). The most common primary tumor site varied by race, with the lung being the most common in white patients, and the rectum being the most common in Asian/Pacific Islander, American Indian/Alaskan Native, and African American patients. Additionally, survival duration varied by histologic grade. In multivariate analysis of patients with well-differentiated to moderately differentiated NETs, disease stage, primary tumor site, histologic grade, sex, race, age, and year of diagnosis were predictors of outcome ($P < .001$).

Conclusion
We observed increased reported incidence of NETs and increased survival durations over time, suggesting that NETs are more prevalent than previously reported. Clinicians need to be become familiar with the natural history and patterns of disease progression, which are characteristic of these tumors.

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INTRODUCTION

Neuroendocrine tumors (NETs) consist of a spectrum of malignancies that can arise from neuroendocrine cells throughout the body. These tumors are characterized by their ability to produce peptides that cause characteristic hormonal syndromes. Most are more indolent than other epithelial malignancies; however, they can be aggressive and resistant to therapy. Oberndofer[1] first described these tumors and coined the term carcinoid (or "karzinoide") in 1907.

Although authors have described the incidence of NETs and the racial, sex, and primary tumor site distributions and survival durations in patients with these tumors in the United States, the Netherlands, and the United Kingdom,[2-5] much about them remains unknown. For example, the prevalence of NETs in the general population has not been well described. Furthermore, International Classification of Diseases for Oncology (ICD-O-3) classification of NETs is complex. In particular, a significant number of NETs are not classified using the ICD-O-3 codes associated with carcinoid tumors (8240-8246 and 8249).[6] In our present study, we undertook the most complete analysis of patients with NETs reported to date. We retrospectively analyzed the epidemiology of and prognostic factors for NETs in patients identified in the Surveillance, Epidemiology, and End Results (SEER) database.

Since its inception in 1973, the SEER Program has undergone two major expansions to improve its

representative sampling of the US population. The SEER 9, 13, and 17 registries cover approximately 9.5%, 13.8%, and 26.2%, respectively, of the total US population. In our study, we obtained and analyzed the SEER data based on the November 2006 submission.[7] The data set we used contained a total of 4,926,760 neoplasms in 4,466,501 patients diagnosed from 1973 to 2004.

METHODS

ICD-O-3 histology codes were used to identify NETs. These codes correspond to the following clinical/histologic diagnoses: islet cell carcinoma (8150), insulinoma (8151), glucagonoma (8152), gastrinoma (8153), mixed islet-cell/exocrine adenocarcinoma (8154), vipoma (8155), somatostatinoma (8156), enteroglucagonoma (8157), carcinoid (8240), enterochromaffin cell carcinoid (8241), enterochromaffin-like cell tumors (8242), goblet cell carcinoid (8243), composite carcinoid (8244), adenocarcinoid (8245), neuroendocrine carcinoma (8246), and atypical carcinoid (8249). Small-cell (8002 and 8040-8045) and large-cell neuroendocrine carcinoma (8013) of the lung, pheomochromocytoma (8700), paraganglioma (8680, 8693), and medullary carcinoma of the thyroid (8510) were excluded.

Because a unified staging system for NETs is lacking, the SEER staging system was used for analysis. Tumors were classified as localized, regional, or distant. A localized NET was defined as an invasive neoplasm confined entirely to the organ of origin. A regional NET was defined as a neoplasm that (1) extended beyond the limits of the organ of origin directly into surrounding organs or tissue, (2) involved regional lymph nodes, or (3) fulfilled both of the aforementioned criteria. Finally, a distant NET was defined as a neoplasm that spread to parts of the body remote from the primary tumor.

There is no accepted uniformed grading system for malignant NETs. Pathologists in the United States typically use the terms "carcinoid tumor" or "islet-cell tumor" to denote well-differentiated NETs (G1). The term "atypical carcinoid" is frequently used to describe a moderately differentiated carcinoid and is classified as G2 tumor, poorly differentiated tumors are classified as G3 tumors, and anaplastic tumors are classified as G4 tumors. Tumors with mixed differentiation, such as adenocarcinoid and goblet-cell carcinoid tumors, are classified as having mixed histology.

Comparisons of patients, tumor characteristics, and disease extension were performed using the χ^2 test. One-way analysis of variance was used for comparison of continuous variables between groups. Survival durations were measured using the actuarial or Kaplan-Meier method and compared using the log-rank test. The statistical independence between prognostic variables was evaluated using the Cox proportional hazards model.

SEER*Stat software program (version 6.3.5; National Cancer Institute, Bethesda, MD) was used for incidence and limited-duration prevalence analysis.[7] The counting method, which estimates prevalence by counting the number of persons (first NET for patients with multiple primaries) who are known to be alive at a specific date and adjusting for those lost to follow-up, was used for prevalence analyses.[5,8,9] The expected number of cases lost to follow-up that were included in the prevalence data was calculated using conditional survival curves for cohorts by age, sex, race, year of diagnosis, and primary tumor site. All other statistical calculations were performed using SPSS (version 14.0; SPSS Inc, Chicago, IL). Comparative differences were considered statistically significant when P was less than .05.

RESULTS

Incidence and Prevalence

We identified a total of 35,825 NETs in 35,618 patients in the SEER registries. Using population files linked to the SEER database, we calculated the incidence of NETs per 100,000 per year age-adjusted to the 2000 US standard population. Because the SEER 9, 13, and 17 registries are linked to different population data sets, we computed the age-adjusted incidence for three time periods: SEER 9, 1973 to 1991; SEER 13, 1992 to 1999; and SEER 17, 2000 to 2004. We noted a significant increase in reported annual age-adjusted incidence from 1973 (1.09/100,000) to 2004 (5.25/100,000; Fig 1A). Separate time-trend analyses of the SEER 9, 13, and 17 registries showed significant increases in the reported incidence of NETs ($P < .001$ in all three analyses). Detailed incidence data for 2000 to 2004 are presented in Table 1. We also performed separate time-trend analyses by primary tumor site (Fig 1B) and disease stage at diagnosis (Fig 1C). These analyses showed statistically significant increases in the reported incidence rates over time at all primary sites ($P < .001$) and disease stages ($P < .001$).

In the SEER 9 registry, the estimated 29-year limited-duration prevalence of NETs on January 1, 2004, was 9,263. We projected this prevalence into the US standard population and matched by sex, race, and age. The resulting estimated 29-year limited-duration prevalence of NETs on January 1, 2004, in the United States was 103,312 cases or 35/100,000.

Patient Characteristics

Of the 35,618 patients with NETs identified in the SEER database, 18,614 (52%) were women and 17,004 (48%) were men. Eighty-one percent of the patients were white, 12% were African American, 5% were Asian/Pacific Islander, and 1% were American Indian/Alaskan native. The race of the remaining 1% of the patients was unknown. The median age at diagnosis was 63 years (mean, 62; standard deviation, 15).

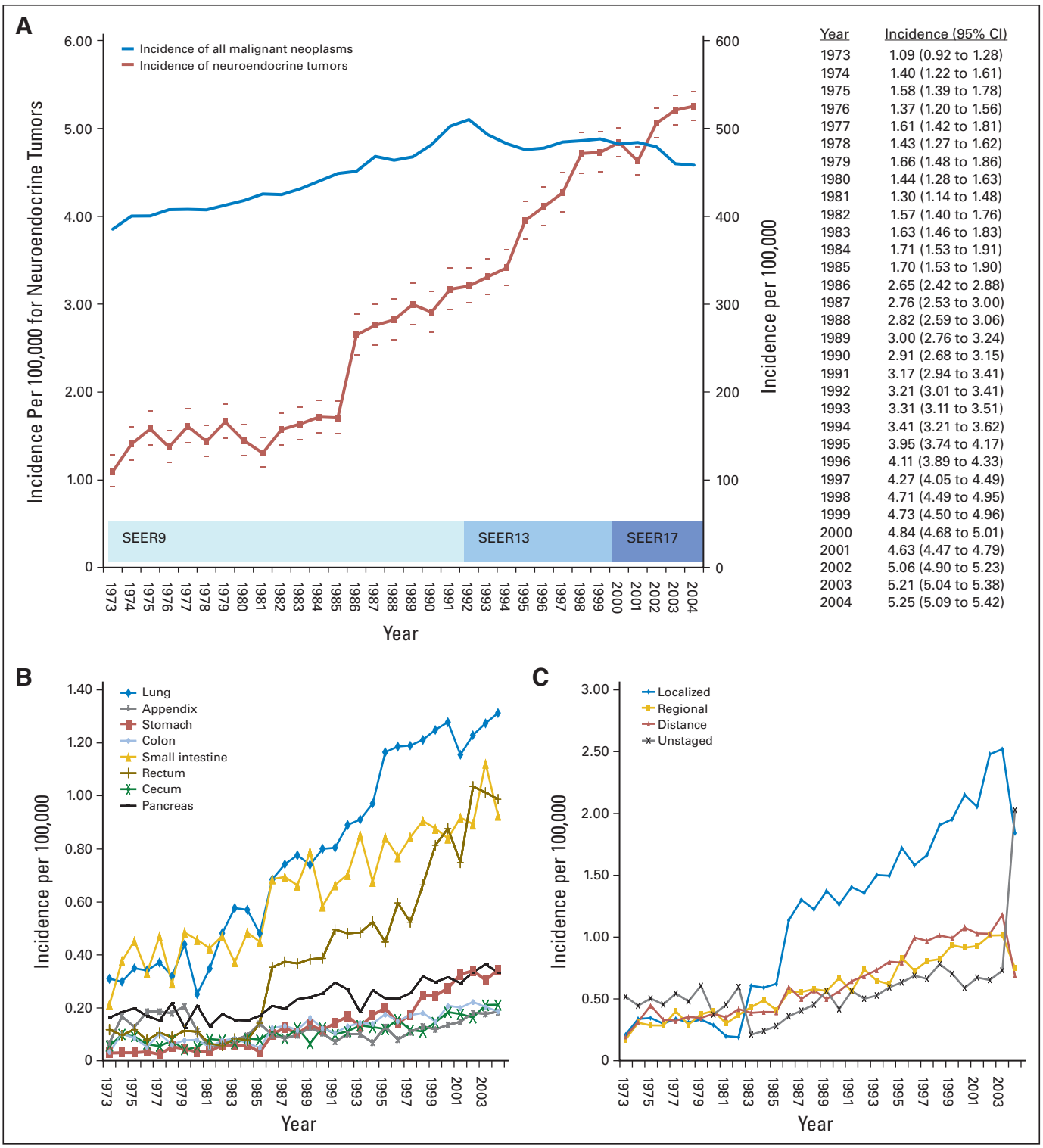
NETs are commonly classified by embryonic origin as foregut, midgut, or hindgut tumors. Of the 35,825 cases, 14,844 (41%) were foregut NETs, 9,266 (26%) were midgut, and 6,963 (19%) were hindgut; in the remaining 4,752 (13%), the primary tumor site was unknown or could not be classified using this system. The disease stage in 7,270 cases (20%) went unreported; of the remaining 28,515 cases, 14,162 (40%) were localized, 6,718 (19%) were regional, and 7,635 (21%) were distant.

Primary Tumor Site

The locations of the primary tumors in these patients varied significantly by sex ($P < .001$; Table 1). Female patients were more likely to have a primary NET in the lung, stomach, appendix, or cecum, whereas male patients were more likely to have a primary tumor in the thymus, duodenum, pancreas, jejunum/ileum, or rectum. The primary tumor sites also varied significantly by race ($P < .001$; Table 1). In particular, the lung was the primary NET site more often among white patients (30%) than among patients in the other racial groups ($P < .001$). Additionally, jejunal/ileal NETs were more common in white (17%) and African American (15%) patients than in Asian/Pacific Islander and American Indian/Alaskan Native patients ($P < .001$). In contrast, rectal NETs occurred at a markedly higher frequency among Asian/Pacific Islander (41%), American Indian/Alaskan Native (32%), and African American (26%) patients than among white (12%) patients ($P < .001$).

Age at Diagnosis

We next examined age at diagnosis of NET by race, sex, and primary tumor site. Overall, African American, Asian/Pacific Islander,



Year	Incidence (95% CI)
1973	1.09 (0.92 to 1.28)
1974	1.40 (1.22 to 1.61)
1975	1.58 (1.39 to 1.78)
1976	1.37 (1.20 to 1.56)
1977	1.61 (1.42 to 1.81)
1978	1.43 (1.27 to 1.62)
1979	1.66 (1.48 to 1.86)
1980	1.44 (1.28 to 1.63)
1981	1.30 (1.14 to 1.48)
1982	1.57 (1.40 to 1.76)
1983	1.63 (1.46 to 1.83)
1984	1.71 (1.53 to 1.91)
1985	1.70 (1.53 to 1.90)
1986	2.65 (2.42 to 2.88)
1987	2.76 (2.53 to 3.00)
1988	2.82 (2.59 to 3.06)
1989	3.00 (2.76 to 3.24)
1990	2.91 (2.68 to 3.15)
1991	3.17 (2.94 to 3.41)
1992	3.21 (3.01 to 3.41)
1993	3.31 (3.11 to 3.51)
1994	3.41 (3.21 to 3.62)
1995	3.95 (3.74 to 4.17)
1996	4.11 (3.89 to 4.33)
1997	4.27 (4.05 to 4.49)
1998	4.71 (4.49 to 4.95)
1999	4.73 (4.50 to 4.96)
2000	4.84 (4.68 to 5.01)
2001	4.63 (4.47 to 4.79)
2002	5.06 (4.90 to 5.23)
2003	5.21 (5.04 to 5.38)
2004	5.25 (5.09 to 5.42)

Fig 1. These graphs show the incidence of neuroendocrine tumors (NETs) over time, by site and by disease stage. (A) Annual age-adjusted incidence of NETs by year (1973 to 2004). The incidence is presented as the number of tumors per 100,000 (with 95% CIs) age-adjusted for the 2000 US standard population. Cases were selected from the Surveillance, Epidemiology, and End Results database (1973 to 2004) using International Classification of Diseases for Oncology histology codes 8150 to 8157, 8240 to 8246, and 8249. (B) Time-trend analyses of the incidence of NETs by primary tumor site (1973 to 2004). Statistically significant increases in incidence at all sites are shown ($P < .001$). (C) The incidence of NETs by disease stage at diagnosis. Statistically significant increases in incidence at all stages are shown ($P < .001$).

Table 1. Incidence and Distribution of NETs by Sex and Race in the SEER 17 Registry (2000-2004)

	Incidence*							Fraction Within Sex and Racial Groups (%)					
		Sex		Race				Sex		Race			
Distribution	All Cases	Male	Female	White	African American	Asian/P Islander	AI/AN	Male	Female	White	African American	Asian/P Islander	AI/AN
All cases	5.00	5.35	4.76	4.92	6.82	3.19	3.07						
Disease stage													
Localized	2.01	2.00	2.05	1.86	3.24	1.68	1.66	47	52	47	57	65	61
Regional	0.88	0.99	0.79	0.90	1.06	0.38	0.52	24	23	25	21	15	19
Distant	1.03	1.18	0.92	1.08	1.17	0.49	0.48	29	25	28	22	20	20
Unstaged	1.08	1.18	1.01	1.08	1.36	0.53	0.53						
Primary tumor site													
Lung	1.35	1.30	1.40	1.45	1.17	0.50	0.70	24	30	30	18	15	22
Thymus	0.02	0.02	0.01	0.02	0.01	0.04	0.00	1	0.2	0.4	0.1	1	1
Stomach	0.30	0.29	0.31	0.29	0.39	0.23	0.35	4	6	5	5	6	9
Duodenum	0.19	0.24	0.16	0.15	0.64	0.18	0.03	4	3	2	7	4	2
Jejunum/ileum	0.67	0.80	0.57	0.71	0.88	0.09	0.09	18	14	17	15	4	5
Cecum	0.16	0.16	0.17	0.17	0.21	0.04	0.09	3	4	4	3	1	1
Appendix	0.15	0.14	0.16	0.16	0.14	0.03	0.02	3	4	4	3	2	1
Colon	0.20	0.23	0.17	0.18	0.38	0.12	0.22	4	4	4	5	4	6
Rectum	0.86	0.92	0.81	0.66	1.80	1.25	1.00	16	14	12	26	41	32
Pancreas	0.32	0.38	0.27	0.32	0.36	0.25	0.20	8	6	7	6	8	10
Liver	0.04	0.03	0.04	0.04	0.05	0.01	0.07	1	1	1	1	0.4	1
Other/unknown	0.74	0.84	0.69	0.77	0.79	0.45	0.30	14	14	15	12	12	11

Abbreviations: SEER, Surveillance, Epidemiology, and End Results database; NETs, neuroendocrine tumors; P Islander, Pacific Islander; AI/AN, American Indian/Alaskan native.
*Age-adjusted annual incidence per 100,000 to the 2000 US standard population.

and American Indian/Alaskan Native patients were younger at diagnosis than white patients were ($P < .001$). We observed no difference in age at diagnosis by sex ($P = .44$). The ages at diagnosis did varied significantly by primary tumor site ($P < .001$). Details regarding age at diagnosis are presented in Table 2.

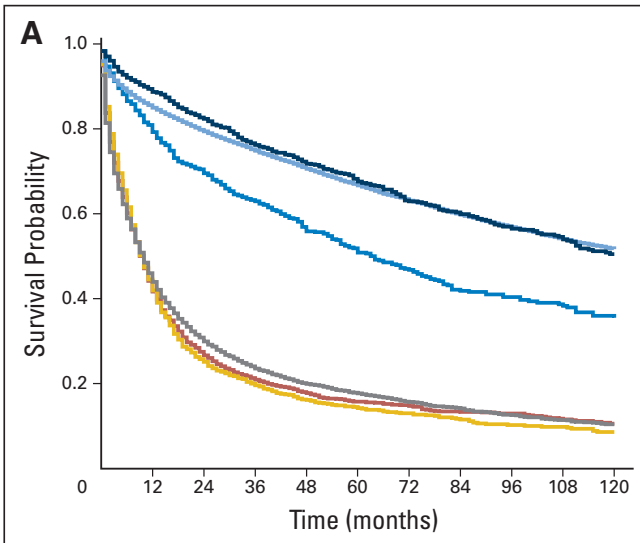
Tumor Stage

Next, we examined factors associated with extent of disease and observed a strong correlation between primary tumor site and disease stage, among the 28,515 cases where stage information was available (Table 2; $P < .001$). We also found that histologic grade was strongly

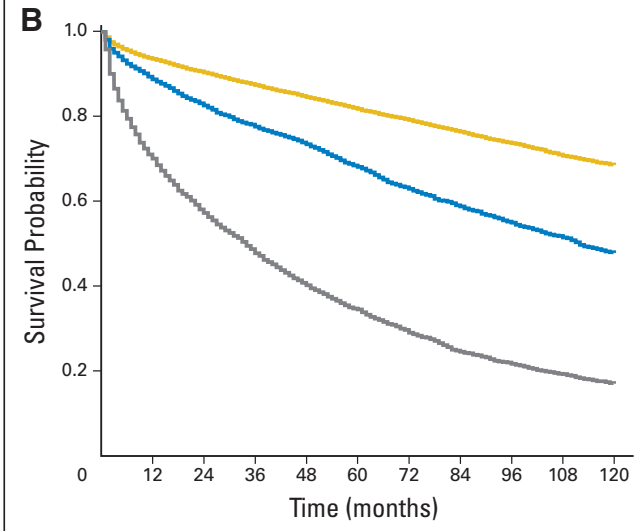
Table 2. Age and Disease Stage at Diagnosis of NETs by Race, Sex, and Primary Tumor Site

	Age at Diagnosis (years)			Disease Stage (%)		
Characteristic	Median	Mean	Standard Deviation	Localized	Regional	Distant
Race						
White	64	62	15	47	25	28
Black	59	59	14	57	21	22
Asian/P Islander	59	59	14	65	15	20
AI/AN	58	57	16	61	19	20
Sex						
Male	63	62	14	47	24	29
Female	63	62	15	52	23	25
Primary tumor site						
Lung	64	62	15	49	23	28
Thymus	59	56	16	28	41	31
Stomach	65	64	15	76	9	15
Duodenum	67	65	14	81	10	9
Jejunum/ileum	66	65	13	29	41	30
Cecum	68	66	14	14	42	44
Appendix	47	48	18	60	28	12
Colon	65	64	14	45	23	32
Rectum	56	57	13	92	4	5
Pancreas	60	59	15	14	22	64
Liver	67	64	15	45	27	28

NOTE. Cases selected from the SEER Program database (1973-2004) using ICD-O-3 histology codes 8150-8157, 8240-8246, and 8249.
Abbreviations: NETs, neuroendocrine tumors; P Islander, Pacific Islander; AI/AN, American Indian/Alaskan native.

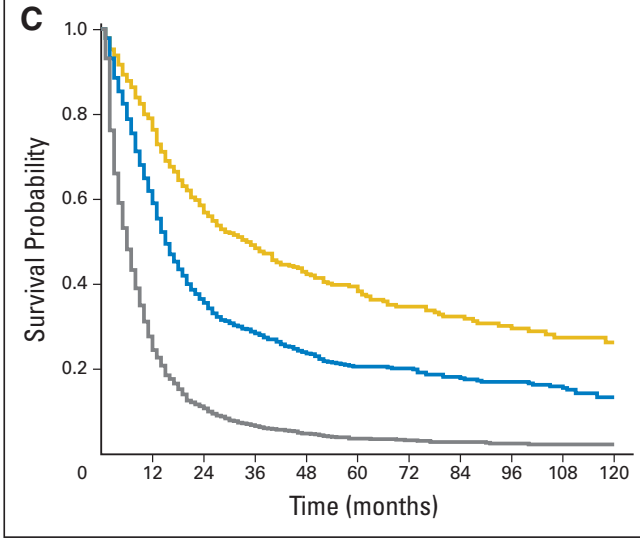


	Median Survival	
	Months	95%CI
Carcinoid/islet cell: well-differentiated	124	101 to 147
Carcinoid/islet cell: unspecified grade	129	124 to 134
Carcinoid/islet cell: moderately differentiated	64	56 to 72
Neuroendocrine: poorly differentiated	10	9 to 11
Neuroendocrine: anaplastic	10	9 to 11
Neuroendocrine: unspecified grade	10	9 to 11



	Median Survival	
	Months	95%CI
Localized	223	208 to 238
Regional	111	104 to 118
Distant	33	31 to 35

	Survival probability		
Year	Localized	Regional	Distant
1	.94	.89	.70
2	.90	.83	.57
3	.87	.78	.48
4	.85	.73	.40
5	.82	.68	.35
6	.79	.63	.29
7	.76	.59	.25
8	.74	.55	.22
9	.71	.51	.19
10	.69	.48	.17



	Median Survival	
	Months	95%CI
Localized	34	27 to 41
Regional	14	13 to 15
Distant	5	4.5 to 5.5

	Survival probability		
Year	Localized	Regional	Distant
1	.76	.59	.25
2	.57	.36	.11
3	.48	.28	.07
4	.42	.24	.05
5	.38	.21	.04
6	.35	.20	.03
7	.32	.18	.03
8	.30	.17	.03
9	.28	.15	.02
10	.27	.13	.02

Fig 2. Survival duration by (A) histology (B) well- and moderately differentiated histology, and (C) poorly differentiated histology. Neuroendocrine tumor cases identified at autopsy or solely on the basis of death certificates were excluded. Median survival durations are presented in months (with 95% CIs).

linked with disease stage ($P < .001$). Among patients with NETs with explicitly stated tumor histologic grades, 21% of those with well-differentiated (G1) tumors and 30% of those with moderately differentiated (G2) tumors had synchronous distant metastasis at diagnosis, whereas 50% of those with poorly differentiated (G3) tumors or undifferentiated (G4) tumors had synchronous distant metastasis at diagnosis.

Other factors associated with disease stage included race and sex (Table 2). White patients were the most likely to present with advanced disease ($P < .001$), with 28% having synchronous distant metastasis at diagnosis. Also, male patients were more likely to have metastasis at presentation than female patients were (29% *v* 25%; $P < .001$).

Survival

For survival analyses, we excluded 521 cases that were identified at autopsy or solely on the basis of death certificates. The median overall survival duration in the remaining 35,097 cases was 75 months. When we examined survival by histologic grade (Fig 2A), we found that the median survival duration in patients with G1 and G2 NETs was 124 and 64 months, respectively. Patients with G3 and G4 tumors had identical survival curves; the median survival duration in these patients was 10 months. Among cases where histologic grade was not explicitly stated, those with ICD-O-3–designated neuroendocrine histology and those with G3 or G4 tumors had identical survival curves; the median survival duration in these patients was 10 months. The survival curves for those with ICD-O-3–designated carcinoid or islet cell histology but an unspecified tumor grade were similar to those for patients with G1 tumors; the median survival duration in these patients was 129 months. The difference in survival duration between the patients with G1, G2, and G3/G4 NETs was statistically significant ($P < .001$).

Survival for G1/G2 tumors. We found several factors, including disease stage ($P < .001$), to be predictors of outcome. The median survival durations in patients with G1/G2 NETs who had localized, regional, and distant disease was 223 months, 111 months, and 33 months, respectively (Fig 2B). We then examined potential prognostic factors for survival duration stratified by disease stage and found the primary tumor site to be a powerful predictor of survival duration ($P < .001$). The median survival durations among patients with localized NETs varied from greater than 360 months (appendiceal tumors) to 111 months (jejunal/ileal tumors) to 50 months (liver tumors). Among patients with regional NETs, the median survival durations varied from 360 months (appendiceal tumors) to 36 months (colon tumors [excluding cecal and rectal tumors]) to 14 months (liver tumors). In addition, among patients with metastasis, the median survival durations varied from 56 months (jejunal/ileal tumors) to 5 months (colon tumors [excluding cecal and rectal tumors]). Details regarding the results of these analyses by primary tumor site are presented in Figure 3A.

Another significant predictor of outcome was histopathology. In addition to tumor grade, the presence of adenocarcinoma features in mixed-histology NETs has been thought to portend a poor prognosis. We compared the survival durations in patients with G1, G2, and mixed-histology NETs stratified by disease stage. Those with G1 tumors had the best outcomes in all stage groups ($P < .001$; Fig 3B). Interestingly, patients with local/regional mixed-histology tumors had better outcomes than did those with G2 NETs. However, among patients with metastatic disease, those with mixed-histology tumors had worse outcomes than did those with G2 NETs.

Age at diagnosis ($P < .001$; Fig 3C), sex ($P < .001$; Fig 3D), and race ($P < .001$; Fig 3E) were also prognostic of survival. Women had better survival durations than men did in all stage categories. Also, Asian/Pacific Islander and American Indian/Alaskan Native patients had the best survival durations among patients with localized disease (median survival duration not reached), whereas white patients had the best survival durations among patients with metastatic disease. We also examined the effect of age at diagnosis on survival by separating the patients into three groups (≤ 30, 31 to 60, and > 60 years). We found age to be a strong predictor of survival duration ($P < .001$; Fig 3C).

Next, we sought to determine whether the survival durations improved in patients with NETs over time. Because the somatostatin analog octreotide was the only new drug introduced for use against NETs during this period (in 1987), we compared the survival durations in patients who received diagnoses from 1973 to 1987 with those who received diagnoses from 1988 to 2004 (Fig 3G). Although the survival durations did not improve significantly among patients with localized NETs (hazard ratio [HR] = 0.96; 95% CI, 0.87 to 1.06; $P = .43$) or regional NETs (HR = 0.91; 95% CI, 0.82 to 1.01; $P = .08$), they improved dramatically among patients with metastatic disease (HR = 0.67; 95% CI, 0.62 to 0.73; $P < .001$).

Finally, we performed multivariate survival analysis of G1/G2 NETs using the Cox proportional hazards model. We included potentially prognostic parameters such as disease stage, primary tumor site, histology, age, sex, race, and period of diagnosis (1973 to 1987 and 1988 to 2004) in this model. We found that all of the parameters that were significant in the univariate analysis were also significant in the multivariate analysis (Table 3).

Survival for G3/G4 tumors. Poorly differentiated NETs, which are also known as high-grade NETs, are aggressive and associated with poor survival. We analyzed the survival of 4,054 patients with G3/G4 NETs in the SEER registries (1973 to 2004). The median survival durations in patients with localized, regional, and distant disease were 34 months (95% CI, 27 to 41 months), 14 months (95% CI, 13 to 15 months), and 5 months (95% CI, 4.5 to 5.5 months), respectively (Fig 2C).

DISCUSSION

In this study, we took advantage of the vast amount of data collected by the SEER Program to examine the largest series of NET cases reported to date with a focus on incidence, prevalence, and prognostic factors. Similar to those of previous reports,[3] our results indicated a significant increase in the reported incidence of NETs over time. This increase was likely caused in part by improvements in classification of these tumors. Also, widespread use of endoscopy for cancer screening likely contributed to the increase in reported incidence of rectal carcinoid NETs. Whether changes in dietary habits, environmental factors, and use of certain medications such as proton pump inhibitors resulted in increased reported incidence of NETs of various types is unknown.

Prevalence of a disease is defined as the number of people alive on a certain date in a population who have never had a diagnosis of that disease. In our study, we used the counting method[8-10] to estimate prevalence from incidence and follow-up data. Complete prevalence can be determined using this method with registries containing data obtained over long periods of time. Given the long survival durations

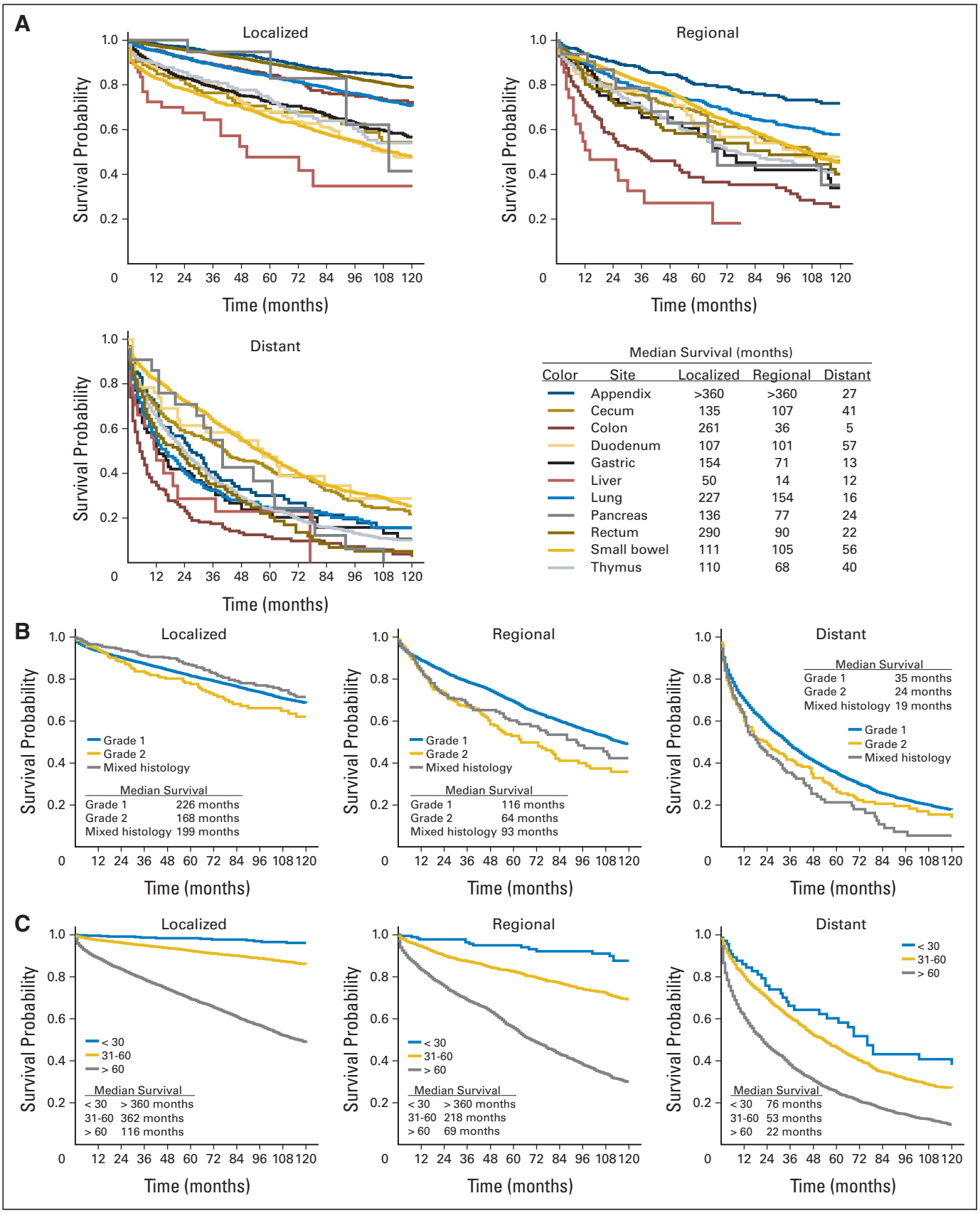


Fig 3. (A) Survival duration by primary tumor site. Neuroendocrine tumor cases identified at autopsy or solely on the basis of death certificates were excluded, as were those with missing site and/or stage data. Median survival durations are presented in months. (B) Survival duration by histology. G1 tumors had the best outcome in all staging groups ($P < .001$).

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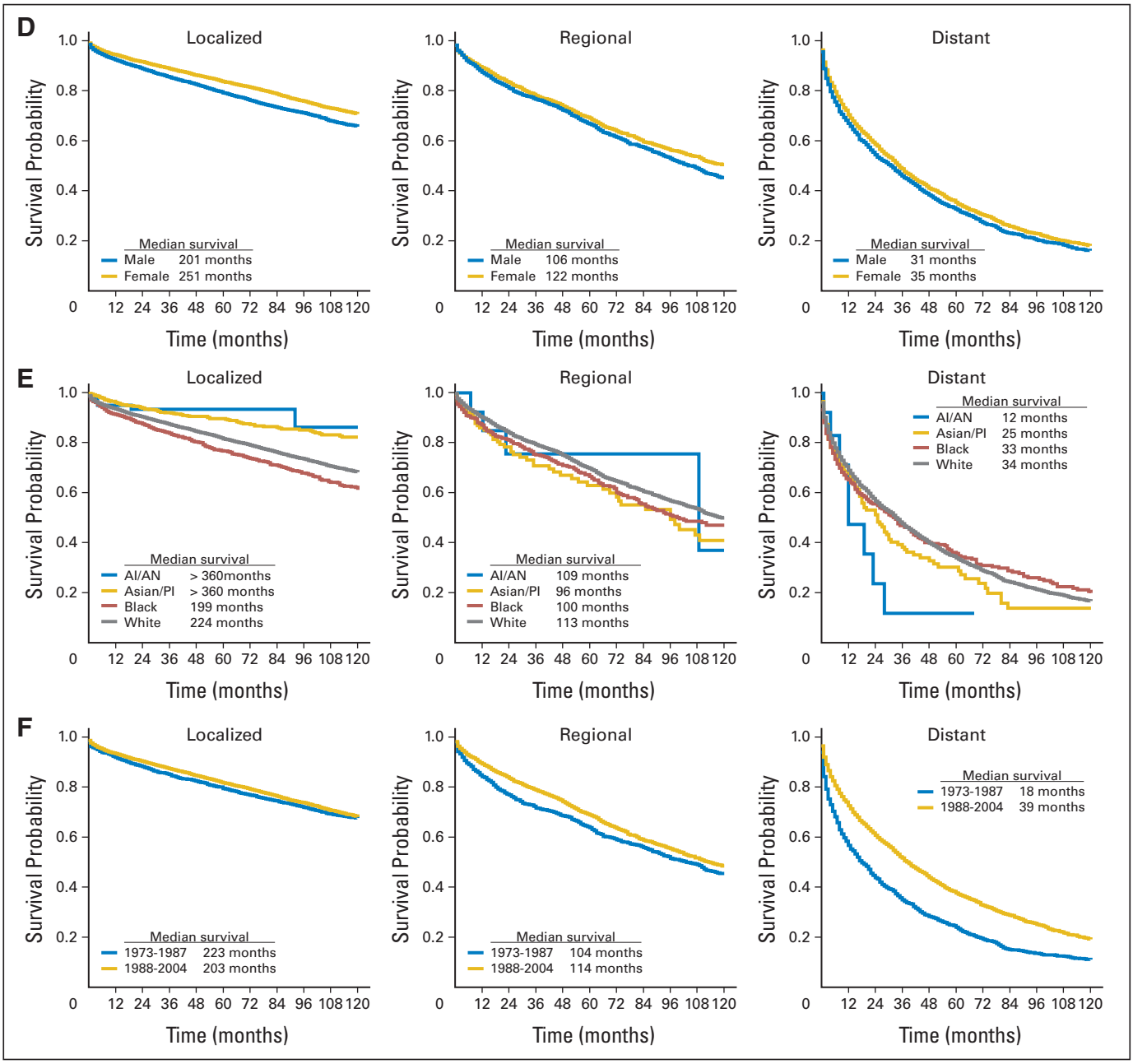

Fig 3 (Continued). (C) Survival duration by age at diagnosis. Patients were separated into three groups according to their age at diagnosis (≤ 30, 31 to 60, and > 60 years). Age was found to be a strong predictor of outcome ($P < .001$). (D) Survival duration by sex. Women had statistically significantly longer survival durations over all three categories histologies ($P < .001$). (E) Survival duration by race. Patients were separated into four categories on the basis of race (American Indian/Alaskan Native [AI/AN], Asian/Pacific Islander [Asian/PI], African American, and white). American Indian/Alaskan Native and Asian/Pacific Islander patients had the longest survival durations for localized tumors, whereas white patients had the longest survival durations for metastatic disease. (F) Survival duration by period of diagnosis. Patients were separated into two groups by year of diagnosis (1973 to 1987 and 1988 to 2004). Patients with metastatic disease had an improvement in median survival duration ($P < .001$; from 8 to 39 months). There were no significant improvements in survival duration among patients with localized or regional disease. Each set of three graphs shows localized, regional, and distant survival from left to right.

often experienced by patients with NETs, we report here only 29-year limited-duration prevalence, which estimates the number of people alive on January 1, 2004, who were diagnosed with NET during the preceding 29 years. Clearly, however, NETs are more common than generally believed. For example, when compared with other GI neoplasms, the estimated 29-year limited-duration prevalence of NETs of 103,312 in 2004 makes these tumors significantly more common than esophageal cancer (28,664), gastric cancer (65,836), pancreatic cancer (32,353), and hepatobiliary cancer (21,427) in the United States.[11]

Using multivariate survival analysis, we found that disease stage, primary tumor site, histology, age, sex, race, and period of diagnosis (1973 to 1987 and 1988 to 2004) were important predictors of outcome. We found the primary tumor site to be perhaps the most useful

Table 3. Survival Analysis of Patients with Well-Differentiated to Moderately Differentiated NETs: Univariate and Multivariate Cox Proportional Hazards Analysis of G1/G2 NETs Diagnosed From 1973 to 2004

		Univariate		Multivariate		
Parameter	Median Survival (months)	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Multivariate *P*
Disease stage						
Localized	223	1*	—	1*	—	< .001
Regional	111	1.89	1.79 to 2.01	1.60	1.50 to 1.71	
Distant	33	4.93	4.68 to 5.21	3.85	3.60 to 4.11	
Primary tumor site						
Jejunum/ileum	88	1*	—	1*	—	< .001
Lung	193	0.53	0.50 to 0.57	1.01	0.93 to 1.08	
Thymus	77	1.12	0.82 to 1.53	1.47	1.06 to 2.03	
Stomach	124	0.83	0.75 to 0.91	1.54	1.38 to 1.73	
Duodenum	99	0.89	0.78 to 0.99	1.42	1.24 to 1.62	
Cecum	83	1.16	1.05 to 1.29	1.06	0.96 to 1.18	
Appendix	NR	0.33	0.29 to 0.37	0.66	0.57 to 0.76	
Colon	121	0.93	0.84 to 1.03	1.54	1.38 to 1.71	
Rectum	240	0.32	0.29 to 0.34	0.74	0.67 to 0.82	
Pancreas	42	1.65	1.53 to 1.78	1.65	1.53 to 1.79	
Liver	23	2.20	1.76 to 2.75	2.92	2.25 to 3.79	
Histology						
Well-differentiated	134	1*	—	1*	—	< .001
Moderately differentiated	64	1.67	1.53 to 1.82	1.26	1.15 to 1.40	
Mixed	135	1.02	0.92 to 1.14	1.65	1.45 to 1.88	
Sex						
Female	145	1*	—	1*	—	< .001
Male	114	1.21	1.16 to 1.26	1.20	1.14 to 1.25	
Race						
White	126	1*	—	1*	—	< .001
AI/AN	NR	0.56	0.36 to 0.87	0.79	0.50 to 1.26	
Asian/P Islander	204	0.65	0.58 to 0.72	0.94 (0.83 to 1.07)		
African American	117	1.04	0.98 to 1.10	1.28	1.19 to 1.37	
Age, years						
≤ 30	NR	1*	—	1*	—	< .001
31-60	247	3.31	2.74 to 4.00	3.03	2.41 to 3.81	
≥ 61	71	10.08	8.36 to 12.15	9.23	7.34 to 11.61	
Year of diagnosis						
1973-1987	95	1*	—	1*	—	< .001
1988-2004	138	0.75	0.72 to 0.79	0.73	0.69 to 0.77	

Abbreviations: NET, neuroendocrine tumor; NR, not reached; AI/AN, American Indian/Alaskan Native; P Islander, Pacific Islander.
*Referent.

predictor of outcome in patients with NETs. Using the primary tumor site as a prognostic marker, we were better able to separate outcomes into categories. We therefore included a table of survival duration by primary tumor site and disease stage for patients who received diagnoses from 1988 to 2004 as a practical guide for clinicians in Table 4.

In our analyses, we did not observe a statistically significant difference in survival duration among patients with local and regional NETs over time. However, we observed a dramatic improvement in survival duration among patients with metastatic NETs diagnosed in the later period (1988 to 2004). One possible explanation is that the introduction of octreotide in 1987 improved the control of carcinoid syndrome and changed the natural history of NETs. For example, carcinoid crisis with severe flushing, diarrhea, and hemodynamic instability, which was a major cause of morbidity and mortality in the past, now occurs rarely. Organ failure, which tends to occur later in the course of illness, is now the major cause of mortality. Whereas many researchers have speculated that octreotide has a disease-stabilizing effect in patients with NETs,[12-14] conclusive data from randomized human studies are lacking.

We acknowledge that our analysis of data obtained from the SEER registries likely underestimated the total number of patients with NETs. Only patients with malignant NETs are included in the SEER registries. Thus, data on many small, benign-appearing tumors (ie, appendiceal tumors) likely are excluded from the registries. Whereas histologic evidence of invasion of a basement membrane defines malignant behavior for most epithelial malignancies, the definition of malignant behavior for NETs is more complex. In the absence of obvious malignant behavior, such as direct invasion of adjacent organs and metastasis to regional lymph nodes or distant sites, classifying a NET as benign or malignant may be difficult. Thus, whereas SEER registry data provide important information about malignant NETs, the extent to which these data underestimate the frequency of small, benign-appearing NETs is unknown.

Table 4. Survival Analysis of Patients with Well-Differentiated to Moderately Differentiated NETs: Actuarial Survival by Disease Stage and Primary Tumor Site in Patients With G1/G2 NETs Diagnosed From 1988 to 2004

Primary Tumor Site	Localized				Regional				Distant			
	Median Survival (months)	Survival Rate (%)			Median Survival (months)	Survival Rate (%)			Median Survival (months)	Survival Rate (%)		
		3-Year	5-Year	10-Year		3-Year	5-Year	10-Year		3-Year	5-Year	10-Year
Thymus	92	93	93	52	68	78	65	49	40	62	32	0
Lung	NR	89	84	70	151	77	72	56	17	34	27	15
Pancreas	NR	83	79	58	111	73	62	46	27	42	27	11
Liver	47	64	43	—	14	32	27	—	12	34	26	0
Gastric	163	80	73	56	76	75	65	43	13	33	25	9
Duodenum	112	80	68	48	69	75	55	44	57	60	46	27
Jejunum/ileum	115	73	65	49	107	83	71	46	65	70	54	30
Cecum	135	74	68	55	107	78	71	44	55	61	48	23
Colon	NR	90	85	74	52	60	46	33	7	20	14	6
Rectum	NR	94	90	80	90	74	62	47	26	37	24	3
Appendix	NR	93	88	72	NR	86	78	67	31	42	25	11

Abbreviations: NET, neuroendocrine tumor; NR, not reached.

At present, surgery is the only curative treatment for NETs, and is recommended for most patients for whom cross-sectional imaging suggests that complete resection is possible.[15,16] Although NETs generally have a better prognosis than adenocarcinomas at the same site, NETs are incurable once they advance to unresectable metastatic disease. New therapeutic approaches for NETs, such as peptide receptor radiotherapy and systemic agents targeting vascular endothelial growth factor and mammalian target of rapamycin, are under development.[17]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: James C. Yao
Financial support: James C. Yao
Administrative support: James C. Yao
Collection and assembly of data: James C. Yao, Cecile Dagohoy, Jeannette E. Mares
Data analysis and interpretation: James C. Yao, Manal Hassan, Alexandria Phan, Colleen Leary, Jean-Nicolas Vauthey, Asif Rashid, Douglas B. Evans
Manuscript writing: James C. Yao, Asif Rashid, Douglas B. Evans
Final approval of manuscript: James C. Yao, Jeannette Mares, Eddie K. Abdalla, Jason B. Fleming, Douglas B. Evans

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