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The Distal Predilection of Small Bowel Neuroendocrine Tumors

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Abstract

Background—The small bowel (SB) is the most common site of neuroendocrine tumors (NETs) of the GI tract. These are described as being predominantly jejunoileal, but their exact locations within the SB have not been well defined. We sought to determine prospectively the spectrum of SBNET locations.

Methods—Patients undergoing exploration for SBNET primaries had measurement of bowel length, tumor locations, and resection length recorded. Correlations of clinicopathologic factors were performed, and analysis done utilizing Welch's *t* test, Chi square test, and the Kaplan-Meier method.

Results—Measurements were recorded in 123 patients, 107 of whom had complete information. Multifocal tumors (MTs) were found in 69 (56%) and unifocal (UTs) in 54 (44%) patients. Only 1 of 107 patients had a tumor within 100 cm of the ligament of Treitz (LT), whereas 77 of 107 (72%) had tumors within 100 cm of the ileocecal valve (ICV). No MTs were found within 100 cm of LT, whereas 41 of 60 (68%) patients had all (10) or at least one tumor (31) located within 100 cm of the ICV. MTs required a mean resection length of 108 versus 59 cm for UTs ($p < 0.01$). Seventy-seven percent of UTs (36/47) were within 100 cm of ICV. Tumors occurring only between > 100 cm from the LT and ICV were seen in 29 of 107 (27%) patients.

Conclusions—SBNETs are frequently multifocal and most commonly located within 100 cm of the ICV. SBNETs are less prevalent proximally in the small bowel, which may result from anatomic differences in enterochromaffin cell density, hormonal factors, or environmental exposures in the distal SB.

The incidence of neuroendocrine tumors (NETs) is rising, reaching 6.98 cases per 100,000 population in 2012, an increase of almost 640% compared with rates in 1973.¹ Small bowel NETs (SBNETs) also surpassed adenocarcinoma as the most common small bowel malignancy, and general surgeons are encountering these patients with increasing frequency.²

SBNETs can be subclassified as either duodenal or jejunoileal. The latter is difficult to subcategorize, because there is no clear anatomical transition point between the jejunum and ileum. Duodenal tumors differ from jejunoileal tumors in that they are considered foregut in origin and are commonly incidentally discovered on endoscopy. Jejunoileal SBNETs are of midgut origin, and studies defining their location in the context of total small bowel length (SBL) have been lacking, which is important for surgical decision-making.

Most studies of SBNETs report that the most common location is in the ileum. Moertel et al.³ reported in 1961 that 2% of SBNETs were in the duodenum, 7% in the jejunum, 89% in the ileum, and 2% in Meckel's diverticula. Unfortunately, there is no clear anatomic transition from jejunum to ileum, so descriptions of SBNET locations are generally imprecise. For example, a review of SBNETs in the Surveillance, Epidemiology and End Results (SEER) registry reported that although 68% of cases where the site was specified (including duodenal) were ileal tumors, the location of nearly half of tumors were unknown.⁴

The incidence of multifocality is another important feature of SBNETs, which influences the amount of bowel resection. Multifocality has been reported to occur in 13–45% of SBNET series, and the decision of how much to bowel to resect should be made within the context of knowing the total SBL.^{3,5–7} The few studies that have looked at SBL have reported a mean linear length of 459–564 cm.^{8–11} In this study, we reviewed the exact tumor location for all of our patients undergoing primary operation for SBNETs, the incidence of multifocality, the length of resected bowel, and the total SBL to better understand anatomical considerations important to the management of these patients.

METHODS

An Institutional Review Board-approved surgical database was queried for patients presenting for resection of SBNETs at a single institution. Patients were excluded if they had duodenal tumors, prior bowel resection, or insufficient intraoperative documentation. All patients underwent resection by a single surgeon, who routinely measured the location of each tumor relative to the ligament of Treitz (LT) and ileocecal valve (ICV), the total SBL, and the length of the resected specimen. Measurements were performed utilizing a standard 15-cm plastic ruler placed on the antimesenteric border of the small bowel during palpation, with care taken not to stretch or grossly deform the bowel. Measurements were documented within the operative note and these values, not pathology reports, were used along with other clinicopathologic data within the database.

Small bowel location was divided into three domains: those tumors occurring within 100 cm of the LT (designated as Proximal or P), those found within 100 cm of the ICV (Distal or D), and those located greater than 100 cm from both the LT and ICV (Middle or M). This was done in an attempt to describe tumors that were definitively within the jejunum (proximal group) and those definitively within the ileum (distal group), because there is no clear anatomic boundary between these two anatomic sites. In cases where multifocal disease resulted in tumors occurring in more than one domain, the patients were categorized as Middle-Distal (MD). These groups were then compared to determine if there were

differences in survival or other clinicopathologic characteristics using the Kaplan-Meier method, Welch's *t* test, and Chi square test. In addition, logistic regression and Welch's *t* test were used to determine if any clinical factors were associated with a difference in total SBL.

RESULTS

Between 2001 and 2017, there were 209 patients identified who underwent surgical resection of SBNETs, of whom 123 met criteria for inclusion in this study. There were 73 men and 50 women with a mean age at surgery of 61 (range 30–84) years (Table 1). Multifocal tumors were identified in 69 of 123 (56.1%) patients. The most common grade of tumors was G1, with 60 (49%) primary tumors meeting this definition, and the most common T stage was T3 (49%). The majority (96%) had lymph node involvement and distant metastases (81%). The mean tumor size was 2.0 (range: 0.4–6.6) cm. Complete measurements defining the exact location of primary tumors (P, M, D, or MD) were recorded in 107 of 123 patients, and the distribution of these tumors is shown in Fig. 1. The 16 patients in whom the primary tumor location was not recorded were missing some component of measurement but were included to provide further information regarding either multifocality, total SBL, or resection length.

Patients had tumors located distally (< 100 cm from ICV) in 72% (77/107) of cases (Table 2). This number includes 31 patients with multifocal disease who had tumors in both the distal and middle sections (MD group). Patients had tumors in the distal 100 cm of small bowel in 77% of unifocal and 68% of multifocal cases. Patients with multifocal disease most commonly had tumors within the middle section for 50 of 60 (83%), and 31 of 60 of these patients also had tumors in the distal section (MD group).

One patient with a proximal tumor and the 31 patients in the MD group were excluded from clinicopathologic comparisons due to the small sample size and tumors located in two domains, respectively. These analyses focused on unifocal patients and multifocal patients with clear delineation of tumors, i.e., those who had distal only tumors (*n* = 10) or middle-only tumors (*n* = 19). There was no significant difference in grade, T stage, rate of lymph node involvement, distant metastases, or preoperative biochemical markers between the middle (*n* = 46) and distal (*n* = 29) groups. Distal tumors were significantly more likely to be unifocal in 36 of 46 (78%), and larger than middle tumors, which were 2.3 versus 1.6 cm, respectively (*p* < 0.01 for both; Table 3). On survival analysis, there was no significant difference in median progression-free survival (PFS) for distal and middle tumor patients (1.68 vs. 2.02 years., respectively) or median overall survival (OS) (6.61 years vs. not reached, respectively; Table 3). This remained true on subgroup analysis of unifocal and multifocal tumors, with the exception that the median OS in the multifocal distal tumors was significantly decreased (4.67 years) compared with middle tumors (median not reached, *P* = 0.04).

The total SBL was recorded in 83 of 123 patients, with a mean length of 530 (range 320–845) cm. Patients with unifocal and multifocal tumors had similar SBL (529 vs. 530 cm, respectively, *P* = 0.97), mean size of largest lymph node (1.89 vs. 1.92 cm, respectively, *P* = 0.93), and mean number of positive nodes (4.93 vs. 5.96, respectively, *P* = 0.47). Patients in

the unifocal group had significantly less small bowel removed than in the multifocal group (59 vs. 108 cm, $p < 0.01$). Linear regression identified male sex and increased height as having a statistically significant association with increased SBL (Table 4). When these same variables were tested by multivariate analysis, only patient height remained as an independent variable associated with SBL ($p < 0.01$).

DISCUSSION

This study presents a thorough description of SBNET location in relation to the LT and ICV and the distribution of multifocal tumors. The results support the hypothesis that SBNETs arise most commonly in the ileum, and more specifically, within the final 100 cm of the small bowel. Only one patient had a tumor within 100 cm of the LT, whereas the majority (72%) of SBNET patients had tumors in the distal 100 cm of the small bowel. That number increases to 93% if the cutoff is raised to the distal 150 cm of small bowel. Moertel et al.³ found a similar phenomenon in SBNET location in 137 necropsy and 72 surgical specimens, reporting that 92.5% (185/200) of SBNETs arising distal to the LT were actually in the ileum. They further reported that for ileal SBNETs, 14% were upper, 18% middle, and 68% were in the lower ileum, with 56% within the last 2 feet. The SEER data presented by Hari et al.⁴ corroborate these findings on a larger but less granular scale, with 89% (2567/2891) of tumors distal to the LT reportedly occurring in the ileum. This assessment, however, could be highly inaccurate given that 46% of patients in the database did not have a tumor location recorded, and the accuracy of tumor location recorded in tumor registries is likely very imprecise. Modlin et al.¹² came to a similar conclusion in their analysis of 13,715 carcinoid tumors in SEER, where they described an increased propensity for SBNET development moving distally along the small bowel.

In the current study, there were not many clinical differences between distal and middle tumors, but the percentage of distal tumors was significantly more pronounced in unifocal as compared to multifocal disease (78% vs. 34, $p < 0.01$), although this result may be skewed by the exclusion of the 31 multifocal patients with tumors in both the distal and middle segments. Distal tumors also tended to be larger (2.3 cm) than middle tumors (1.6 cm, $p < 0.01$). Overall, tumor location did not have an impact on PFS or OS, but on subgroup analysis, multifocal tumors that occurred only in the distal segment had a shorter median OS than multifocal tumors that occurred only within the middle segment (4.67 years vs. not reached; $P = 0.04$).

The propensity for tumor formation in the distal ileum may relate to environmental contributors specific to the terminal ileum. It is the site of bile salt and vitamin B12 absorption, glucagon-like peptide 1 (GLP-1) expression, and may have more stasis of its contents due to the braking actions of the ileocecal valve. Sjolund and colleagues reported an increase in cells staining for glucagon/Glicentin in the distal ileum.¹³ These findings may be a secondary result of bile acid stimulated release of GLP-1, as described by Brighton et al.¹⁴ in their study of transgenic mice with fluorescently labeled L-cells (which are GLP-1 secreting apical cells located within the ileum and colon). The hypothesis that GLP-1 may have a role in distal SBNET formation or maintenance is supported by the findings of Wada and Yagihashi, which demonstrated GLP-1 receptor (GLP-1R) expression in all of their

midgut SBNETs, which is not only stimulated by GLP-1 but also by glucagon.¹⁵ Additionally, the proliferative effects of GLP-1 activation were detailed by Koehler et al.¹⁶ They described an increase in polyp size and number, specifically in the distal small bowel, in rats treated with the GLP-1R agonist Exenatide, which suggested a proliferative effect of GLP-1. These results imply that there are important histological, functional, and transcriptional changes occurring in the terminal ileum that have not been completely defined.

Anatomically, the distal ileum has decreased villus height, absence of *plicae circulares* and increased lymphoid aggregates.^{17–19} However, it is not clear that there are more enterochromaffin (EC) cells in the terminal ileum, which would be one possible explanation for why SBNETs are more common here. Studies staining for 5-HT in both the guinea pig and opossum GI tracts revealed the highest density of stained cells in the pylorus and a similar density of cells seen moving from the duodenum to the proximal and distal small bowel.^{20,21} Few studies have been performed in humans, but Singh et al. reported on the incidence of argentaffin staining throughout the GI tract in human fetuses. He reported that the highest density of stained cells was seen in the duodenum, and the density decreased in a cranio-caudal direction until this increased again in the terminal ileum.²² The presence of increased lymphoid tissue in the terminal ileum could be another predisposing factor to SBNETs, because inflammation has been shown to increase the number of endocrine cells in the small and large bowel.^{19,23–26} Hernandez-Trejo et al.²⁷ also reported that pro-inflammatory cytokines increased the number of chromogranin A-producing cells in colonic mucosa of mice. Whether this increased density of lymphoid tissue in the terminal ileum with increased potential for inflammation leads to a higher incidence of SBNETs remains an unanswered question at this time.

There was a high percentage of multifocal disease within this patient cohort, which was found in 69 of 123 (56%) patients—higher than the 13–45% described in other published series.^{3,5–7,28} It remains to be seen if this finding is secondary to an increased rate of multifocal tumor identification in patients referred to our center, or more likely, that this increase was due to a more thorough evaluation of the small bowel for tumors by careful palpation. The average span of multifocal tumors was 97 cm, and the average resection length was 108 cm, which was significantly longer than the average of 59 cm resected from patients with unifocal tumors ($p < 0.01$).

We demonstrated that the mean small bowel length (SBL) (LT to ICV) in our SBNET patient cohort was 530 cm, which is very similar to the range of mean SBLs reported by prior studies of normal living controls (range 459–564 cm).^{8–11} Guzman et al.⁸ reported measurement of SBL in 393 patients undergoing intestinal bypass for obesity or hyperlipidemia and found a mean jejunoileal length of 491 cm. Nordgren and colleagues looked at SBL in 594 patients with inflammatory bowel disease and 77 controls and reported a mean length of 564 cm in the controls—the longest reported.¹⁰ Teitelbaum et al.¹¹ documented a mean SBL of 506 cm in 240 patients undergoing laparotomy for colorectal resection. Hosseinpour et al.⁹ compared the length of small bowel in 100 live patients compared with 30 cadavers and found a mean SBL of 459 versus 632 cm, respectively. The factors that were significantly correlated with increasing SBL in the current study were male

sex and increasing height (Table 4). Nordgren et al. and Teitelbaum et al. also noted the influence of height and male sex in their studies, whereas Guzman et al. and Hounnou et al. found that male sex but not height had significant influence on SBL.^{8,10,11,29} Multivariate analysis revealed that patient height was the only factor that was independently associated with a significant difference in SBL in our cohort, a finding also seen in the study by Teitelbaum et al.

This study demonstrates that not only do SBNETs more commonly occur in the ileum, but also that more than two-thirds of patients have a tumor in the final 100 cm of the small bowel, and very few tumors occur in the proximal jejunum. This indicates that there is something inherent to the terminal ileum that makes it a more favorable site for SBNET formation, and thus further studies enumerating the density of EC cells along the small bowel, as well as clarifying environmental and hormonal influences, are needed to shed more light on this phenomenon. We also found a higher incidence of SBNET multifocality than previously reported through careful inspection. Finally, we also confirmed the mean length of the human small bowel in vivo and demonstrated its correlation with patient height.

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FIG. 1.
Tumor location along the small bowel. The bowel length was standardized to 500 cm with the ileocecal valve designated as 0 and the ligament of Treitz designated as 500. The location of unifocal tumors are displayed in blue. The span of multifocal tumors are displayed by black lines with yellow markers at each end with the number of tumors in that span noted to the left

TABLE 1

Patient and tumor characteristics

Sex	
Male	73 (59%)
Female	50 (41%)
Mean age at surgery (yr)	61.2 (30.7–84.3)
Multifocal tumors	69/123 (56%)
Mean tumor size (cm)	2.02 (range 0.40–6.60)
Grade ^a	
G1	60 (49%)
G2	47 (38%)
G3	1 (1%)
Not specified	15 (12%)
T stage ^a	
T1	4 (3%)
T2	18 (15%)
T3	61 (49%)
T4	40 (33%)
Positive lymph nodes	116/121 (96%)
Distant metastases	100/123 (81%)
Location	
Proximal	1 (1%)
Middle	29 (27%)
Distal	46 (43%)
Middle-Distal	31 (29%)
NS	16

NS not specified

^aStage and grade based on WHO staging system

TABLE 2

Location of tumors and focality

	Distal (< 100 cm from ICV)	Middle (> 100 cm from LT and ICV)	Proximal (< 100 cm from LT)
All tumors (<i>n</i> = 107)	77/107 (72%) ^{<i>a</i>}	60/107 (56%) ^{<i>a</i>}	1/107 (1%)
Unifocal (<i>n</i> = 47)	36/47 (77%)	10/47 (21%)	1/47 (2%)
Multifocal (<i>n</i> = 60)	41/60 (68%) ^{<i>a</i>}	50/60 (83%) ^{<i>a</i>}	0/60 (0%)

^{*a*} 31 patients had tumors spanning in both distal and middle domains

TABLE 3

Comparison of middle only versus distal only groups

	Distal (n = 46)	Middle (n = 29)	p value
Unifocal	36/46 (78%)	10/29 (34%)	< 0.01
Mean tumor size (cm)	2.3	1.6	< 0.01
Grade	-	-	0.89
G1	29 (63%)	10 (35%)	
G2	15 (33%)	14 (48%)	
G3	0 (0%)	0 (0%)	
NS	2 (4%)	5 (17%)	
T stage	-	-	0.67
T1	1 (2%)	2 (7%)	
T2	6 (13%)	5 (17%)	
T3	21 (46%)	13 (45%)	
T4	18 (39%)	9 (31%)	
Positive nodes	93%	97%	0.50
Distant metastases	74%	93%	0.10
Preop CGA, ng/ml (mean)	2038	2097	0.97
Preop serotonin, ng/ml (mean)	977	1247	0.14
Mean follow-up (yr)	1.65	1.67	0.97
Median PFS (yr)			
All	1.68	2.02	0.18
Unifocal	1.68	NR	0.55
Multifocal ^a	1.72	2.02	0.11
Median OS (yr)			
All	6.61	NR	0.12
Unifocal	6.61	NR	0.52
Multifocal ^a	4.67	NR	0.04

Bold values indicate $p < 0.05$

CGA chromogranin A; NR not reached; NS not specified; OS overall survival; PFS progression-free survival

Excludes MD group patients

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TABLE 4

Factors affecting small bowel length

Factor	Univariate R ²	<i>p</i> value	Multivariate <i>p</i> value
Male sex	0.09	< 0.01	0.60
Age	– 0.01	0.46	0.53
Height	0.22	< 0.01	< 0.01
Tumor number	0.01	0.20	0.21
Multifocal	– 0.01	0.97	0.10
No. of positive lymph nodes	– 0.01	0.52	0.97

Bold value indicates $p < 0.05$