

A Three-Decade Analysis of 3,911 Small Intestinal Neuroendocrine Tumors: The Rapid Pace of No Progress

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- OBJECTIVES:** Small intestinal neuroendocrine tumors (SI-NETs) are the most common gastrointestinal neuroendocrine tumor, but their natural history and outcome remain poorly defined, which hinders both the prediction of disease progression and appropriate therapeutic options. We examined patterns, incidence, prognosis, and outcomes of these tumors over a 30-yr period.
- METHODS:** Data were extracted from the NCI's SEER registry (1973–2002). Incidence rates, distribution, and 5-yr survival rates were analyzed and adjusted (U.S. decennial census data).
- RESULTS:** Of the 18,641 NETs, 3,911 (21.0%) were SI-NETs, of which 1,953 (49.6%) were ileal. Since 1973, both SI-NET and its ileal variant have increased annually by 3.8% and 2.1%, respectively. Ileal tumors, as a percentage of SI tumors, have increased from 52% to 63.6%. The age-adjusted incidence of ileal, small intestinal, and digestive system NETs has increased 225%, 460%, and 720% over 30 yr. Ileal tumors have specifically increased in prevalence in white (274%) and black (500%) men and women (213% and 286%, respectively); an overall increase of fourfold in blacks and 2.4-fold in whites. Although 83.3% of SI-NETs were staged, 83.7% were histologically ungraded. Five-year survival rates for SI-NETs were $62.6 \pm 1\%$ (all stages), 73.8% (localized), 72% (regional), and 43.2% (distant). These have not significantly altered since 1973 ($P = 0.11$).
- CONCLUSIONS:** SI-NETs have increased, particularly in men and in the black population, which may be due to *in vivo* changes, increased clinical and pathological awareness, or increased detection of tumors. SI-NETs are malignant, diagnosed late, and survival rates have remained unchanged over 30 yr.

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INTRODUCTION

Although carcinoids were formerly considered rare tumors, an increased clinical and pathological focus as well as the advent of biochemical and immunohistochemical diagnostic technology has led to a greater awareness of the disease (1). More recently, it has become apparent that the term “carcinoid” is archaic and refers to a heterogeneous group of neoplasms that are better classified as gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) (1).

Although NETs were described in 1888 by Lubarsch, he failed to recognize their unique nature, and in 1907, Oberndorfer (2) defined the neoplasm as *karzinoide* (carcinoma-like), opining that they were benign. In the century since this original observation, the neuroendocrine background of carcinoids has been established and their cell of origin, receptor and secretory profile, functional regulation, and transcriptome have been delineated (3–5). Although NETs can arise almost anywhere within the gastrointestinal (GI) tract, they are commonest in the ileum and the appendix (6). Of particular significance is the observation that GEP-NETs appear

to exhibit very different prognoses depending upon their site and presumably their cell of origin (6–8).

In general, NETs arise from the “diffuse” neuroendocrine system initially proposed by Feyrter (9), and therefore can occur in the bronchopulmonary system as well as the gut. The small intestine and the ileum in particular is the commonest digestive system NET site, comprising 21% of all carcinoids and 38% of GI-NETs (6). The clinical relevance of SI-NETs is that their clinical symptomatology (sweating, flushing, diarrhea) is generally not apparent until hepatic metastasis has occurred and the ability of the liver to metabolize the bioactive secretory agents of the lesion exceeded (1). Under rare circumstances, perforation, bleeding, or obstruction of the small intestine may result in an early and acute presentation, often presaging a more favorable outcome (1). SI-NETs are thus rarely diagnosed early, usually have regional or metastatic disease on presentation, and may present with vascular or bowel obstruction or even right-sided cardiac fibrosis (1).

The ability of clinicians to predict the progression of SI-NETs and define rational management strategies is limited.

An exploration of the epidemiology of SI-NETs therefore is of considerable importance in allowing an appreciation of the natural history of the disease and the “effects” of therapy on outcome. The purpose of our investigation was to describe the patterns and time trends for SI-NETs with the intent of establishing an appreciation of incidence, prognosis, and outcome. To establish this information, we have utilized the current epidemiological data available from the Surveillance, Epidemiology, and End Results (SEER) cancer registry program (1973–2002) (10).

METHODS AND MATERIALS

Data were extracted from the SEER program, compiled by the National Cancer Institute (NCI) (10). Established in 1973, the SEER program is a set of 18 geographically defined, population-based, central cancer registries and three supplemental registries in the United States. This program contains information for more than 3 million cases of *in situ* and invasive cancers, with approximately 160,000 new cases added annually. The SEER Program represents approximately 15% of the U.S. population.

The present data were retrieved from the SEER-9 public-use file, which includes population-based data from the original nine registries for the 30-yr time period between 1973 and 2002. Other registries, such as the SEER-11, -12, and -13 registries, were excluded so that time-trend data could be consistently evaluated. All subtypes of NET histology were included as described by the *International Classification of Disease for Oncology* (including 8,240–8,246, 8,249) (11). Information regarding the incidence, prevalence, and distribution of all NETs and specifically those arising within the small intestine were analyzed. Particular emphasis was placed on differentiating incidence from prevalence. Incidences based on site, male-to-female ratio, and ethnicity were calculated and

were age-adjusted using the U.S. decennial census data (12). Time trends were evaluated by dividing the study period into 5-yr intervals on the basis of year of diagnosis, and were also evaluated by means of a weighted, least-squares method to compute the estimated annual incidence percentage change (EAPC) and percentage change from 1973 to 2002. Histological grade and tumor stage upon diagnosis of the patient were also evaluated and assessed. Overall, 5-yr survival rates were calculated and then grouped by histological grade and tumor stage at presentation (localized, regional, distant, unknown). SI-NETs were examined as a group and the ileal data determined as a subset of this information. SEER*Stat 6.1 was the primary analytic tool utilized for these computations (<http://seer.cancer.gov/ScientificSystems/SEERStat>).

Statistical analyses were undertaken using Prism 4 (GraphPad Software, San Diego, CA) when sample sizes were adequate. These included the 2-tailed Fisher’s test, Kruskal-Wallis test, or χ^2 test. Odds ratios (OR) were calculated and included when appropriate. A $P < 0.05$ was considered significant.

RESULTS

Incidence and Prevalence: Gender, Race, and Time

In total, 18,641 cases of NETs were reported over the 30-yr SEER period (1973–2002). Of these, 55.0% occurred in the digestive system (excluding the oral cavity and pharynx). Specific sites of high distribution included the small intestine (21.0%), colon (11.8%), and rectum (11.7%). An evaluation of trends revealed that the absolute number of diagnosed NETs has increased from 999 cases in 1973–1977 to 6,398 in 1998–2002. Digestive system NETs and SI-NETs have also increased: from 1973 to 1977, 622 and 278 tumors were reported; between 1998 and 2002, 3,555 and 1,112 tumors were reported, respectively (Fig. 1).

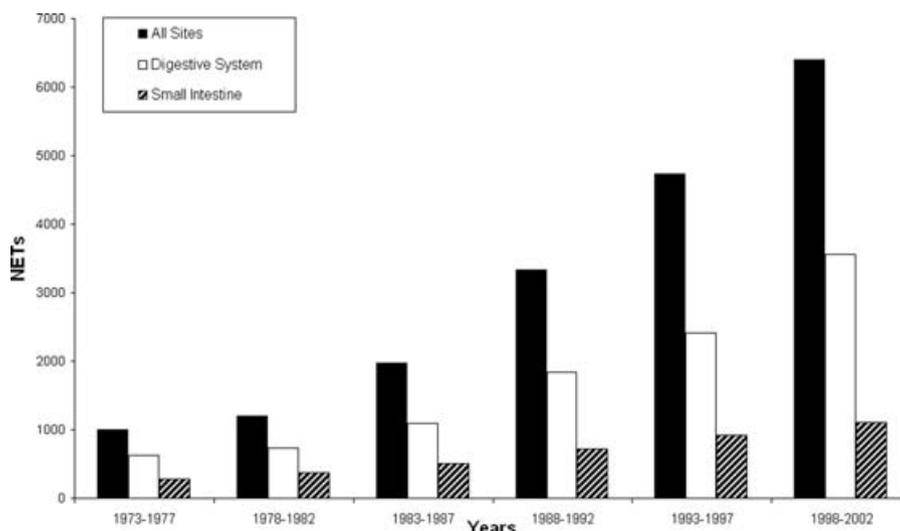


Figure 1. Changes in SI-NET incidence, 1973–2002. The number of NETs at all sites, digestive system, and small intestine has increased over the 30-yr study period.

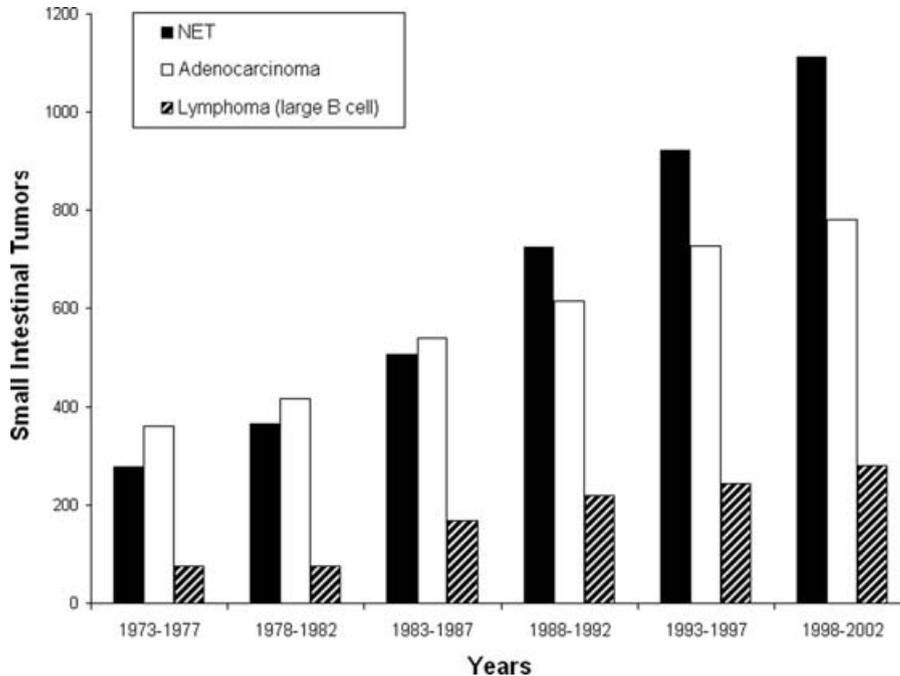


Figure 2. Small intestinal neoplasia incidence, 1973–2002. Over the 30-yr study period, the number and percentage of SI-NETs, adenocarcinomas, and lymphomas have all increased. Proportionately, NETs have increased to the greatest extent.

During the study period, 11,194 cases of small intestinal cancer were reported. The majority of these tumors were malignant NETs (34.9%) and adenocarcinomas (31.1%). Over time, SI-NETs, as a percentage of all tumors in the small intestine, have increased from 27.2% (1973–1977) to 38.6% (1998–2002), whereas adenocarcinomas have decreased from 35.3% (1973–1977) to 27.1% (1998–2002) (Fig. 2). The alterations in tumor type are statistically significant ($P < 0.0001$, 2-tailed χ^2 test).

The majority of NETs occurred in the ileum (49.9%) (Table 1). These have increased from 52% (1973–1977) to 63.6% (1998–2002), while adenocarcinomas have decreased from 18.6% (1973–1977) to 12.2% (1998–2002) at this site ($P = 0.0007$, OR 0.54, 2-tailed χ^2 test).

We next examined the yearly age-adjusted incidence based on site. The age-adjusted incidence for all NETs has increased more than sixfold, from 0.85 in 1973 to 5.4 in 2002. For the same time period, there was a more than fourfold increase

in incidence in SI-NETs (from 0.2 to 0.9), and a twofold increase in ileal NETs (from 0.2 to 0.4). The annual incidence rate of NETs has increased in all sites, 6.3% ($P < 0.05$); SI-NETs, 3.8% ($P < 0.05$); and ileal NETs, 2.1% ($P < 0.05$). The percent increase in incidence over 30 yr was: NETs at all sites (533%), digestive system (626%), small intestine (353%), and ileum (134%) ($P < 0.05$).

For all sites and across the population, the NET incidence was 3.0 per 100,000 population. Evaluation of NET age-adjusted incidence by site, ethnicity, and gender is shown in Table 2. Of the 18,641 NETs, 8,825 (47.4%) were in men and 9,816 (52.6%) in women. When male:female ratios were adjusted to population ratios from the U.S. Census, there was an almost equal distribution in men and women at all sites in 1998–2002 (ratio 0.99). These ratios, however, have changed over time; there was a higher prevalence of NETs in women in 1973–1977 across all sites, the digestive system, small intestine, and the ileum with male:female ratios of 0.71, 0.71, 0.93,

Table 1. NETs of the Small Intestine (SEER-9 Registry 1973–2002)

Site	1973–1977		1978–1982		1983–1987		1988–1992		1993–1997		1998–2002		Total Period 1973–2002	
	No. of Patients	%	No. of Patients	%										
Small intestine	278	—	367	—	508	—	725	—	921	—	1,112	—	3,911	—
Duodenum	10	3.6%	10	2.7%	37	7.3%	80	11.0%	132	14.3%	178	16.0%	447	11.4%
Jejunum	20	7.2%	29	7.9%	38	7.5%	54	7.4%	53	5.8%	52	4.7%	246	6.3%
Ileum	196	70.5%	224	61.0%	262	51.6%	357	49.2%	424	46.0%	490	44.1%	1,953	49.9%
Meckel's diverticulum	0	—	4	1.1%	10	2.0%	13	1.8%	18	2.0%	25	2.2%	70	1.8%
Overlapping lesions (ileocecum)	3	1.1%	2	0.5%	2	0.4%	10	1.4%	9	1.0%	17	1.5%	43	1.1%
Small intestine, NOS	49	17.6%	98	26.7%	159	31.3%	211	29.1%	285	30.9%	350	31.5%	1,152	29.5%

NOS = not otherwise specified.

Table 2. Incidence of NETs by Site, Sex, and Ethnicity (SEER-9 Registry 1973–2002)

Site	All Races			White			Black			Other		
	Male and Female	Male	Female									
All sites	2.97	3.2	2.83	2.91	3.12	2.81	4.1	4.51	3.81	2.05	2.39	1.76
Digestive system	1.63	1.5	1.51	1.51	1.65	1.41	2.95	3.46	2.59	1.44	1.72	1.19
Small intestine	0.63	0.75	0.54	0.62	0.74	0.53	1.07	1.41	0.84	0.2	0.24	0.17
Duodenum	0.07	0.09	0.06	0.05	0.06	0.04	0.3	0.42	0.21	0.08	0.09	0.07
Jejunum	0.04	0.05	0.03	0.04	0.06	0.03	0.05	0.06	0.04	0.01	0.02	0
Ileum	0.31	0.36	0.28	0.33	0.37	0.29	0.36	0.48	0.28	0.06	0.07	0.06
Meckel's diverticulum	0.01	0.02	0.01	0.01	0.02	0.01	0.01	0.01	0	0	0	0
Overlapping lesions (ileocecum)	0.01	0.01	0.01	0.01	0.01	0	0.02	0.01	0.02	0.01	0	0.01
Small intestine, NOS	0.19	0.23	0.16	0.18	0.22	0.15	0.34	0.42	0.28	0.04	0.05	0.02

Rates are per 100,000 and age-adjusted to the 2000 U.S. Census population.

and 0.88, respectively, which increased to 0.99, 1.05, 1.13, and 1.18 in 1998–2002. Similar trends were also observed in white, black, and other (Latin, Asian, Native American) ethnicity groups. The most striking alteration in the male:female ratio occurred in the ileal NETs of the black population, where the male:female ratio of 0.6 in 1973–1977 increased to 2.4 in 1988–1992. Gender differences were statistically significant in the digestive system carcinoids ($P < 0.0001$, OR 0.66, 2-tailed χ^2 test), and almost attained significance in small intestinal ($P = 0.056$, Kruskal-Wallis test) and ileal ($P = 0.07$, OR 0.74, 2-tailed Fisher's test) NETs. This indicates that the number of tumors has increased in men.

Comparing NETs between the different ethnic groups revealed higher prevalence among the black population. A total of 15,496 of the 18,641 cases occurred in the white population, compared with 2,082 cases in the black population. These values yielded a "crude" white:black ratio of 7.4. Upon scaling the crude ratio with population ratios of the U.S. Census (12), there was a lower prevalence from 1973 to 2002 in the white population compared with blacks in all sites (white:black ratio of 0.9) and more notably in the ileum (0.7), but the prevalence was similar in the small intestine (1.07). These differences were significant, with the black population displaying an increase in digestive system NETs between 1973 and 1977 and 1998 and 2002 ($P < 0.002$, OR 0.53, 2-tailed Fisher's test).

Further examination demonstrated that blacks had an incidence of 4.1/100,000, which was 1.4 times greater than whites. The incidence of NETs in the digestive system was almost double in the black population (3.0/100,000) compared with whites (1.5). The incidence within the small intestine was 0.6, the highest within the digestive system, and of the sites within the small intestine, the highest incidence of NET was the ileum (0.3), with similar incidence values between blacks (0.36) and whites (0.33) and a higher incidence among both white (0.37) and black (0.48) men compared with women (0.29 and 0.28, respectively).

In addition, there was a 6.6- and fourfold increase in small intestinal and ileal NET cases in the black population from 1973–1977 to 1998–2002, and over the same time, a 3.7-

and 2.4-fold increase in the white population (Fig. 3). Over this time period, there was an increase in carcinoid prevalence in the white population at all sites, from a black:white ratio of 0.6 in 1973–1977 to 0.9 in 1998–2002. A similar trend was seen in the digestive system (0.6 in 1973–1977, 1.26 in 1998–2002) and the ileum (0.4 in 1973–1977, 0.6 in 1998–2002).

Tumor Staging and Histological Grade

The distribution of the SEER data by site and stage was examined to evaluate the propensity of individual sites of NETs to develop *in situ*, regional, or distant metastases (Table 3). Regional spread was classified as direct transmural extension and regional lymph node involvement, and distant spread was classified as disease spread to distant lymph nodes and/or distant organs such as the liver. Localized staging was identified in 44.2% of NETs (all sites), 45.4% (digestive system), 31.3% (small intestine), and 22.5% (ileum) (Table 3). In both the small intestine and ileum, the majority of NETs were nonlocalized (64.4% and 75.3%, respectively). In contrast, gastric, appendiceal, and colon/rectal NETs were mostly localized at presentation (61.3%, 60.5%, and 59.8%, respectively). Of all NETs evaluated, 14.7% were unstaged, whereas only 4.3% of small intestinal and 2.2% of ileal NETs were unstaged.

Evaluation of histological grading of NETs at diagnosis revealed that a substantial percentage of tumors remained ungraded (83.7%) ($P < 0.0001$, Fisher's test), hence histological assessment cannot be adequately assessed as a predictive outcome or progression parameter in the SEER database. In the digestive system, small intestine, and ileum, NETs were ungraded in 88.1%, 92.4%, and 93.2%, respectively. Of the NETs that were graded in the small intestine, 4.2% of tumors were well differentiated (grade I), 2.2% were moderately differentiated (grade II), 1% were poorly differentiated (grade III), and 0.3% were undifferentiated (grade IV). In the ileum, 4.1% were well differentiated, 1.84% moderately differentiated, 0.72% poorly differentiated, and 0.2% undifferentiated.

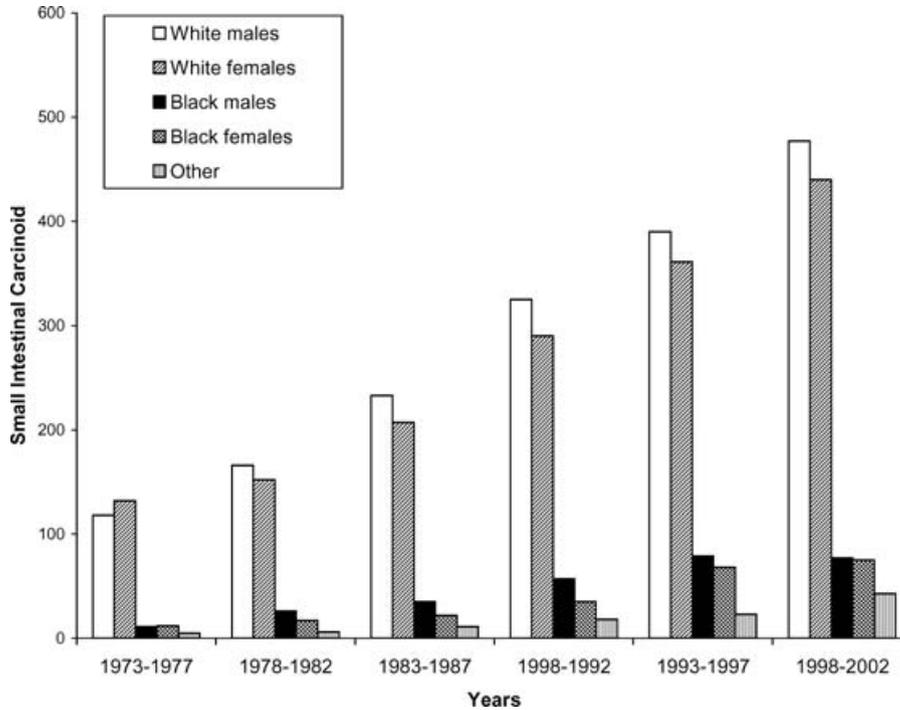


Figure 3. Alterations in SI-NET prevalence based on ethnicity, 1973–2002. The number of NETs has increased in all ethnicities. The black and white population exhibited a 6.6-fold and 3.6-fold increase throughout the study period, respectively.

Five-Year Survival Rates

Five-year survival rates for NETs at all sites (assessed at 5-yr intervals) have decreased from 64.6% in 1973–1977 to 56.9% in 1993–1997 (Fig. 4). In 1973–1977, overall survival rates were: digestive system (59.1%), small intestinal (54.5%), and ileal (55.7%) NETs *versus* 67.0%, 67.8%, and 68.5%, respectively in 1993–1997. When analyzed as a group from 1973–1997, there was no statistically significant difference between the 5-yr intervals ($P = 0.968$). Subanalysis demonstrated that NETs at all sites exhibited a significant decrease in survival ($P < 0.002$, OR 1.25, 2-tailed χ^2 test) between 1973–1977 and 1993–1997. Although digestive system, small intestinal, and ileal NETs trend toward higher survival, these values were not statistically significant between 1973–1977 and 1993–1997 ($P = 0.11$).

The 5-yr survival rates based on site and metastatic dissemination for NETs (all sites, digestive system, and small intestinal) were calculated. The observed 5-yr survival rate for NETs in all sites (and all stages) was $58.6 \pm 0.4\%$, with the highest 5-yr survival rate for localized disease (81.9%), and worse prognoses for regional (60.4%) or distant (22.5%) spread ($P < 0.0001$, Kruskal-Wallis test).

The overall 5-yr survival rate for SI-NETs ($62.6 \pm 1\%$) was lower but not significantly different from other digestive system NETs ($64.8 \pm 0.6\%$). This lower trend was also reflected in survival for localized disease (83.9% *vs* 73.8%, $P < 0.0001$, OR 2.06, 2-tailed Fisher's test). Small intestinal and ileal NETs had similar regional (72.0% and 72.3%) and distant (43.2% and 46.4%) 5-yr survivals. Significant differences in survival were noted for localized *versus* distant

disease ($P < 0.001$, 2-tailed Fisher's test) in small intestinal and ileal NETs.

We next evaluated whether histological grading had an impact on 5-yr survival rate. Because a substantial percentage of NETs are ungraded ($>84\%$), a rigorous statistical analysis cannot be undertaken with confidence. With this caveat, for NETs at all sites, well-differentiated grade I tumors have a higher observed 5-yr survival rate ($66.8 \pm 2.2\%$) than those with grade II (moderately differentiated) tumors ($54.5 \pm 2.9\%$), grade III (poorly differentiated) tumors ($17.7 \pm 1.4\%$), or grade IV (undifferentiated) tumors ($21.4 \pm 1.9\%$) (Fig. 5). A similar pattern was observed in digestive system NETs and SI-NETs, both of which decreased with increasing histological grade (grade I, $68.4 \pm 2.9\%$, $70.9 \pm 4.5\%$, Grade II $52.2 \pm 4.1\%$ and $62.4 \pm 7.5\%$, grade III $17 \pm 1.4\%$ and $27.3 \pm 9.7\%$, grade IV $14.3 \pm 3.6\%$ and $28.6 \pm 17.1\%$). The overall 5-yr survival for ileal NETs was $64.1 \pm 1.4\%$ (*vs* $62.6 \pm 1\%$: small intestine). The survival rate for grade I ileal tumors was 72.2%, grade II 51.6%, grade III 21.4%, and grade IV 50.0%.

An analysis of the data combining staging and histology revealed that a less advanced histological grade and lower tumor stage was associated with better 5-yr survival. For all NETs, including those within the digestive system and small intestine, the best prognosis was for localized grade I (well differentiated) tumors (76.2–84.2% 5-yr survival), and the worst prognosis was for grade III (poorly differentiated) tumors with distant metastases (2.3–14.7% 5-yr survival) (Table 4). As noted, the small sample numbers preclude robust statistical analyses, but they are consistent with predicted

Table 3. Different Stages of NETs by Site (SEER-9 Registry 1973–2002)

Tumor Stage <i>In Situ</i> Site	Localized		Regional		Distant		Unstaged		Total No. of Patients		
	No. of Patients	% of Total Tumors									
All sites	23	0.12%	8,240	44.20%	4,045	21.70%	3,589	19.25%	2,744	14.72%	18,641
Digestive system	19	0.19%	4,657	45.42%	2,401	23.42%	2,377	23.18%	799	7.79%	10,253
Small intestine	2	0.05%	1,224	31.30%	1,444	36.92%	1,074	27.46%	167	4.27%	3,911
Duodenum	2	0.45%	298	66.67%	40	8.95%	45	10.07%	62	13.87%	447
Jejunum	0	—	80	32.52%	94	38.21%	66	26.83%	6	2.44%	246
Ileum	0	—	440	22.53%	875	44.80%	595	30.47%	43	2.20%	1,953
Meckel's diverticulum	0	—	52	74.29%	12	17.14%	3	4.29%	3	4.29%	70
Overlapping lesions	0	—	6	13.95%	20	46.51%	16	37.21%	1	2.33%	43
Small intestine, NOS	0	—	348	30.21%	403	34.98%	349	30.30%	52	4.51%	1,152

NOS = not otherwise specified.

outcome based upon pathological data and suggest that the use of histological grading and local staging is clinically relevant and should be the standard of care to facilitate development of an accurate prognostic index (13–15).

DISCUSSION

This analysis of over 18,640 NET patients over 30 yr with special focus on SI-NETs represents, to date, the largest and most diverse epidemiological study of these tumors. Although the study of NETs has been advanced by novel technologies (1), epidemiological data on SI-NETs are scarce and rely on a few large population-based studies and some smaller institutional series (16–19). Overall evaluation therefore has been limited by divergent denominators and potential referral biases. The SEER data set is the most accurate, standardized, and comprehensive record available for any tumor type and is accepted as an adequate representation of the general population within the United States (20, 21).

The predominant digestive system NET is the SI-NET (38.1%). Earlier studies have reported similar percentages (23–44%) (16, 17, 22). Within the small intestine, malignant NETs constitute 35% of all lesions while in the ileum these tumors constitute 58% of all lesions, data broadly consistent with a large study of small intestinal cancer (1,244 cases) in western Canada in 1993 (23). Over time, small intestinal and ileal NETs, as a percentage of SI tumors, have significantly increased from 27.2% and 52.1% in 1973–1977 to 38.6% and 63.6% in 1998–2002, whereas over the same time period, small intestinal adenocarcinomas have decreased. Other epidemiological studies of small intestinal cancer have reported higher percentages of adenocarcinomas in the small intestine and ileum, ranging from 21% to 40%, but these studies comprised modest sample sizes and are limited to one locality (24–26).

A global assessment of EAPC from the SEER database demonstrates that, with an overall increase in incidence of 3.8% and 2.1% per annum from 1973 to 2002, small intestinal and ileal NETs have increased (+3.5 and +1.4) more than other cancers, such as breast (+1.1%), lung (+0.6%), esophagus (+0.6%), and colon/rectum (–0.6%) (10).

A general advance in diagnostic techniques and awareness of small intestinal neoplasia overall may be reflected in the increase in SI-NET identification. The increase in ileal NETs is currently inexplicable, but is of considerable interest given that the ileum comprises only 23% of the length of the small intestine (23). Other studies have noted this is the site of >75% of all SI-NETs (6). Ileal NETs are the most common malignant neoplasm of the small intestine, and when compared with the duodenum and jejunum, occur 6.5–8.2 times more frequently, exceeding the incidence of ileal adenocarcinomas by more than twofold (6, 23, 25). The reasons for this are unknown but may be related to the specific biology of the enterochromaffin cell in this region.

Gastric and rectal NETs have increased at rates of 9.4% and 11.1% per annum, respectively (27). Both areas

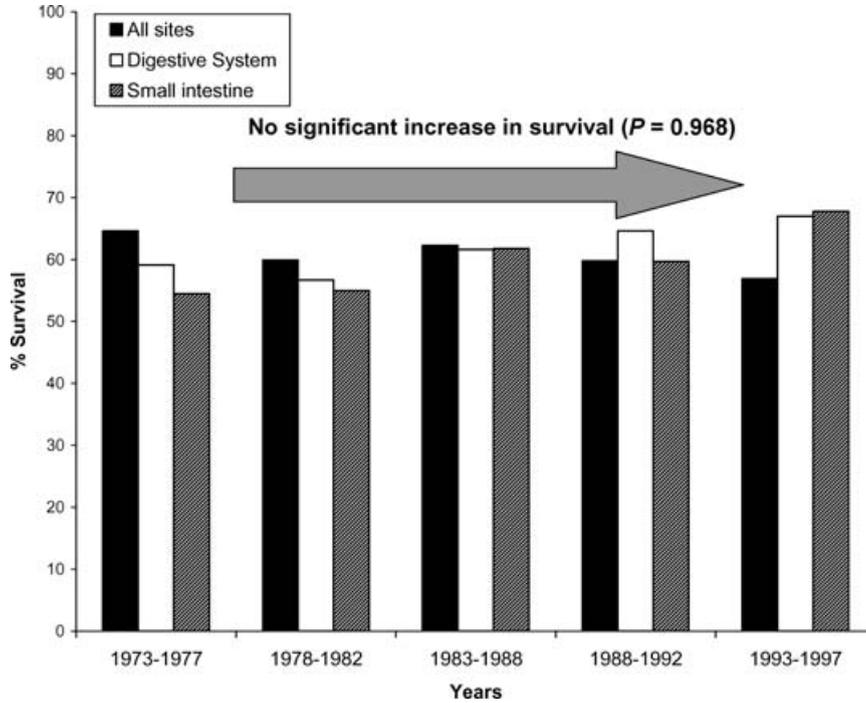


Figure 4. Overall 5-yr survival rates of NETs at all sites, the digestive system, and small intestine (1973–1997). The alterations in 5-yr survival of digestive system and SI-NETs did not attain statistical significance ($P > 0.1$).

are commonly visualized with upper GI endoscopy and colonoscopy, now widely employed to assess symptomatology. It is likely that capsule endoscopy may increase the detection of SI-NETs and result in a better appreciation of their “real” prevalence (28). The problem, however, remains that

diagnostic investigation is usually initiated by symptomatology, and in the vast majority of patients, symptomatology is indicative of metastasis (1).

Racial and gender disparities in NET incidence were notable in this study. Soga reviewed 1,102 jejuno-ileal NETs

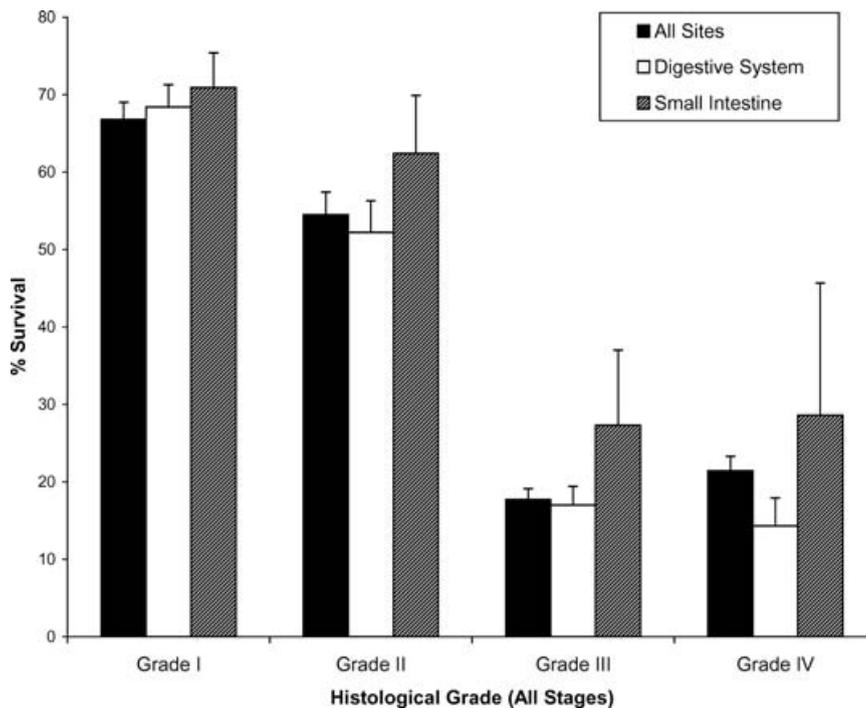


Figure 5. Overall 5-yr survival rates of all stages of NETs: all sites, the digestive system, and small intestine (1973–1997) adjusted to include histological grade. In all groups, the 5-yr survival rate tended to decrease with increasing histological grade.

Table 4. Five-Year Survival Rates of SI-NETs (SEER-9 Registry 1973–2002)

Stage	Histological Grade			
	I	II	III	IV
Localized	76.20%	81.70%	66.70%	50%
Regional	79.60%	49.80%	35.70%	n.d.
Distant	58.60%	59.50%	14.70%	25%

n.d. = insufficient data to calculate survival.

(8), and noted a higher prevalence in men. We, however, observed that the trend between men and women has changed over the years. Between 1972 and 1976, there was greater prevalence of NETs in women, which although considered a true difference, may represent diagnostic bias due to the overall greater appendectomy and laparotomy/laparoscopy rates among women (29).

Currently, the prevalence in men is rising, especially in the black male population, with a seven- and fivefold increase in small intestinal and ileal NETs compared with a three- and twofold increase in white women since 1973. Digestive system NETs also exhibited an 11-fold increase in black men compared with a fourfold increase in white women. The reason for these increases in the black male population is unclear but may represent either a genetic (alterations in chromosomes 18, 5, 16, 9p, and 11q) (30) or a hormonal relationship, as has been defined for gastrin-mediated gastric carcinoid disease (1).

While the current study demonstrates that the highest incidence of NETs occurs in black men, time-trend analyses (1973–1990) by others have also noted an increasing carcinoid incidence in white men (31). Such changes may reflect socioeconomic variables, including better quality medical care and more regular screening in the white population. These gender and racial differences may also be due to variations in occupational or lifestyle factors, such as diet. Although there are some data identifying risk factors associated with NETs, no specific etiologic pattern exists for carcinoids (29, 32).

Of substantial clinical relevance is the observation that at the time of diagnosis, patients with small intestinal and ileal NETs had significant nonlocalized disease (64.4% and 73.2%). This reflects at least two issues: firstly, that SI-NETs are covert unless they have an acute surgical presentation (this occurs in ~11% of cases) (8) and second, the small intestinal EC cell behaves in a more malignant fashion than the gastrin-driven gastric enterochromaffin (ECL) cell (1, 8). The percentage of NETs with evidence of metastasis at presentation was highest in the ileum (30%) compared with NETs at all sites (19%). Saha *et al.*, in a 44-yr study of 112 GI-NETs, reported that 18% of 17 patients with jejuno-ileal NETs died of liver metastases within 8 months of diagnosis (18). In another study (1938–1982), Olney *et al.* observed that 33% of 79 SI-NETs exhibited metastatic disease, and that the greatest frequency of metastasis occurred with primary tumors of the ileum (40%) (33). Similarly, Berge and Linell, in an

autopsy analysis, found that most carcinoid metastases originated from tumors of the small intestine (34). These data emphasize the malignant potential of SI-NETs. This is an important clinical issue because the delay in diagnosis of NETs from first report of symptoms is an average of 7 yr (1).

The prognosis of NETs has changed little over the 30-yr study period. Sixty-seven percent and 75% of small intestinal or ileal NETs present with regional or distant spread and have 43–46% 5-yr survivals. In contrast, 66.7% of duodenal NETs present with localized disease (5-yr survival of 71.5%). Meckel's diverticulum and appendiceal NETs (both 83%, 5-yr survival) (35, 36) support that recognition of symptoms, surveillance by endoscopy, and the ability to detect localized disease are relevant in increasing survival.

Analyzing data by histological grade can be used to predict survival. However, the majority of lesions in the SEER database are ungraded tumors (small intestine 92.4% and ileum 93.2%), making a valid assessment not feasible. Nevertheless, grading and staging when combined appear to provide a more effective measure of patient prognosis than staging alone. A combination of distant disease and a higher grade was generally associated with poor survival (Table 4). While histological grade has been cited as an equivocal measure of clinical outcome (37), a correlation between grade and stage in the current study suggests that this combination may provide a more comprehensive method to predict the clinical behavior of SI-NETs and assess prognosis.

Clinicians can currently, however, only rely on stage as a defining predictive factor for survival. The recently adopted international histological classification with unified criteria for establishing the degree of malignancy will provide useful information in this context (38). It is, however, likely that in the molecular era of genomics and proteomics, a more sophisticated classification system than a purely histologic pattern-based scheme will evolve and previous indicators of prognosis (invasiveness, mitotic rate, etc.) (39, 40) will be replaced by gene expression fingerprints and molecular profiles (41). The World Health Organization (WHO) established updated criteria in 2000 for classification of GEP-NETs (38), but this classification is not widely applied.

In conclusion, the incidence of SI-NETs has increased over the past three decades, both as a site-specific disease process and as a percentage of small intestinal cancers. The results of our study imply that there is a substantial predisposition for digestive system, small intestinal, and ileal NETs in men and the black population. The steady rise in the incidence of NETs in the white male population is also noteworthy, but this may reflect the uneven distribution of health-care delivery. Our evaluation of 3,911 SI-NETs confirms that these lesions display aggressive malignant potential and require attention in terms of improved clinical awareness, more sophisticated diagnosis, and the development of novel therapeutic interventions. It is apparent that clinicians and patients require education with regard to diagnosis of this disease, and early diagnostic tools and therapeutic strategies must be established lest a further 30 years elapse without significant progress.

STUDY HIGHLIGHTS**What Is Current Knowledge**

- Small intestinal neuroendocrine tumors (SI-NETs) are the most common gastrointestinal neuroendocrine tumor.
- Their natural history and outcome remains poorly defined.

What Is New Here

An examination of patterns, incidence, prognosis, and outcomes of these tumors over a 30-year period in the Surveillance, Epidemiology, and End Results (SEER) database indentified:

- Since 1973, both SI-NET and its ileal variant have increased annually by 3.8% and 2.1%, respectively.
- The age-adjusted incidence of ileal, small intestinal, and digestive system NETs has increased 225%, 460%, and 720% respectively over 30 years.
- Ileal tumors have specifically increased in prevalence in white (274%) and black (500%) males and in females (213% and 286%, respectively).
- Five-year survival rates have not significantly altered since 1973.

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CONFLICT OF INTEREST

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