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ORIGINAL ARTICLE

Impact of Nodal Staging for Small Bowel Carcinoid: More is Better!

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ABSTRACT

Current guidelines for small bowel carcinoid (SBC) do not specify the extent lymph node (LN) staging required. Our aim was to determine whether analyzing more LNs in patients who undergo surgical resection for SBC correlated with improved survival. The Surveillance, Epidemiology, and End Results (SEER) database was queried to identify patients undergoing surgical resection for histologically confirmed SBC from 1988-2009. The number of LNs examined was categorized into 0, 1 to 6, 7 to 11 and 12+ nodes. Patient demographics and tumor characteristics were assessed by Logrank and Cox regression analysis. The median number of LNs examined for all 2796 patients was 4.00 (mean 6.83). For all stages of jejunal and ileal tumors examined, increased nodal sampling was associated with significantly improved survival ($p < 0.001$). On regression analysis, older age, non-white race, larger tumor size, higher T-stage and number of LNs examined were predictive of worse survival. For jejunal and ileal SBC, adequate lymphadenectomy, consisting of 12 lymph nodes, correlates with significantly improved survival. Presently, no guideline exists for SBC LN staging, but it is critical to ensure adequate surgical staging in patients who undergo resection for jejunal and ileal SBC.

Keywords: Small bowel carcinoid, Lymph nodes, Survival.

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INTRODUCTION

Carcinomas of the small intestine account for less than 5% of all gastrointestinal (GI) malignancies, yet recent studies have demonstrated a worldwide increase in the number of neuroendocrine tumors of the small intestine.[1] In the past four decades, there has been a 300 to 500% increase in the incidence of neuroendocrine tumors in the United States as well as Sweden and Norway.[2-6] Nearly 75% of all carcinoids are found in the GI tract with the small bowel being the most common location (45%).[6,7]

Small bowel carcinoids (SBC) typically present with metastatic disease, but several studies have demonstrated long-term overall survival for all stages. The current National Comprehensive Cancer Network (NCCN) guidelines for locoregional SBC tumors include specific options for management based on primary tumor site.[8] More specifically, duodenal SBC tumors can be treated with endoscopic resection or local surgical resection. Lymphadenectomy (LAD) is not required for duodenal tumors while bowel resection with regional LAD is required for jejunal and ileal tumors. However, there are currently no specified guidelines regarding the extent of LN examination for SBC.

Using a population-based study, we wanted to determine whether analyzing more lymph nodes (LNs) in patients who undergo surgical resection for SBC improves survival.

MATERIALS AND METHODS

We conducted a population-based retrospective study between 1988 and 2009 using the Surveillance, Epidemiology and End Results (SEER) database, which is one of the largest cancer research sources from the National Cancer Institute. The SEER database consists of 13 population-based cancer registries that represent approximately 28% of cancer patients in the United States. The data is collected from cancer registries across the United States. It includes information such as demographic, primary site, geographic region, histology, stage at diagnosis, treatment and tumor characteristics. We queried the database for patients with a histologic diagnosis of carcinoid involving the following sites: duodenum, jejunum, ileum and other overlapping lesions. Malignant carcinoids of the small intestine were defined using SEER codes for cancer site and histology. Tumor characteristics were analyzed, including tumor location, tumor size, tumor grade and AJCC TNM stage. We excluded all patients with distant metastatic disease, unknown number of LNs examined and more than one primary malignancy. Univariate survival analysis was performed using Kaplan Meier method and log-rank test. Multivariate survival analysis was performed using Cox hazard proportional model adjusting for age, gender, race, year of diagnosis, tumor location, tumor size, tumor grade, stage, number of and lymph nodes examined. All statistical analysis was conducted using SPSS version 19.0 software (Chicago, IL, USA), with p-value less than 0.05 considered significant.

RESULTS

Of the 11,510 patients identified, 7,078 were excluded for inadequate staging information, 776 were excluded for metastatic disease and 860 were excluded for having more than one primary. After exclusion criteria were applied,

2,796 patients were eligible for analysis. Patient demographics based on the number of LNs examined are shown in Table 1. Kaplan-Meier survival curves demonstrated a survival benefit for patients with at least 1 LN examined compared to those with 0 LNs examined (Graph 1A, $p < 0.001$). For duodenal SBC, there was no statistically significant difference in survival based on whether LNs were examined (Graph 1B, $p = 0.827$). However, for jejunal and ileal SBC, examining at least 1 LN correlated with a survival benefit compared to those with 0 LNs examined (Graph 1C, $p < 0.001$). Additionally, for jejunal and ileal SBC, Kaplan-Meier survival curves demonstrated statistically significant improvement in overall survival in those with >12 LNs examined compared to those with 0, 1-6 and 7-11 LNs (Graph 2, $p < 0.001$). This improvement in survival was maintained after a subgroup analysis based on AJCC staging for jejunal and ileal SBC was performed for node negative (stage I/II/IIIa, Graph 3A, $p = 0.003$) and node positive (stage IIIb, Graph 3B, $p = 0.001$) patients.

After adjusting for patient demographics, tumor characteristics and TNM stage, multivariable regression analysis demonstrated that examination of less than 12 LNs correlated with a decrease in survival for with jejunal and ileal SBC. Other factors that positively affected survival included younger patient age, male gender, white race, tumor size less than 1 cm and lower T-stage (Table 2).

DISCUSSION

Historically, the management of GI carcinoids had been challenging due to insufficient data regarding predictive

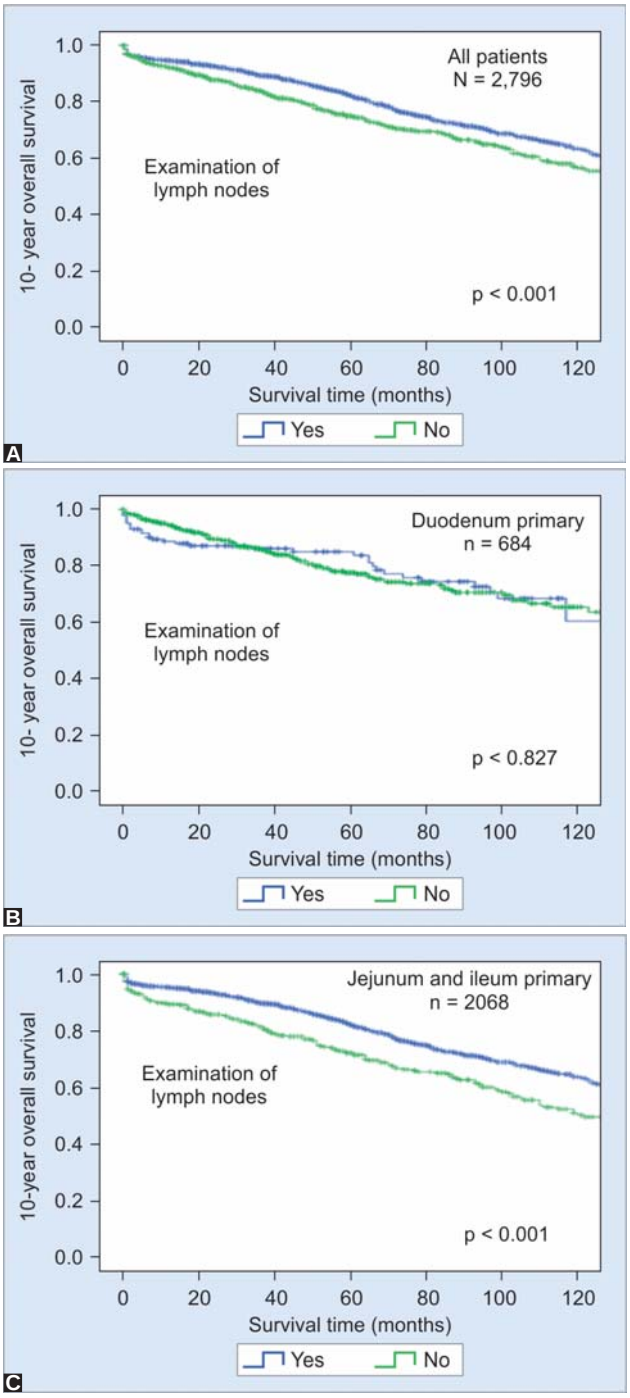
Table 1: Patient demographics (n = 2,796)

	Number of LNs examined			
	0	1-6	7-11	12+
n	966	728	442	660
Cases (%)	34.5	26	15.8	23.6
Mean age (years)	64	62.2	61.6	59.1
Gender (%)				
Female	47	46.3	51.1	50.9
Male	53	53.7	48.9	49.1
Race (%)				
White	74.7	82.8	86.7	88.8
Black	18.1	14.8	11.1	8.8
Asian/Other/Unknown	7.1	2.3	2.3	2.4
Year of diagnosis (%)				
1988-1992	7	8	7.2	4.7
1993-1997	10	14.4	9.7	6.7
1998-2001	15	19.1	16.3	12.6
2001-2005	31.3	30.6	30.8	30.2
2006-2009	36.6	27.9	36	45.9
Tumor location (%)				
Duodenum	55.9	13.5	5.4	3.3
Jejunum	8.6	10.9	8.8	4.8
Ileum	34.5	73.9	84.2	89.7
Overlapping lesion	1	1.8	1.6	2.1
Tumor size (cm) (%)				
< 1	42.4	26.8	20.6	19.7
1-2	22.2	37.6	38.2	39.5
> 2	7.6	23	31.7	34.3
Unknown	27.8	12.6	9.5	6.5
Tumor grade (%)				
Well-differentiated	12.5	11.8	14.7	18.3
Moderately-differentiated	3.1	3.3	3.2	3.8
Poorly-differentiated	0.6	1	0.7	0.3
Unknown	83.7	83.9	81.4	77.6
AJCC stage (%)				
I	59.2	17	6.6	5.5
II A	14.5	9.5	4.1	2.9
II B	19.3	10.2	7.2	3.6
III A	19.3	4.7	2.3	2
III B	N/A	58.7	79.9	86.1

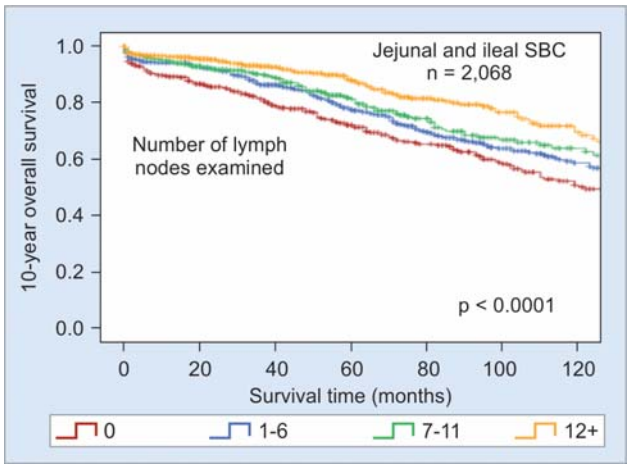
prognostic variables. As a result, a meaningful staging system did not exist. Over time, several studies revealed a significant difference in tumor biology and survival based on the primary organ site of carcinoid tumors.[6,9-12] Various studies have reported a superior 5-year observed survival rates for localized carcinoids of the rectum (90%), appendix (88%) and colon (85%) when compared to the cecum (68%) and small bowel (65-73%).[13] These discrepancies led to the establishment of a separate staging system for GI carcinoids based on the primary organ site.[14]

With the incidence of SBC on the rise in many countries such as the United States, Norway and Sweden, SBC are now the most common carcinoid of the GI tract.[11,12,15,16] The clinical manifestations of SBC are typically vague and nonspecific. They are commonly found incidentally at the time of laparoscopy or endoscopy. Patients with local and regional disease are thought to have a favorable prognosis, but a majority of patients present with metastatic disease. Advances in endoscopy, double balloon enteroscopy computed-topography (CT) and magnetic resonance imaging (MRI) have improved our ability to detect and clinically stage SBC.[17-22]

Upper gastrointestinal series (UGIS)/small-bowel follow-up through (SBFT) remain a mainstay in the evaluation of SB tumors due to its simplicity, diagnostic value and cost. The utilization of double contrast method of enteroclysis has increased the detection sensitivity to almost 90%; however, it is only used in 50 to 60% patients being evaluated for SB pathology due to limitations such as lack of visualization of a luminal lesion and the need for a highly-skilled radiologist.[23] CT enteroclysis (CTE) has become a superior modality for the evaluation of SBC because it allows the exploration of the entire SB as well as extraintestinal involvement. CTE can detect SBC that are only 5 mm in size with a negative and positive predictive value for SBC of 100 and 94.7% respectively.[24,25] Similarly, MR enteroclysis (MRE) has also been advocated due to its ability to assess mucous membranes and pathological changes around the bowel for SBC, and studies have shown a 95% diagnostic accuracy for SB tumors.[20,21,26]

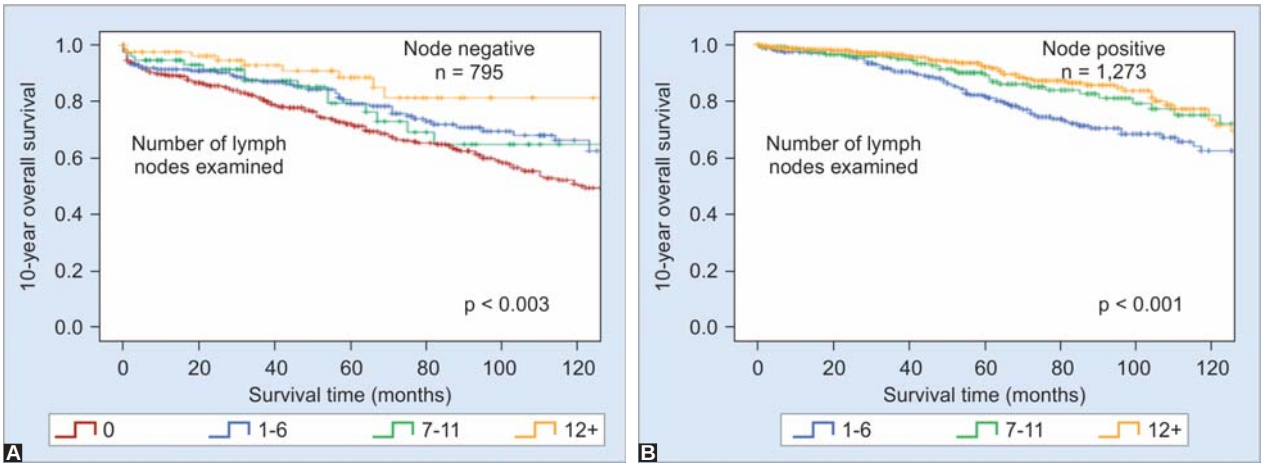


Graphs 1A to C: Overall survival based on whether lymph node were examined (A) All patients, (B) Duodenal primary, (C) Jejunal and ileal primary. Yes = at least 1 lymph node examined and No = 0 lymph nodes examined



Graph 2: Survival based on the number of lymph nodes examined and for stage I-IIIB patients with jejunal and ileal primary

More than 20 years ago, capsule endoscopy technology emerged as a superior modality for identification of SB tumors and the advancements in camera technology and image capture have revolutionized the technique.[22,27] However, the advent of push-pull endoscopy (double-balloon) has challenged the need for capsule endoscopy given its superior diagnostic yield, superior screening ability and therapeutic potential for SBC. Capsule endoscopy and push-pull endoscopy are now advocated as complementary studies in the work-up of SB tumors.[23,27] Additionally, for patients with carcinoid syndrome, octreotide scanning is a powerful tool for localizing SBC with a 90% sensitivity rate, but for those lacking carcinoid symptoms, the sensitivity rate drops to 60%.[19,23]



Graphs 3A and B: Survival based on the number of lymph nodes examined and stage for patients with jejunal and ileal primary, (A) AJCC stage I/II/IIIa (node negative), (B) AJCC stage IIIb (node positive)

Table 2: Adjusted Cox proportional hazards regression model for 10-year overall survival in patients with stage I to III small bowel carcinoid for jejunum and ileum tumors

Category	*Subcategory*	*Hazard ratio*	*p-value*
Age	per year	1.07	<0.001
Gender	Male	1	0.025
	Female	1.202	
Race	White	1	0.006
	Black	1.545	
	Asian/Other/Unknown	1.229	
Year of diagnosis	1988-1992	1	0.223
	1993-1997	0.711	
	2008-2001	0.646	
	2002-2005	0.673	
	2006-2009	1.01	
Tumor location	Ileum	1	0.942
	Jejunum	0.999	
	Overlapping lesion	0.873	
Tumor size (cm)	<1	1	<0.001
	1-2	0.922	
	>2	1.228	
	Unknown	1.443	
Tumor grade	Well-differentiated	1	0.411
	Moderately-differentiated	2.016	
	Poorly-differentiated	1.126	
	Unknown	1.303	
T-stage	T1	1	0.046
	T2	1.092	
	T3	1.334	
	T4	1.396	
N-stage	N0	1	0.807
	N1	5.723	
Nodes examined	0	1	0.031
	1-6	0.901	
	7-11	0.798	
	12+	0.194	

Several studies have challenged the hypothesis that advances in technology have increased detection of SBC as the explanation to the increased incidence of SBC in the past few decades.[5,9,16] Furthermore, overall survival has remained constant for all SBC, but there has been conflicting data regarding the prognosis of SBC based on primary tumor site and more importantly, the TNM staging when comparing duodenal and jejunal or ileal SBC.[3,4,28] The current NCCN guidelines contain varying surgical treatment algorithms based on primary site of the SBC rather than TNM stage.[8] Jejunal and ileal tumors were considered to have a poorer prognosis compared to duodenal SBC and other GI carcinoids. The current standard of care is that duodenal SBC tumors can be treated with endoscopic resection or local surgical resection without lymph node sampling while bowel resection with regional LAD is recommended for jejunal and ileal tumors.

Lymph node involvement remains a significant predictor of survival for GI adenocarcinomas and carcinoids, yet unlike GI adenocarcinomas, there are currently no specified guidelines regarding the extent of LN examination for GI carcinoids.[29-31] Our study demonstrated that the lack of lymph node examination for all SBC was associated with an inferior 10-year survival compared to patients with at least 1 LN examined (56.5% *vs* 63.2% respectively, $p < 0.001$). While this was statistically significant for all SBC patients, this correlation was not observed for duodenal SBC (64% *vs* 60%, $p = 0.827$) compared to jejunal/ileal SBC (50% *vs* 63.5%, $p < 0.001$). This supports the NCCN guidelines that LN examination is not necessary for duodenal SBC.

Analysis of the extent of LN examination for jejunal and ileal SBC revealed that patients with at least 12 LN examined had a 10-year survival of 69% compared to those with 0, 1-6 or 7-11 LN examined (50%, 58% and 63%, respectively, $p < 0.001$). A subset analysis of these patients based on LN examination and LN positivity confirmed the importance of adequate LN examination regardless of LN positivity status. Currently, node-negative SBC include Stage I (T1N0M0), Stage IIA (T2N0M0), Stage IIB (T3N0M0) and Stage IIIA (T4N0M0) while node-positive SBC include Stage IIIB (T1-4N1M0).[14] For nodenegative SBC of the jejunum and ileum, patients with at least 12 LNs examined had a superior 10-year survival advantage compared to those with less or zero (72% *vs* 63% and 50%, respectively, $p = 0.003$). For node-positive SBC of the jejunum and ileum, patients with at least 12 LNs examined had a superior 10-year survival advantage compared to those with 1-6, 7-11 and >12 (62% *vs* 72.1% *vs* 73.3%, respectively; $p = 0.001$). Multivariable regression model for SBC of the jejunum ileum confirmed that the number of LNs examined remained a positive predictor of survival.

One reason for the significantly improved survival is likely multifactorial, but the stage migration phenomenon must be considered given that the higher number of LN examined theoretically decreases the risk of missed nodal involvement. However, we observed that both node-positive and node-negative patients with SBC of the jejunum and ileum had significantly improved survival if at least 12 LNs were examined. Variations in pathologic processing and technique as well as extent of surgical resection must also be considered as an increasing mindfulness of total number of LNs examined. Tumor size and T-stage are an integral part of the TNM staging for SBC. In addition to the number of LNs examined, our study confirmed that smaller, well-differentiated tumors had a superior survival advantage after multivariable analysis, while nodal involvement was not an independent predictor of survival for jejunal and ileal SBC.

There are several limitations to using a population-based database. The database lacks information on margin status which may be critical for duodenal SBC due to the limited resections done at this site compared to jejunal and ileal tumors. Patient co-morbidities and perioperative complications are also not available in the SEER database. While chemotherapy data is not available in the SEER database, the majority of SBC patients with locoregional disease are treated with excision or surgical resection only so it is unlikely the addition of this data in our study population would impact the survival and conclusions of our study. We also excluded patients with more than one primary and it is common for patients with SBC to have more than one primary. Lastly, recurrence data is not available in the SEER database.

CONCLUSION

In the largest study to date evaluating the impact of LN analysis in SBC, we demonstrate that the extent of LN examination is important for both node-negative and node-positive SBC of the jejunum and ileum. Extent of lymphadenectomy correlated with significantly improved survival. Based on our findings, we recommend that surgeons should aim to achieve a minimum of 12 nodes as part of the regional lymph node dissection for SBC of the jejunum and ileum. Presently, no mandate exists for SBC LN staging, but it is critical to ensure adequate surgical staging in patients who undergo resection for jejunal and ileal SBC. Further investigations should be done to confirm these findings.

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