Revised Staging Classification Improves Outcome Prediction for Small Intestinal Neuroendocrine Tumors

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ABSTRACT

Purpose

Small intestinal (SI) neuroendocrine tumors (NETs) have heterogeneous outcomes. The NET societies have recently proposed a TNM staging classification. In this study, we used population-based data to assess the validity of the staging system.

Patients and Methods

We identified patients with SI-NETS diagnosed between 1988 and 2009 from the Surveillance, Epidemiology, and End Results registry. We used Kaplan-Meier analysis to assess disease-specific survival according to TNM status. Cox models were constructed to evaluate differences in prognosis after controlling for potential confounders.

Results

We identified 6,792 patients with SI-NET. Although the current staging system was predictive of prognosis, there was overlap among some groups (stage I/IIA, $P = .36$; stage IIB/IIIB, $P = .70$). Additionally, stage IIIB patients had better survival than stage IIIA patients ($P < .001$). Adjusted analyses showed similar outcomes for T1 versus T2 disease (hazard ratio [HR], 1.02; 95% CI, 0.63 to 1.66). Patients with T3 (HR, 3.60; 95% CI, 2.28 to 5.69) and T4 (HR, 5.50; 95% CI, 3.42 to 8.86) tumors had significantly worse survival than patients with T1 disease. N1 involvement conferred worse survival in T1 (HR, 3.08; 95% CI, 1.75 to 5.44) and T2 disease (HR, 2.73; 95% CI, 1.84 to 4.07) but not in T3 (HR, 0.99; 95% CI, 0.76 to 1.30) or T4 (HR, 0.98; 95% CI, 0.71 to 1.35) disease. A revised classification showed no overlap in survival across groups.

Conclusion

Progressively more advanced T status is associated with worse SI-NET prognosis. Regional lymph node involvement is a marker of worse survival only among patients with T1 or T2 status. These results suggest that revisions to the current staging classification may be helpful.

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INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (NETs) are uncommon but increasingly prevalent neoplasms with variable biologic behavior. Of these NETs, small intestinal NETs (SI-NETs) are the most common, representing the most frequent small bowel neoplasm.¹⁻³ The diagnosed incidence of SI-NETs has tripled over the last three decades, likely from frequent use of abdominal radiologic imaging and endoscopic procedures.^{1,4} The clinical presentation and course can range from asymptomatic incidentally detected, localized lesions to potentially lethal metastatic disease with carcinoid syndrome.

Accurate standardized staging of SI-NET cancers is critical in selecting treatment to optimize outcomes of these patients. Cancer societies have attempted to establish staging criteria; however, these classifications never achieved widespread

acceptance because of their complexity.^{5,6} In 2006, the European Neuroendocrine Tumor Society (ENETS) proposed a TNM staging and grading classification based on expert consensus.^{7,8} Shortly afterward, the American Joint Committee on Cancer (AJCC), WHO, and North American Neuroendocrine Tumor Society published similar guidelines.⁹⁻¹² Although there are minor differences across these classifications, the ENETS and AJCC guidelines are identical for SI-NETs (Data Supplement). The TNM classification has recently been validated for pancreatic NETs in institutional American and European studies. However, the prognostic significance of the system has not been properly validated in SI-NETs, particularly in large population-based samples.¹³⁻¹⁶

We hypothesized that TNM could discriminate patients with different prognoses using a population-based registry. In this study, we used the

National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry to validate the TNM staging system, and we offer a potential revision to predict more accurately the prognosis of patients with SI-NET.

PATIENTS AND METHODS

Study Population

Patients were identified from the SEER database, a national cancer registry that collects information from all incident malignancies in multiple geographic areas of the United States.¹⁷ From the most recent release of SEER, we selected all NETs of the small intestine (site codes: C170 to 173, 178, and 179; histologic codes: 8240 to 8250, 8150 to 8156, and 9091) diagnosed between 1988 and 2009. Adults 18 years of age and older with pathologically confirmed NETs and without a history of other cancers were included in the study. We excluded patients diagnosed at autopsy or on death certificate or cancers with incomplete staging information.

Demographic data such as sex, age, race/ethnicity, and marital status were obtained from SEER. TNM status was assigned according to staging criteria from the North American Neuroendocrine Tumor Society, ENETS, and AJCC. We used SEER data on primary tumor size, depth of invasion, local extension, lymph node involvement, and presence/absence of distant metastases to determine TNM categories. Information about use of surgery was obtained from SEER. Type of surgery was classified into the following groups: partial or total resection (surgical codes 20 to 40); debulking surgery (surgical codes 50 to 60); or resected, not otherwise specified (surgical code 90). Other patients were classified as unresected (surgery codes 0, 10 to 14, and 99).

Survival time was calculated as the period from date of diagnosis until death or last time of follow-up (December 31, 2009). We used disease-specific survival as the main study outcome to evaluate differences in cancer prognosis based on stage. Cause of death was determined using SEER data abstracted from death certificates. Individuals who were alive at last follow-up or who died from non-NET causes were treated as censored observations. This study was exempt from institutional review board review.

Statistical Analysis

We used descriptive statistics to report the basic sociodemographic characteristics of study patients and stage distribution. We first constructed Kaplan-Meier curves to estimate disease-specific survival up to 10 years after diagnosis separately for each T, N, and M category. Follow-up data were reported up to 10 years after diagnosis to assess long-term outcomes of these relatively slowly progressive tumors while avoiding estimating survival curves with a small number of patients; the log-rank test was used to compare survival between groups. Then, we combined these T, N, and M categories and estimated disease-specific survival curves according to stage (I, II, III, and IV). Potential overlaps in outcomes among groups were further investigated by estimating survival for all possible T and N combinations (ie, T1N0M0, T2N0M0, and so on). On the basis of our findings, we devised a revised grouping of T, N, and M categories and assessed disease-specific survival based on this new staging classification. We also conducted these analyses within site strata to assess the performance of the modified classification among jejuno-ileal versus duodenal NETs. We used Cox proportional hazards models to evaluate the association between TNM groups and disease-specific survival after adjusting for age, sex, race, and surgery. To assess the staging system while controlling for the effect of treatment, we conducted secondary analyses limiting the cohort to nonmetastatic patients who underwent surgery. All analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC) using two-sided *P* values.

RESULTS

From SEER, we identified 10,372 patients with small bowel NETs diagnosed after 1988. We excluded 2,420 patients (23%) who had

other primary cancers, 51 patients (< 0.1%) who were not pathologically confirmed, and 1,109 patients (11%) who had incomplete staging information, leaving a final cohort of 6,792 study patients. Demographic characteristics of study patients are listed in Table 1. The mean patient age was 63 years (standard deviation, 17 years), 52% were men, and 74% were white. Overall, 42% of NETs were located in the ileum, 23% in the duodenum, and 6% in the jejunum. According to current staging criteria, 11%, 26%, 49%, and 14% of patients had

Table 1. Demographics and Clinical Characteristics of Study Patients

Characteristic	No. of Patients (N = 6,792)	%
Age, years		
Mean	62.4	
Standard deviation	13.3	
Male	3,554	52.3
Race/ethnicity		
White	5,126	75.5
Black	968	14.2
Hispanic	467	6.9
Other	231	3.4
Marital status		
Single	834	12.3
Married	4,179	61.5
Separated/divorced	590	8.7
Widowed	874	12.9
Unknown	315	4.6
Cancer site		
Duodenum	1,285	18.9
Jejunum	420	6.18
Ileum	3,063	45.1
Meckel's diverticulum	63	0.9
Overlapping lesion of small intestine	89	1.3
Small intestine, NOS	1,872	27.6
T status*		
T1	853	14.9
T2	1,765	30.8
T3	2,129	37.1
T4	991	17.3
N status*		
N0	2,798	48.1
N1	3,017	51.9
M status		
M0	5,815	85.6
M1	977	14.4
Stage based on current ENETS/AJCC system		
I	726	10.7
IIA	1,186	17.5
IIB	596	8.8
IIIA	290	4.3
IIIB	3,017	44.4
IV	977	14.4
Surgery		
Local excision or therapy	837	12.3
Partial/simple resection	3,373	49.7
Total resection	897	13.2
Debulking/radical surgery	900	13.2
No surgery or unknown	785	11.6

Abbreviations: AJCC, American Joint Committee on Cancer; ENETS, European Neuroendocrine Tumor Society; NOS, not otherwise specified.

*T and N status for patients with metastatic disease not reported.

stage I, II, III, and IV disease, respectively. With regard to treatment, 5,264 patients (77%) underwent surgical resection (of these, 81% underwent partial or total resection and 19% underwent debulking surgery). The remainder either underwent local excision or therapy or did not undergo surgical resection. Overall, 91% of patients with nonmetastatic SI-NETs underwent resection.

Kaplan-Meier analysis showed progressively worse disease-specific survival with more advanced T status (T1 to T4; $P < .001$; Fig 1A). Ten-year survival rates were 94% (95% CI, 92% to 96%), 90% (95% CI, 88% to 92%), 78% (95% CI, 75% to 81%), and 67% (95% CI, 62% to 72%) for T1, T2, T3, and T4, respectively. Similarly, patients with N1 (regional) lymph node involvement had worse 10-year survival (77%; 95% CI, 74% to 80%) compared with patients with node-negative, N0 disease (87%; 95% CI, 85% to 89%; $P < .001$; Fig 1B). Presence of distant metastasis (M1 status) was associated with worse 10-year disease-specific survival (M1: 42%; 95% CI, 38% to 46%; M0: 82%; 95% CI, 80% to 84%; $P < .001$; Fig 1C).

Survival curves according to current stage groups are shown in Figure 2. Overall, disease-specific survival was significantly different across stages ($P < .001$). Patients with stage I and IIA cancer had comparable survival (10-year survival: 95%; 95% CI, 93% to 97% ν 93%; 95% CI, 90% to 96%, respectively; $P = .36$). Likewise, survival rates for stage IIB and IIIB were equivalent (10-year survival: 77%; 95% CI, 71% to 83% ν 77%; 95% CI, 74% to 80%, respectively; $P = .70$). Disease-specific survival was worse for stage IIIA (10-year survival: 68%; 95% CI, 59% to 77%) than for stage IIIB (10-year survival: 77%; 95% CI, 74% to 80%; $P < .001$). Stage IV cancers had the worst outcomes (10-year survival: 42%; 95% CI, 38% to 46%).

We also assessed disease-specific survival of SI-NET patients by T and N combinations. These curves showed that the best outcomes were attained by patients with T1N0, T2N0, and T1N1 disease ($P = .65$). These cancers had similar 10-year disease-specific survival rates of 95% (95% CI, 93% to 97%), 93% (95% CI, 90% to 96%), and 90% (95% CI, 80% to 100%), for T1N0, T2N0, and T1N1, respectively. Patients with T2N1 disease had the next best 10-year survival rate of 86% (95% CI, 81% to 91%). Patients with T3N0 disease (10-year survival: 77%; 95% CI, 71% to 83%) and T3N1 disease had similar survival (10-year survival: 78%; 95% CI, 74% to 82%; $P = .34$). Patients with T4N0 and T4N1 disease represented a distinct group with relatively poor outcomes (10-year survival: 68%; 95% CI, 59% to 77% ν 67%; 95% CI, 61% to 73%, respectively; $P = .34$). Patients with M1 disease had the worst 10-year survival of all (42%; 95% CI, 38% to 46%).

Adjusted analyses showed that patients with T2N0 versus T1N0 disease had similar disease-specific survival (hazard ratio [HR], 1.02; 95% CI, 0.63 to 1.66; Table 2). However, patients with T3N0 and T4N0 disease had worse disease-specific survival (T3N0: HR, 3.60; 95% CI, 2.28 to 5.69; T4N0: HR, 5.50; 95% CI, 3.42 to 8.86) compared with patients with T1N0 disease.

The impact of N1 disease varied according to T status. Compared with patients with T1N0 disease, patients with T1N1 disease had worse disease-specific survival (HR, 3.08; 95% CI, 1.75 to 5.44). Similarly, T2N1 status conferred worse survival compared with T2N0 disease (HR, 2.73; 95% CI, 1.84 to 4.07). In contrast, N1 disease was not associated with increased mortality among patients with T3 disease (T3N1 ν T3N0: HR, 0.99; 95% CI, 0.76 to 1.30) or T4 disease (T4N1 ν T4N0: HR, 0.98; 95% CI, 0.71 to 1.35). Overall, M1 disease was

Fig 1. (A) Disease-specific survival stratified by T status. Disease-specific survival was progressively worse with increasing T status ($P < .001$; T1, blue line; T2, gold line; T3, gray line; T4, red line). (B) Disease-specific survival stratified by N status. Patients with N1 (gold line) involvement had worse disease-specific survival than those with N0 (blue line) disease ($P < .001$). (C) Disease-specific survival stratified by M status. M1 (blue line; M0, gold line) status was associated with worse neuroendocrine tumor-specific survival ($P < .001$).

associated with significantly worse survival (HR, 12.15; 95% CI, 8.08 to 18.28).

On the basis of these findings, a modified staging classification was tested. This system categorized patients into the following five groups: T1N0 and T2N0; T1N1 and T2N1; T3N0 and T3N1; T4N0 and T4N1; and M1 disease. As shown in Figure 3, disease-specific survival was significantly different without overlap across these revised

Fig 2. Disease-specific survival according to current staging system. There was overlap of survival in patients with stages I and IIA disease ($P = .36$), as well as in patients with stages IIB and IIIB disease ($P = .70$). In addition, patients with stage IIB disease had better survival than those with stage IIIA disease ($P < .001$). Stage IV patients had the worst survival.

groups ($P < .001$). Similar results were obtained among patients with jejunoileal ($P < .001$) and duodenal ($P < .001$) NETs. Unadjusted and multiple regression analyses limited to nonmetastatic SI-NETs treated with surgery showed similar results as in the full cohort.

DISCUSSION

SI-NETs are a heterogeneous group of neoplasms with a wide range of outcomes. In recent years, efforts to create a robust staging system to assist treatment decisions led to the development of the ENETS/AJCC staging system. However, this classification has not been broadly validated. In this study, we used population-based data to assess long-term disease-specific survival in these relatively indolent and increasingly prevalent cancers. Although we confirmed the importance of T, N, and M status as prognostic factors, our results suggest a need to modify the current classification. Our proposed system may help to better discriminate prognosis of patients with SI-NET and guide evaluation of current and new treatments for this disease.

Table 2. Influence of T and N Status on Risk of Disease-Specific Mortality

Disease Status	Reference	Hazard Ratio	95% CI
Effect of T status			
T2N0	T1N0	1.02	0.63 to 1.66
T3N0	T1N0	3.60	2.28 to 5.69
T4N0	T1N0	5.50	3.42 to 8.86
Effect of N status			
T1N1	T1N0	3.08	1.75 to 5.44
T2N1	T2N0	2.73	1.84 to 4.07
T3N1	T3N0	0.99	0.76 to 1.30
T4N1	T4N0	0.98	0.71 to 1.35
Effect of T and N status			
T2N1	T1N0	2.79	1.73 to 4.50
T3N1	T1N0	3.58	2.36 to 5.45
T4N1	T1N0	5.38	3.49 to 8.30

Fig 3. Disease-specific survival according to the revised staging classification. There is no overlap of survival among prognostic groups.

The current ENETS/AJCC staging system was developed by consensus at international meetings in Europe and the United States. After development, the validity of the classification has been evaluated in a small number of studies, although mostly limited to gastroduodenal and pancreatic NETs.^{14,18-21} Two recent studies have assessed the current classification in SI-NETs. Jann et al¹³ used retrospective data from 270 patients recruited at two European tertiary-care centers. The study showed that although stage IV SI-NETs had the worst outcomes, patients with stage I, II, and III disease had similar 5-year disease-specific survival. In an American study assessing the current classification in jejunal-ileal NETs, Strosberg et al²² studied 5-year overall survival in 691 patients treated at a single cancer center. The study only found a significant difference in survival among nonmetastatic (stages I, II, and III) versus metastatic (stage IV) disease. However, most deaths in patients with SI-NET are a result of comorbidities, a factor that may limit the ability to identify differences across groups. Both of these studies had relatively small sample sizes and were subject to referral bias because they were performed at tertiary centers. In addition, these studies evaluated 5-year survival rates, which may not provide sufficient follow-up for this relatively slowly progressive disease. Therefore, there is still a need to validate the recently proposed staging classification.

Our study is consistent with previous work demonstrating the overall usefulness of the TNM-based system.^{13,22,23} However, we found overlap in survival estimates among some subgroups of patients with early-stage disease. In addition, we discovered a differential effect of N1 disease according to T status. Our analyses showed that lymph node involvement was associated with worse survival in patients with early (T1 or T2) disease but not among patients with more advanced (T3 and T4) disease. Potential clinical ramifications are that among patients with early (T1 or T2) disease, detection of N1 disease by cross-sectional or functional imaging could prompt more aggressive surveillance and treatment. In contrast, with late (T3 or T4) disease, detection of regional lymph node involvement by imaging modalities might not necessarily change patient outcomes. On the basis of these findings, we revised the existing classification and developed a system that better discriminates outcomes of these patients. This system

needs to be further validated in an independent population before it can be adopted in clinical practice.

Because of the relative low prevalence and indolence of these tumors, the lack of a widely accepted staging system, and the paucity of randomized controlled trials, the work-up and treatment of patients with SI-NETs has remained unusually heterogeneous. Accurate, standardized staging with appropriate differentiation of patients with SI-NET is the first step in optimizing treatment and outcomes of these patients. These advances would improve prediction and communication of prognosis with patients and enable informed decision making. They would also allow accurate comparison of outcomes in patients who undergo different treatments. This highlights the importance of our proposed changes in staging in advancing the field.

The major strengths of our population-based study were our large sample of SI-NETs and extended survival data. Both of these features enabled us to detect differences in outcomes, particularly among patients with early disease who have relatively good prognosis and may not experience disease progression for many years. Another strength is that the classification seems to work well in both jejunoileal and duodenal NETs. Nearly all previous studies have been limited to a few institutional centers. However, because we used a population-based registry, this study reflects a wider SI-NET experience without referral bias. Our primary analyses included patients treated with and without resection. However, more than 90% of patients with nonmetastatic SI-NETs in SEER underwent surgery, and secondary analyses limited to resected patients showed consistent results.

A limitation of this study was that we did not have information regarding tumor grade. In the ENETs classification, tumor grade is reported using either the mitotic or the Ki-67 labeling index, both of which are markers of proliferation. Institutional studies have previously shown tumor grade to be a prognostic indicator.^{18,20,21} However, the tumor stage and mitotic index/Ki-67 status are treated independently in the current system, and current guidelines do not specify how to combine these data. Moreover, SI-NETs tend to be lower grade; thus, mitotic index may be less informative in this patient population.¹³ Additionally, although the mitotic index and Ki-67 status are frequently performed at tertiary-care institutions with NET expertise, they have not always been routinely adopted in community settings. Thus, regardless of the lack of tumor grade information, our study provides useful information about the validity of the TNM component of the ENETs/AJCC system. Another limitation was that

cause of death was abstracted from death certificates; therefore, there is a potential for misclassification. However, NET-specific survival rates in SEER are consistent with those reported in prior studies with more detailed information about the cause of death.

In conclusion, although the current ENETs/AJCC TNM classification allows for discrimination of clinical outcomes in patients with SI-NET, our findings suggest that this system should be further refined. The proposed revised staging classification reflects our findings that T1 and T2 disease have similar outcomes as well as the differential effect of N1 involvement among patients with early versus advanced T status, two findings that may directly impact clinical care. Although this system may allow for better prediction of patient outcomes, our results will need to be replicated in other cohorts before adoption in clinical practice.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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