Original Article

Prognostic Value of Lymph Node Evaluation in Small Bowel Adenocarcinoma

Analysis of the Surveillance, Epidemiology, and End Results Database

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BACKGROUND: The presence of distant metastases and the completeness of resection are important prognostic factors in patients with small bowel adenocarcinoma (SBA); however, the influence of lymph node metastasis on patient outcome has not been well characterized. The objective of the current study was to evaluate the impact of the number of positive and negative lymph nodes on survival after curative resection. **METHODS:** Patients who had SBA diagnosed between 1988 and 2005 were identified from the Surveillance, Epidemiology, and End Results (SEER) registry. Cox proportional hazards regression analyses were performed after adjusting for age, sex, race, tumor stage, tumor grade, and primary site. Five-year disease-specific survival (DSS) was determined, all patients were categorized according to the total lymph nodes (TLNs) assessed, and patients with stage III disease also were categorized according to the number of positive lymph nodes (PLNs) and the PLN-to-TLN ratio (the lymph node ratio [LNR]). **RESULTS:** In total, 1991 patients (n = 1216 with stage I/II SBA and n = 775 with stage III SBA) were analyzed. Survival depended on the TLNs assessed. The 5-year DSS rate for patients with stage II disease was associated with the TLNs assessed (44%, 69%, and 83% for 0 TLNs, 1-7 TLNs, and >7 TLNs, respectively). The 5-year DSS for patients with stage III disease was associated with the number of PLNs (58% and 37% for <3 PLNs and ≥3 PLNs, respectively). Among patients with stage III disease, the LNR was even more predictive of survival than stratification by the number of PLNs. **CONCLUSIONS:** Survival after surgical resection for stage I, II, and III SBA was associated with the TLNs assessed. Stratifying patients with stage III disease into those with <3 PLNs and ≥3 PLNs significantly improved prognostication. ***Cancer*** **2010;116:5374–82.** © *2010 American Cancer Society.*

KEYWORDS: adenocarcinoma, small intestine, small bowel, prognosis, lymph nodes, curative resection.

Small bowel adenocarcinoma (SBA) is a rare malignancy that had an estimated incidence of 2000 in the United States during 2008.[1,2] The majority of patients present with locoregional disease and undergo surgical resection. Most studies that have evaluated the prognostic factors for SBA are small, single-institution, retrospective series. In these studies, the most consistently identified predictors of a poor outcome have been the presence of metastatic disease, limited surgical resection, and lymph node involvement.[3-9]

In several other tumor types, stratification by the number of positive lymph nodes (PLNs) provides powerful prognostic information and has become an important component of standard staging systems for these cancers. More recently, improvements in prognostication from stratification according to the total lymph nodes (TLNs) assessed have been demonstrated in gastric, esophageal, pancreatic, and colorectal cancers.[10-13] Particularly in colorectal cancer, the improved outcomes observed with increasing numbers of lymph nodes removed and examined has led several organizations, including the American Society of Clinical Oncology, to recommend assessing a minimum number of lymph nodes for the optimal pathologic staging of stage II colorectal cancer.[14,15] In SBA, the impact that the numbers of both involved and uninvolved lymph nodes have on the outcome of patients who undergo curative resection has not been studied rigorously.

According to the sixth edition of the American Joint Committee on Cancer (AJCC) staging for small bowel cancer, patients with any number of metastatic lymph nodes are classified with pathologic N1 (pN1) disease.[16] A previous

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population-based analysis of SBA stratified patients who were identified in the National Cancer Database from 1985 to 1990. Patients >75 years old, distant metastatic disease, positive surgical margins, and lymph node involvement as binary categorical predictors adversely impacted survival. In this earlier series, the 5-year disease-specific survival (DSS) rate for patients with stage II disease (T3-T4N0M0) was 48%, whereas the 5-year DSS for patients with stage III disease (TxN1M0) was 30%.[17] A more contemporary analysis of outcomes for this tumor type, along with an evaluation of additional factors that may further refine prognosis, would provide valuable information for both patients and physicians. In addition, this information may provide a better understanding of those patients at highest risk for recurrence, enabling physicians to better identify those patients who might benefit most from additional therapy. The objectives of the current study were to perform a contemporary evaluation of outcomes after curative resection for SBA and to further examine the influence of lymph node evaluation on outcomes by performing a detailed examination of the impact of the total number and the number of positive and negative lymph nodes on stage-stratified survival.

MATERIALS AND METHODS

Patients

Data from the Surveillance, Epidemiology and End Results (SEER) cancer registry (version 2008), spanning the years 1988 to 2005, were used in this study. SEER is a population-based registry sponsored by the National Cancer Institute that collects incidence and survival data for approximately 26% of the US population. The SEER registry routinely collects data on patient demographics, primary tumor site, tumor morphology, disease stage at diagnosis (according to the AJCC since 1988), first course of treatment, patient follow-up for vital status, and cause of death. On the basis of these data elements, AJCC sixth edition stage assignment was determined for each patient.

Eligible patients were ages 18 years to 90 years who had a histologic diagnosis of adenocarcinoma (International Classification of Diseases for Oncology and Related Health Problems 10th Revision code) of the duodenum (C17.0), jejunum (C17.1), ileum (C17.2), or small bowel not otherwise specified (C17.9). All patients had undergone cancer-directed surgery, which was defined as local excision or radical resection with a specimen available for pathologic review. Exclusion criteria included: in situ disease and lack of histology; survival for <1 month; cancer reporting source from a nursing home, hospice, autopsy, or death certificate; and whether incomplete data regarding tumor and lymph node status precluded assigning an AJCC sixth edition disease stage. The majority of exclusions were because patients were lacking information to allow staging for the current analysis (77%).

Statistical Analysis

Survival outcomes were determined using SEER data through December 2005, and DSS was estimated using the Kaplan-Meier method. Patients were censored if they died from causes other than small bowel cancer or if the patient was alive at follow-up. To confirm the cause of death coding within SEER, relative survival analyses also were performed for comparison. The median TLNs assessed across different subsites of the small bowel was compared using a nonparametric equality-of-medians test. To determine the role of TLNs assessed on survival, multivariate Cox regression models were constructed separately for patients with stage I/II disease and patients with stage III disease. Covariates were adjusted in the model on the basis of their clinicopathologic importance and included age, sex, race, T classification, tumor grade, and primary site location. In addition, categories for TLNs assessed were established as 0 TLNs assessed (referent), 1 to 7 TLNs assessed, and >7 TLNs assessed for patients with stage I/II disease and as 1 to 7 TLNs assessed (referent) and >7 TLNs assessed for patients with stage III disease. For stage I/II disease, patients who had no lymph nodes examined (0 TLNs assessed) were separated from those who had 1 to 7 TLNs assessed to conform with the patients who had stage III disease and to allow for comparisons. The 7-TLN cutoff point was selected on the basis of a series of cutpoint analyses using Cox regression incorporating the final models (0 TLNs assessed as reference vs 1-6 and >6 TLNs assessed, 0 TLNs assessed as reference vs 1-7 and >7 TLNs assessed, etc) to maximize the likelihood ratio chi-square value. Because the number of PLNs was correlated positively with the TLNs assessed, no model was evaluated that incorporated both of these variables. A correlation matrix was used to check other possible sources of collinearity between any variables.

For patients with stage III disease, the predictive value of the number of PLNs on survival was evaluated by using a Cox regression model and adjusting for age, sex, race, T classification, grade, and primary site. The number

of PLNs was categorized as <3 PLNs versus ≥3 PLNs. Again, these categories were selected by a series of cutpoint analyses (with 1 PLN as reference vs ≥2 PLNs, with 2 PLNs as reference vs ≥3 PLNs, etc) using the maximum likelihood ratio chi-square value. To account for the correlation between PLN and TLN values, we also evaluated the predictive value of the lymph node ratio (LNR), which is the ratio of PLNs to TLNs, using the log-likelihood ratio test to compare the final models in LNR tertiles with categorized PLNs.

Statistical analyses were performed using Stata MP version 10.1 (release 2009; Stata Inc., College Station, Tex). Because the study used pre-existing data with no personal identifiers, it was exempt from review by our institutional review board.

RESULTS

Clinicopathologic Characteristics

In total, 1991 patients met the eligibility criteria, and their baseline characteristics are listed in Table 1. The median patient age was 67 years (range, 18-90 years), and the disease was stage I in 245 patients, stage II in 971 patients, and stage III in 775 patients. The most common small bowel subsite was the duodenum (46% of patients). The median number of TLNs assessed (interquartile range [IQR]) according to disease stage was 1 (IQR, 0-7) for stage I, 4 (IQR, 0-9) for stage II, and 8 (IQR, 4-13) for stage III. In patients with stage II cancer who had at least 1 lymph node assessed, the median number of TLNs assessed (IQR) was 6 (IQR, 3-12). The median number of TLNs accessed (IQR) in patients with stage II disease was lower in patients with duodenal cancers (median, 3; IQR, 0-9) than in patients with jejunal cancers (median, 5; IQR, 2-10; $P = .01$) and patients with ileal cancers (median, 5; IQR, 2-12; $P < .01$). In patients with stage III SBA, the median number of TLNs assessed (IQR) was the same for duodenal and jejunal primaries (median, 8; IQR, 4-13; $P = .3$) but was slightly higher for ileal primaries (median, 10) compared with duodenum primaries (IQR, 6-15; $P = .05$).

For patients with stage III disease, the median number of PLNs was 2 (IQR, 1-4) and did not differ by subsite. In addition, the LNR was similar across small bowel subsites, with a median LNR (IQR) of 0.33 (IQR, 0.15-0.6) for duodenal lesions, 0.40 (IQR, 0.16-0.69; $P = .63$) for jejunal lesions, and 0.30 (IQR, 0.14-0.54; $P = .28$) for ileal lesions.

Table 1. Clinicopathologic Characteristics of Patients With Small Bowel Adenocarcinoma

Characteristic	No. of Patients (%) Stage I/II, n=1216	Stage III, n=775
Age, y		
<50	180 (15)	93 (12)
50-75	653 (54)	396 (51)
>75	383 (31)	286 (37)
Year of diagnosis		
1988-1993	198 (16)	127 (17)
1994-1999	310 (25)	196 (25)
2000-2005	708 (58)	452 (58)
Sex		
Men	621 (51)	432 (56)
Women	595 (49)	343 (44)
Race		
White	933 (77)	634 (82)
Black	201 (16)	100 (13)
Other	82 (7)	41 (5)
Site		
Duodenum	554 (46)	385 (50)
Jejunum	266 (22)	173 (22)
Ileum	223 (18)	137 (18)
Small bowel NOS	173 (14)	80 (10)
Tumor grade		
Well differentiated	152 (12)	45 (6)
Moderately differentiated	640 (53)	365 (47)
Poorly differentiated	314 (26)	312 (40)
Unknown	100 (9)	53 (7)
Tumor classification		
T1	157 (13)	16 (2)
T2	88 (7)	30 (4)
T3	551 (45)	340 (44)
T4	420 (35)	387 (50)
Tx	157 (13)	2 (0)
Median TLN [IQR]	3 [0-9]	8 [4-13]
Median PLN [IQR]		2 [1-4]
Median LNR [IQR]		0.33 [0.15-0.66]

NOS, not otherwise specified; TLN, total number of lymph nodes assessed; IQR, interquartile range; PLN, total number of positive lymph nodes; LNR, lymph node ratio.

DSS by Stage and Site

By using the reverse Kaplan-Meier method, the median follow-up for the entire cohort was 32 months, and 58% of patients died. Death was because of small bowel cancer in 44% of the patients who died. The Kaplan-Meier 5-year DSS probabilities were 85% for patients with stage I disease, 69% for patients with stage II disease, and 50% for patients with stage III disease (Fig. 1, top). There was no statistically significant difference in survival over the study period when comparing the periods 1988 to 1993,

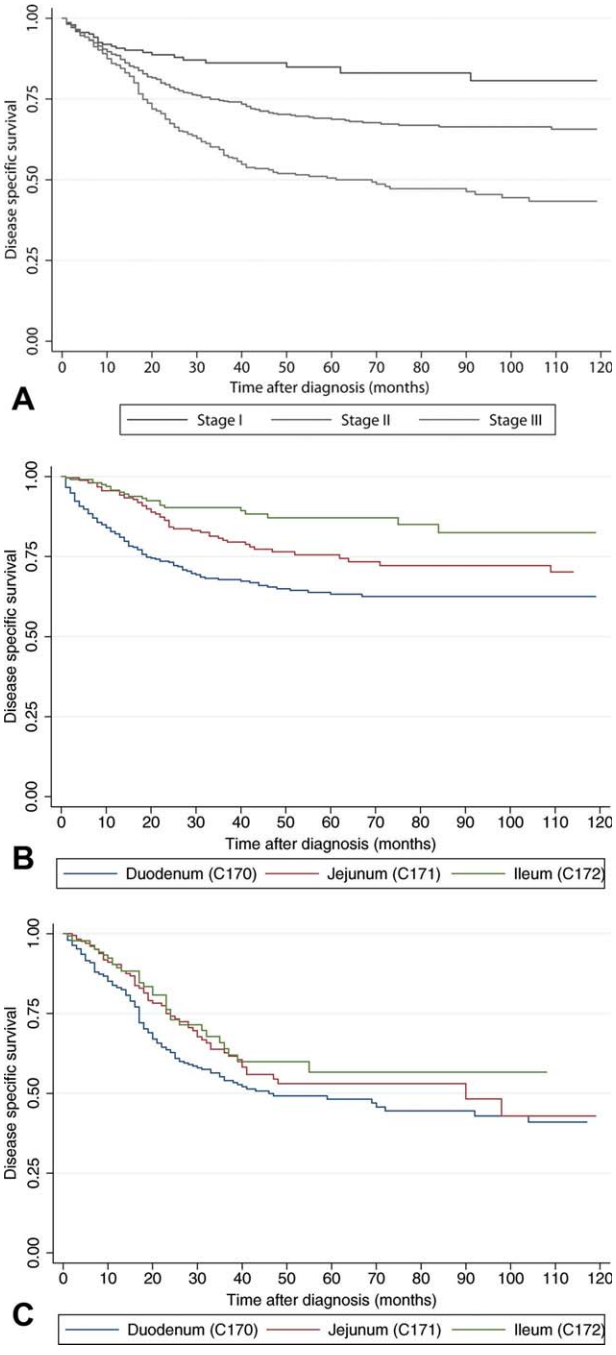

Figure 1. These Kaplan-Meier curves illustrate disease-specific survival stratified by (*Top*) disease stage, (*Middle*) subsite in the small bowel for stage I and II disease, and (*Bottom*) subsite in the small bowel for stage III disease. Codes for the duodenum (C17.0), jejunum, (C17.1), and ileum (C17.2) are from the International Classification of Diseases for Oncology and Related Health Problems 10th Revision.

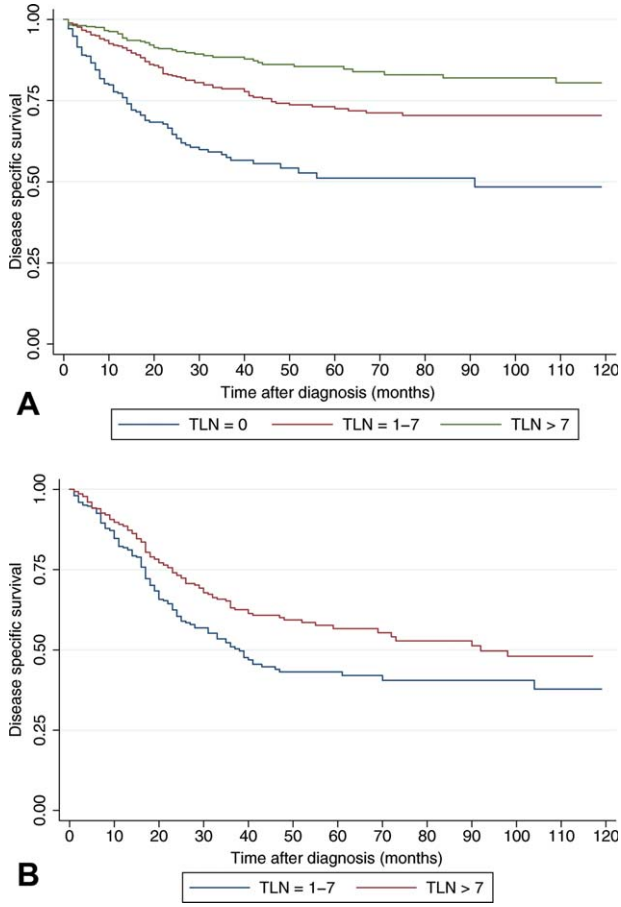

Figure 2. These Kaplan-Meier curves illustrate disease-specific survival stratified by (*Top*) the total number of lymph nodes assessed (TLN) in patients with stage I and II disease and (*Bottom*) the TLNs assessed in patients with stage III disease.

1994 to 1999, and 2000 to 2005 (log-rank *t* test; $P = .56$ for stage I/II; $P = .12$ for stage III). The 5-year DSS rate differed by subsite of the small bowel, and lower overall 5-year DSS was observed in patients who had adenocarcinomas of the duodenum (Fig. 1, middle and bottom).

DSS by Lymph Node Status

Cancer-related mortality was reduced significantly as the TLNs assessed increased among patients with stage I/II disease and patients with stage III disease ($P < .001$) (Fig. 2). The 5-year DSS stratified by stage and TLNs assessed are summarized in Table 2.

For patients with stage III disease, DSS depended on the number of PLNs (Table 2). Cutpoint analysis confirmed by graphic analysis demonstrated that categorization with 1 or 2 PLNs versus ≥ 3 PLNs resulted in the identification of prognostically distinct cohorts (likelihood ratio chi-square = 52.93). Among patients with stage III disease, the LNR was an incrementally better predictor of survival than stratification by the number of

Table 2. Disease-Specific Survival According to Disease Stage, Total Number of Lymph Nodes Assessesed, and Total Number of Positive Lymph Nodes

	% Cumulative 5-Year DSS		
No. of Lymph Nodes	Stage I	Stage II	Stage III
TLN			
0	70	44	
1-7	93	69	43
>7	95	83	56
PLN			
<3			58
≥3			37
LNR[a]			
T1 (0.02-0.2)			63
T2 (0.21-0.5)			53
T3 (0.52-1)			30

DSS indicates disease-specific survival; TLN, total number of lymph nodes assessed; PLN, total number of positive lymph nodes; LNR, lymph node ratio.
[a] Stratified by tertiles.

PLNs, as demonstrated by an improved likelihood ratio chi-square value of 66.68 (log-likelihood ratio test; $P < .01$) (Fig. 3).

The final Cox proportional hazards regression models are provided in Table 3. We constructed 1 model for stage I/II disease and 3 separate models for stage III disease using 3 different variables to account for the influence of lymph node evaluation. In each model and for any stage disease, more TLNs assessed, nonduodenal small bowel subsite, and well differentiated to moderately differentiated tumors were correlated significantly with reduced rates of cancer-related mortality. It is noteworthy that, as the number of TLNs assessed increased, the difference in the 5-year DSS rate by small bowel subsite decreased. For patients who had >7 TLNs assessed, the 5-year DSS rate for duodenal compared with jejunal/ileal subsites was 82% (95% CI, 73%-89%) versus 87% (95% CI, 81%-92%) for stage I/II disease and 58% (95% CI, 48%-66%) versus 57% (95% CI, 45%-66%) for stage III disease; whereas, for patients who had 1 to 7 TLNs assessed, the 5-year DSS rate for duodenal compared with jejunal/ileal subsites was 55% (95%CI, 49%-62%) versus 75% (95% CI,68%-80%) for stage I/II disease and 36%(95% CI, 27%-76%) versus 50%(95% CI, 38%-61%) for stage III disease. The statistical correlations regarding lymph node evaluation among patients with stage I/II disease did not differ when stages I and II were analyzed separately (data not shown).

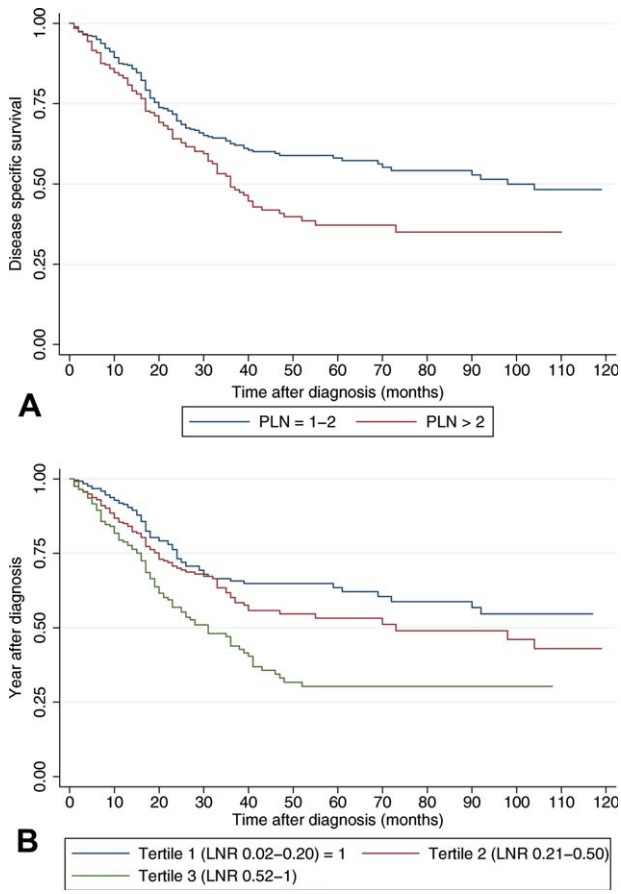

Figure 3. These Kaplan-Meier curves illustrate disease-specific survival stratified by (*Top*) the number of positive lymph nodes (PLN) and (*Bottom*) the lymph node ratio (LNR) in tertiles.

Because of the strong interaction between the number of PLNs and the TLNs assessed in patients with stage III disease, 3 different models were constructed. Higher cancer mortality was predicted by the identification of ≥3 PLNs (hazard ratio, 1.44; 95% CI, 1.12-1.86) or an LNR >0.5 (hazard ratio, 2.08; 95% CI, 1.52-2.84). Conversely, the assessment of >7 TLNs was associated with improved cancer mortality.

DISCUSSION

Improvements in prognostic tools provide valuable information for both patients and physicians. With these improvements comes the potential to tailor appropriate treatment strategies better for different patient groups. In the current study, the survival of patients with SBA depended strongly on both the TLNs examined and the number of PLNs. In both lymph node-positive and lymph

Table 3. Multivariate Analysis of Patients With Small Bowel Carcinoma by Disease Stage

	HR (95% CI)			
Predictor	Stage I/II	Stage III	Stage III	Stage III
TLN				
0	1			
1-7	0.41 (0.31-0.56)		1	
>7	0.24 (0.17-0.35)		0.62 (0.48-0.79)	
PLN				
1-2		1		
≥3		1.44 (1.12-1.86)		
LNR				
0.02-0.2				1
0.21-0.5				1.38 (1.01-1.89)
0.52-1.0				2.08 (1.52-2.84)
Age, y				
<50	1	1	1	1
50-75	0.91 (0.63-1.3)	1.37 (0.88-2.12)	1.46 (0.94-2.26)	1.38 (0.89-2.13)
>75	1.19 (0.80-1.77)	2.05 (1.30-3.22)	2.04 (1.29-3.21)	1.94 (1.23-3.06)
Sex				
Men	1	1	1	1
Women	1.33 (1.03-1.72)	0.85 (0.66-1.09)	0.84 (0.65-1.08)	0.89 (0.69-1.15)
Race				
White	1	1	1	1
Black	1.36 (0.99-1.88)	0.91 (0.61-1.34)	0.88 (0.59-1.3)	0.85 (0.58-1.27)
Other	0.94 (0.56-1.58)	0.86 (0.50-1.49)	0.98 (0.56-1.7)	0.9 (0.52-1.56)
Tumor classification				
T1	1	1	1	1
T2	1.30 (0.59-2.88)	1.25 (0.32-4.74)	1.18 (0.31-4.48)	1.24 (0.32-4.72)
T3	2.11 (1.23-3.6)	2.01 (0.63-6.35)	2.13 (0.67-6.74)	2.06 (0.65-6.53)
T4	4.09 (2.46-6.79)	2.59 (0.82-8.17)	2.76 (0.87-8.71)	2.62 (0.83-8.27)
Tumor grade				
Well/mod	1	1	1	1
Poor	1.68 (1.27-2.22)	1.35 (1.04-1.75)	1.54 (1.19-1.99)	1.43 (1.11-1.84)
Unknown	1.64 (1.07-2.52)	1.15 (0.66-2.01)	1.15 (0.66-2.01)	1.09 (0.62-1.91)
Site				
Duodenum	1	1	1	1
Jejunum/ileum	0.54 (0.40-0.74)	0.73 (0.55-0.97)	0.79 (0.59-1.04)	0.75 (0.56-0.99)
Small bowel NOS	0.56 (0.37-0.84)	1.06 (0.70-1.6)	1.12 (0.74-1.69)	1.05 (0.69-1.58)

HR indicates hazard ratio; CI, confidence interval; TLN, total number of lymph nodes assessed; PLN, total number of positive lymph nodes; LNR, lymph node ratio; NOS, not otherwise specified; Well-mod, well to moderately differentiated; Poor, poorly differentiated; NOS, not otherwise specified.

node-negative disease, increasing the TLNs correlated with improved DSS. In patients with stage II disease, the 5-year DSS rate was 83% for those who had >7 TLNs assessed but fell to 69% when only 1 to 7 TLNs were assessed. In addition, stratification of patients with lymph node involvement according to the number of PLNs (1 or 2 vs ≥3) provided meaningful prognostic information and 5-year DSS rates of 57% and 37%, respectively.

The reason for better outcomes with increasing TLNs assessed is multifactorial and likely relates to surgical technique, pathologic examination, and both patient and tumor variation. For patients with stage I or II disease, the improved outcomes may be related in part to stage migration: In essence, as more lymph nodes are assessed, the chance of having an undetected positive regional lymph node detected decreases; thus, a more homogenous lymph node-negative population emerges. This effect has been demonstrated in patients with stage II colon cancer and may in part explain why, as TLNs assessed increased, the differences in survival among sites decreased.[18,19] In colorectal cancer, the factors that have been correlated with lymph node yields are age, obesity, and tumor

immunogenicity.[20-22] In addition, for colorectal cancer, it has been demonstrated that the number of assessed lymph nodes increases as surgical and hospital volumes increase.[22-26] The exact contribution of each of these factors to the improvement in survival with increasing TLN or whether TLN is a surrogate of overall quality as it pertains to postoperative care, follow-up, or subsequent therapy could not be determined in the current study.

Irrespective of the reasons for these differences, patients with more TLNs assessed have improved survival, and this finding has important implications for clinical prognostication. Our data suggest that improving lymph node evaluation at the time of surgical resection and pathologic evaluation may result in improved outcomes. The lower median TLNs assessed for patients who had stage II disease compared with patients who had stage III disease suggests the potential for an improved diagnosis with improved lymph node evaluation, particularly for the stage II group. This finding may provide added information to guide discussions regarding prognosis and subsequent therapy.

In the current study the number of PLNs assessed was correlated with patient outcome. The stratification of patients into categories of 1 or 2 PLNs versus $\geq$3 PLNs demonstrated a robust difference in outcome. Currently, the AJCC sixth edition does not stratify patients with stage III disease according to the number of PLNs.[16] If our findings can be validated in other datasets, then we believe that future staging systems should incorporate the number of PLNs into lymph node staging. The incorporation of both the number of PLNs and the number of negative lymph nodes (and, thus, the TLNs assessed) to calculate the LNR provided further prognostic power, a finding that is similar to reports from studies in breast cancer, gastric cancer, and colon cancer.[27-29] However, as with studies in those other sites, the best use of the LNR in clinical decision-making remains unclear.

Adjuvant chemotherapy does not have a proven benefit in patients with SBA. To our knowledge, no prospective studies have been conducted, and no retrospective studies have demonstrated that the use of adjuvant chemotherapy lengthens overall survival or DSS.[30-32] In these retrospective series, selection bias may favor the use of adjuvant chemotherapy in patients at the greatest risk of disease recurrence, thus confounding the results. With a better understanding of the prognostic impact of lymph node assessment in patients who undergo curative resection, comparisons between populations with a more homogenous risk of recurrence can be conducted. Despite this lack of evidence for the use of adjuvant chemotherapy in patients with SBA, its use has increased from 8% of patients in 1985 to 24% in 2005.[1] When analyzing the outcomes over time in the current study, we noted no difference in DSS between the period from 1988 to 1993 and the period from 2000 to 2005.This lack of improvement in outcomes for patients with curatively resected SBA over the last 2 decades suggests the need for continued exploration of adjuvant treatment strategies. In particular, the primarily systemic pattern of recurrence and the proven activity of systemic chemotherapy in the metastatic setting continue to provide a strong rationale for further exploration of adjuvant chemotherapy in this rare cancer.[30,31,33]

The effect that the subsite of the small bowel has on patient outcome is controversial. Consistent with our findings, data from the National Cancer Database have demonstrated worse outcomes for patients with duodenal adenocarcinoma than those with jejunal or ileal disease, although this correlation did not incorporate the stage of disease.[17] Several other small, single-institution studies have not reported a difference in survival dependent on a subsite within the small bowel.[9,30,31] Whether a difference in outcome reflects a biologic distinction between tumors of the duodenum compared with tumors of the jejunum and ileum is not known. In the current analysis, after adjusting for covariates, the duodenal site was a poor prognostic factor. It is noteworthy that the impact of a small bowel subsite on outcome decreased as the number of TLNs assessed increased. In patients who had >7 TLNs assessed, the 5-year DSS rate for duodenal primaries versus jejunal/ileal primaries was 80% versus 86% for stage II disease, and 58% versus 57% for stage III disease. This finding suggests that surgical technique and anatomy may be responsible at least in part for the difference in outcome between duodenal and nonduodenal subsites in the small bowel. Unfortunately, our dataset did not allow for a distinction between more radical procedures, such as pancreaticoduodenectomy and more limited resections involving the duodenum only.

There are several strengths and limitations to our analysis. It is noteworthy that the SEER registry currently captures data on 26% of the cancer cases within the United States with good ethnic and geographic representation. Therefore, it is suited for performing relatively large population-based evaluations of rare malignancies like SBA. In addition, as a population-based dataset, it is broadly representative of outcomes and treatment practices in the United States. Our study did require complete

information that would allow us to include stage assignment in the analysis with the resultant threat from selection bias. Because missing data for complete staging were the primary reason for patient exclusion, we did perform imputation for stage. However, the survival in this group of excluded patients was intermediate between the survival of patients with stage III and stage IV disease, indicating a heterogeneous population of patients who were not eligible for categorization for further analysis. Finally, SEER does not provide information regarding comorbidities, performance status, pathologic margin status, detailed information regarding surgical resection for small bowel cancer, or use of adjuvant therapy; therefore, for any individual patient, the findings of this study should be considered in light of those other influences. Despite the lack of information regarding adjuvant therapy, several reports demonstrated the limited use of adjuvant chemotherapy over our study period.[1] In addition, we performed relative survival analyses using our final model to confirm our findings and to permit the reporting of actual DSS probabilities, which we believe are more directly applicable to the community of treating clinicians (data not shown).

In conclusion, increasing the TLNs assessed markedly improves prognostication for patients with stage I, II, and III SBA who undergo resection. Lymph node-negative patients who have >7 TLNs assessed have an excellent prognosis. Stratifying patients with stage III SBA into those with <3 PLNs and those with ≥3 PLNs significantly improves prognostication for these patients, and future staging systems should consider incorporating the number of PLNs into lymph node staging.

CONFLICT OF INTEREST DISCLOSURES

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