Small bowel carcinoid: Location isn’t everything!

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Abstract

AIM: To investigate the prognostic significance of the primary site of disease for small bowel carcinoid (SBC) using a population-based approach.

METHODS: The Surveillance, Epidemiology and End Results (SEER) database was queried for histologically confirmed SBC between the years 1988 and 2009. Overall survival (OS) and disease-specific survival (DSS) were analyzed using the Kaplan-Meier method and compared using Log rank testing. Log rank and multivariate Cox regression analyses were used to identify predictors of survival using age, year of diagnosis, race, gender, tumor histology/size/location, tumor-node-metastasis stage, number of lymph nodes (LNs) examined and percent of LNs with metastases.

RESULTS: Of the 3763 patients, 51.2% were male with a mean age of 62.13 years. Median follow-up was 50 mo. The 10-year OS and DSS for duodenal primaries were significantly better when compared to jejunal and ileal primaries (P = 0.02 and < 0.0001, respectively). On multivariate Cox regression analysis, after adjusting for multiple factors, primary site location was not a significant predictor of survival (P = 0.752 for OS and P = 0.966 DSS) while age, number of primaries, number of LNs examined, T-stage and M-stage were independent predictors of survival.

CONCLUSION: This 21-year, population-based study of SBC challenges the concept that location of the primary lesion alone is a significant predictor of survival.

Key words: Small bowel carcinoid; Primary tumor location; Survival; Prognosis; National Comprehensive Cancer network guidelines

Core tip: Duodenal carcinoids have a significantly better overall survival than jejunal and ileal carcinoids; however, location of small bowel carcinoid is not an independent predictor of survival.

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Table 1 American Joint Committee on Cancer staging for small bowel carcinoid

| Stage | TNM | Size of depth of invasion | Lymph node status | Distant metastases |
|-------|-----|--------------------------|-------------------|-------------------|
| I     | T1N0M0 | Invasion into the lamina propria or submucosa | None | None |
| II    | T2N0M0 | Invasion into the lamina propria and/or submucosa and tumor size > 1 cm | None | None |
| III   | T3N0M0 | Invasion into the submucosa | None | None |
| IIIA  | T4N0M0 | Invasion into the serosa/visceral peritoneum or into nearby organ or structures | None | None |
| IIIB  | T1-4N1M0 | Any | Positive regional lymph nodes | None |
| IV    | T1-4N0-1M1 | Any | Any | Yes |

Source: Ref[9,35], with permission.

INTRODUCTION

Primary malignancy of the small bowel remains a rare entity, with fewer than 8810 new cases expected in 2013[3]. However, this represents a steadily rising incidence with a 66% increase over 2003 estimates[3]. The number of estimated deaths from small bowel malignancy has remained virtually unchanged over the same time period (1110 in 2003 vs 1170 in 2013). The explanation for this phenomenon is multifactorial but centers around a changing histologic profile.

Historically, adenocarcinoma was the predominant histology of small bowel tumors, followed closely by carcinoid tumors. However, in a recent twenty-year analysis (1985-2005), small bowel carcinoids (SBC) surpassed adenocarcinoma in incidence by the year 2000, and by 2005, SBC represented 44.3% of all resected small bowel tumors. Patients undergoing resection for carcinoid histology had better observed five year survival rates (62.6%) than those with adenocarcinoma (32.5%)[3].

SBC are a heterogeneous group of tumors and remain a conundrum when discussing prognosis with patients. Prior investigators have developed survival tables based on the location of the primary lesion, portending a better prognosis for lesions of the jejunum or ileal origin[4]. More recently, a proposed clinical nomogram for small bowel carcinoid does not include location as an independent prognostic factor, relying heavily on histopathologic features, such as percentage of Ki67(+) staining[5].

Location and tumor pathology have each been identified as possible predictors of clinical outcomes for SBC[4-8]. Currently, tumor-node-metastasis (TNM) staging for SBC mainly depends on extent of tumor size and depth, with node positive disease representing Stage IIIB disease (Table 1)[5]. Herein, we analyze a 21-year database of histologically proven SBC to identify independent factors contributing to survival.

MATERIALS AND METHODS

The National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) registry is a government-run database that collects population-based data from 14 regional and three additional cancer registries, which together represent approximately 28% of the United States population. Data in the SEER database contain no patient-specific identifiers and is publicly available; therefore, this study is exempt from institutional board review approval requirements.

Using the NCI’s SEERStat software version 7.1.0, we identified patients with new cases of pathologically confirmed malignant SBC from 1988 to 2009[9]. Quality assurance studies are mandated each year to ensure a 98% case ascertainment. We excluded patients if the location of primary site was unknown or the patients had anatomically-overlapping small bowel lesions. Patients were also excluded if the number of lymph nodes (LNs) examined was unknown. We assessed age, sex, race, tumor location, tumor size, year of diagnosis, geographic region, number of primary tumors, extent of surgical resection, number of LNs examined (LNE), LN positivity, cause of death, and survival in mo. Categories for extent of surgery were defined as follows: local excision (endoscopic excision or surgical enucleation), resection (surgical excision of a segment of bowel ± mesentry), and debulking (resection of primary lesion and other known sites of disease). Data regarding neo-adjuvant or adjuvant chemotherapy or endocrine therapy are not included in the SEER database.

Statistical analysis

Summary statistics and Kaplan-Meier survival curves were generated using SAS Version 9.2 (SAS Institute, Inc., Cary, NC, United States). We determined P-values by a Log-rank test. We performed Cox’s proportional hazard regression analysis incorporating variables with P < 0.1 (is this correct) on the log rank test and built a final model utilizing a stepwise, forward and backward, selection method.

RESULTS

The SEER database contained 6996 adult (> 18 years old) patients with malignant SBC between 1988 and 2009. Of this group, 3763 patients with known tumors of the duodenum (n = 872), jejunum (n = 324) and ileum (n = 2507) that had adequate data on lymph node assessment were included in this study. Patient demographics and
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tumor characteristics of this subset are listed in Tables 2 respectively.

The majority of patients were older than 50 years of age for all primary tumor sites (mean age 62.13 ± 13.06 years), Caucasian, diagnosed after 1998 and had only one primary malignancy (Table 2). While 62.2% of duodenal tumors were treated with local endoscopic excision, 89% of patients with jejunal tumors and 88% of patients with ileal tumors underwent surgical resection. Given that a majority of patients with duodenal tumors underwent local excision, 81% of duodenal resection specimens did not have any assessment of regional LN (LNE = 0) while the majority of those that underwent surgical resection for jejunal and ileal tumors had at least 1 LNE (65% and 80%, respectively).

Patients with duodenal primaries had smaller tumors compared to those with jejunal and ileal tumors as well as lower T-stage. Due to lack of LNE, the N-stage of 81% patients with duodenal tumors was unknown compared to 35% and 20% of those with jejunal and ileal tumors. Patients with jejunal and ileal tumors presented with more advanced primary tumors (T3: 42% and 39%; T4: 32% and 29%, respectively).

We assessed the outcomes based on primary tumor site using Kaplan-Meier OS and DSS. Kaplan-Meier OS estimates. Median follow-up was 50 mo. Based on primary tumor site, patients with duodenal tumors had a significantly higher 10-year OS compared to jejunal and ileal tumors (63.9% vs 53.4% and 50.4%, respectively, \(P = 0.02\), Figure 1A). Similarly, patients with duodenal tumors had a superior 10-year DSS compared to jejunal tumors and ileal tumors (91.7% vs 74.6% and 67.8%, respectively, \(P < 0.001\), Figure 1B).

We investigated the impact of the primary site when combined with other known clinical and pathological determinants of SBC-specific mortality and performed a multivariable regression analysis using a Cox proportional hazards model (Table 3). In this model, primary tumor site was not an independent predictor of DSS; in addition gender, race, extent of surgery and N-stage were not independent predictors of DSS (all \(P > 0.05\)). However, age, number of primaries, number of LNE, T-stage and M-stage were independent predictors of DSS. Patients older than 50 years of age did worse compared to younger patients. Patients with more than one primary malignancy did better compared to those with only one malignancy. Patients with at least one LNE did better than those with zero LNE. Patients with more advanced T-stage and those with metastatic disease also fared worse than with lower T-stage and no evidence of metastatic disease.

**DISCUSSION**

In the past 40 years there has been a 300%-500% increase in the incidence of neuroendocrine tumors (NET)\(^{[4,7,11,12]}\). SBC now represents almost 75% of all gastrointestinal NET and SBC has surpassed adenocarcinoma as the
most common SB malignancy\textsuperscript{[4-13-15]}. For many years, there was inadequate data regarding predictive prognostic variables. As a result, the management of GI carcinoids has been an evolving process. For localized GI carcinoids, it was evident that survival varied significantly based on location of the primary tumor with observed 5-year survival rates favoring carcinoids of the appendix, colon and rectum (85%-90%) relative to those of the stomach (73%), cecum (68%) and small bowel (67%)\textsuperscript{[16]}. As a result, individualized TNM staging systems for GI NET have been established based on the site of the primary tumor\textsuperscript{[9]}. Several studies have reported the observation that duodenal SBC tumors portend a superior survival when compared to SBC tumors of the jejunum and ileum\textsuperscript{[17-19]}. Similarly, we have observed a superior 10-year DSS for duodenal SBC compared to jejunal and ileal SBC. However, this was only statistically significant on univariate analysis and following multivariable regression analysis, primary tumor site was not an independent predictor of survival.

Given the complexity of surgical decision making, it was not surprising that the extent of surgical resection was not an independent predictor of survival, as operative planning is often influenced by a myriad of factors including, but not limited to, radiologic determination of the presence or absence of metastatic disease, assessment of impending obstruction, and potential complications of a proposed procedure. Currently, the National Comprehensive Cancer network (NCCN) guidelines are lacking specific recommendations regarding surgical management; as an example, options for loco-regional

| Parameters          | Reference | Comparison     | HR     | \(P\) vaule |
|---------------------|-----------|----------------|--------|-------------|
| Primary site        | Duodenum  | Jejunum        | 1.020  | 0.752       |
|                     |           | ileum          | 0.956  | 0.966       |
|                     |           | 41-50          | 1.628  | 0.198       |
|                     |           | 51-60          | 2.491  | 0.009       |
|                     |           | 61-70          | 3.643  | < 0.001     |
|                     |           | > 70           | 6.777  | < 0.001     |
| Age                 | \(\leq 40\) | 2+             | 0.461  | < 0.001     |
|                     | 41-50     | 2+             | 0.721  | 0.269       |
|                     | 51-60     | 2+             | 1.067  | 0.647       |
|                     | 61-70     | 2+             | 1.621  | 0.025       |
|                     | > 70      | 2+             | 1.673  | 0.001       |
| Gender              | Male      | Female         | 1.028  | 0.767       |
| Race                | Caucasian | Black          | 1.320  | 0.079       |
|                     | Asian/other| 2+             | 1.243  | 0.489       |
| Number of primaries | 1         | 2+             | 0.461  | < 0.001     |
| Extent of surgery   | Resection | Local excision | 0.721  | 0.269       |
|                     |           | Debulking      | 1.067  | 0.647       |
| Number of lymph nodes examined | 13+ | 0 | 1.621 | 0.025 |
|                     |           | 1-6            | 1.673  | < 0.001     |
|                     |           | 7-12           | 1.525  | 0.008       |
| T-stage             | T1        | T2             | 1.741  | 0.079       |
|                     | T3        | T4             | 3.265  | < 0.001     |
|                     | T4        | TNOS           | 4.793  | < 0.001     |
| N-stage             | N0        | N1             | 1.856  | 0.438       |
|                     |           | Unknown        | 1.527  | --          |
| M-stage             | M0        | M1             | 2.744  | < 0.001     |

\(^{\text{t}}\text{Log-rank test.}\)

Figure 1 Kaplan-Meier estimate. A: Kaplan-Meier estimates of overall survival (OS) according to primary site of small bowel carcinoid (SBC); B: Kaplan-Meier estimates of disease-specific survival (DSS) according to primary site of SBC.
management of a duodenal SBC range from endoscopic excision to pancreaticoduodenectomy.

Perhaps more intriguing is the combination of findings that N-stage was not an independent predictor of survival, yet the number of LNE was a significant predictor. This addresses diagnostic and prognostic challenges not unique to SBC. Patients without adequate lymph node sampling are likely to be under-staged, however the responsibility for this rests not only with the operating surgeon, but with the examining pathologist as well.[20,21] Unlike other histologies, there are no specific recommendations regarding the extent of LN examination required for adequate pathologic staging. Consequently, as demonstrated in our study, a significant portion of patients with SBC lack complete pathologic staging. The association of LNE with increased disease-specific survival could be a surrogate for any number of systems-based variables in a population study such as this; perhaps patients with greater LNE were cared for in a specialized cancer center.

As expected, we also observed that evidence of metastatic disease is an independent predictor of survival. Currently, cytoreductive surgery with R0 resection has prolonged survival for SBC, but it has not been studied in a controlled fashion, and may be affected by selection bias and underlying tumor biology.[22] To date, for patients with unresectable or metastatic disease, options for adjuvant therapy are limited and that have not been proven to be efficacious for SBC. Somatostatin analogues and targeted therapies such as mTOR inhibitors and tyrosine-kinase inhibitors have been shown to increase time to progression of disease, but no studies have demonstrated a statistically significant DSS benefit in a metastatic setting.[23,24]

In this study, we confirmed that patients with early stage disease do better regardless of primary tumor site. Therefore, early detection and treatment could significantly impact outcomes for SBC. In recent years, there have been substantial advances in our ability to detect and clinically stage SBC.[25-29] Computed tomography and magnetic resonance enteroclysis, capsule endoscopy and octreotide scanning have been shown to have greater than a 90% sensitivity rating for detection and localization of SBC.[30-34]

This study, like many population-based studies, has its limitations. Although this is a large sample size, a majority of the patients had ileal primaries compared to duodenal. Due to the treatment and current NCCN guidelines for SBC, patients with duodenal tumors usually do not have LNs examined and as result, lack complete TNM staging. While the NCCN guidelines propose resection and regional lymphadenectomy for jejunal and ileal tumors, more than a quarter of those patients did not have adequate surgical and pathologic staging in the database. The SEER database lacks indications and specific surgical technique performed as well patient co-morbidities and peri-operative mortality that may play a role in surgical decision making. Recurrence is a common occurrence with SBC and this information is not discernible in the SEER database. Similarly, synchronous or metachronous metastasis are also not specified[35,36].

In the largest study to date evaluating the impact of primary site in SBC, we revealed that primary site is not an independent predictor of SBC-specific survival. We also observed that more than 25% of patients with jejunal and ileal SBC are not receiving the standard of care surgical treatment with a regional lymphadenectomy as per the NCCN guidelines. Further studies are needed to assess the extent of surgical resection and adequate LAD for all stages of jejunal and ileal SBC.

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