

Kendall J. Keck<sup>1</sup>, Aaron T. Scott<sup>1</sup>, Jessica E. Maxwell<sup>1</sup>, Alan F. Utria<sup>1</sup>, Andrew M. Bellizzi<sup>2</sup>, Thomas M. O'Dorisio<sup>3</sup>, and James R. Howe<sup>1</sup>

<sup>1</sup>University of Iowa Carver College of Medicine Departments of Surgery<sup>1</sup>, Pathology, and Internal Medicine<sup>3</sup>

SUPPORTED BY THE IOWA NEUROENDOCRINE TUMOR SPORE

## Introduction

The Small Bowel (SB) is the most common site of neuroendocrine tumors (NETs) of the GI tract<sup>1</sup>. While most studies of SBNETs report the most common location as the ileum<sup>2</sup>, the exact locations of these tumors have not been well defined. Another important issue relating to SBNETs is the incidence of multifocality. Various studies have reported that from 13 to 45% of patients with SBNETs present with multiple small bowel tumors<sup>3</sup>. Finally, the total length of the small bowel must be taken into account along with the location of the tumor and presence of multifocality when determining the extent of resection for SBNETs. Previous studies have reported the mean length of the small bowel from 459 to 564 cm<sup>4</sup>.

The objective of this study was to review a surgical database of patients undergoing primary operations for SBNETs to determine tumor location, the incidence of multifocality, the length of resected bowel, and the total small bowel length to better understand the anatomical considerations in the management of these patients.

## Methods

A surgical NET database was reviewed and patients undergoing primary resection of SBNETs were identified. Exclusion criteria included duodenal tumors, prior bowel resections, or insufficient operative documentation. All patients underwent resection by a single surgeon and the distance to the ligament of Treitz (LT), the ileocecal valve (ICV), total bowel length, and length of resected specimen were all measured at the time of surgery. The small bowel was divided into 3 domains: proximal (P, within 100 cm of LT), distal (D, within 100 cm of the ICV) and middle (M, greater than 100 cm from both the LT and ICV). Patients with multifocal tumors in both middle and distal domains were classified as middle-distal (MD). Survival and other clinicopathologic characteristics were compared across groups.

## Acknowledgements

This project was supported by funding through T32 Grant: T32CA148062 and SPORE Grant: P50CA174521.

## Results

Characteristic	Count (Percentage)
<b>Sex</b>	
Male	65 (63%)
Female	39 (37%)
<b>Mean Age at Surgery (yrs)</b>	63.9
<b>Multifocal Tumors</b>	61/104 (59%)
<b>Mean Tumor Size (cm)</b>	2.03
<b>Grade</b>	
G1	49 (47%)
G2	39 (38%)
G3	1 (1%)
Not Specified	15 (14%)
<b>T Stage</b>	
T1	3 (3%)
T2	15 (14%)
T3	50 (48%)
T4	36 (35%)
<b>Positive Lymph Nodes</b>	97/102 (95%)
<b>Distant Metastases</b>	84/104 (81%)
<b>Location</b>	
Proximal	1 (1%)
Middle	25 (28%)
Distal	36 (41%)
Middle-Distal	26 (30%)
NA	16

	Distal (<100 cm from ICV)	Middle (>100cm from LT and ICV)	Proximal (<100cm from LT)
All Tumors (n=88)	62/88 (71%)*	51/88 (58%)*	1/88 (1%)
Unifocal (n=36)	28/36 (78%)	7/36 (19%)	1/36 (3%)
Multifocal (n=52)	34/52 (65%)*	44/52 (85%)*	0/52 (0%)

\* 26 patients had tumors spanning in both distal and middle domains

	Distal (n=36)	Middle (n=25)	p-value
Unifocal	28/36 (78%)	7/25 (28%)	<0.01
Tumor size (cm)	2.3	1.5	<0.01
Grade	-	-	0.53
G1	20 (56%)	10 (40%)	
G2	14 (39%)	10 (40%)	
G3	0 (0%)	0 (0%)	
Not Specified	2 (5%)	5 (20%)	
T stage	-	-	0.18
T1	1 (3%)	1 (4%)	
T2	3 (8%)	5 (20%)	
T3	17 (47%)	10 (40%)	
T4	15 (42%)	9 (36%)	
Positive Nodes	91%	96%	0.48
Distant Mets	75%	92%	0.07
Preop CGA (mean)	2609	1970	0.76
Preop Serotonin (mean)	1025	1225	0.33

	Distal (n=36)	Middle (n=25)	p-value
<b>Mean Follow-up (yrs)</b>	2.06	1.90	0.81
<b>Median PFS (yrs)</b>			
All	1.68	2.02	0.17
Unifocal	1.68	NR	0.6
Multifocal*	1.72	2.02	0.12
<b>Median OS (yrs)</b>			
All	6.61	NR	0.12
Unifocal	6.61	NR	0.53
Multifocal*	4.67	NR	0.04

\* Excludes MD group patients; NR = not reached

## Discussion

This study represents the first quantitative description of SBNET location in relation to the LT and ICV. The majority of SBNETs are multifocal and the most common location is within 100 cm of the ICV. The preponderance of distal tumors in this cohort is consistent with previous descriptions of SBNET location, while the incidence of multifocality was higher (59%) than previous studies have reported<sup>3</sup>. The propensity for tumor formation in the distal ileum may relate to different environmental or anatomical factors specific to this location. While the exact mechanism for the distal predilection remains to be discovered, several possible explanations exist, including a hypothetical increased density of enterochromaffin cells in the terminal ileum, different hormone levels (e.g. GLP-1<sup>5,6</sup>), or bile salt resorption. Overall, tumor location did not have a significant impact on PFS or OS.

## Conclusions

The majority of SBNETs are multifocal and occur in the distal ileum. This distal predilection of SBNETs is not well understood, and further studies clarifying the predisposing environmental and anatomical factors in the distal ileum are warranted. Distal tumors were larger and more likely to be unifocal than middle tumors, but there was no significant difference in PFS or OS between distal and middle tumors.

### Work Cited

- Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients with Neuroendocrine Tumors in the United States. *JAMA Oncol.* 2017; 2013(5):239-44.
- Hari DM, Goff SL, Reich HJ, Leung AM, Sim MS, Lee JH, et al. Small bowel carcinoid: Location isn't everything! *World J Gastrointest Surg.* 2013;5(6):239-44.
- Yantiss RK, Odze RD, Farraye FA, Rosenberg AE. Solitary versus multiple carcinoid tumors of the ileum: a clinical and pathologic review of 68 cases. *Am J Surg Pathol.* 2003;27(6):811-7.
- Hosseinpour M, Behdad A. Evaluation of small bowel measurement in alive patients. *Surg Radiol Anat.* 2008;30(8):653-5.
- Wada R, Yagihashi S. The expression of glucagon-like peptide-1 receptor and dipeptidyl peptidase-IV in neuroendocrine neoplasms of the pancreas and gastrointestinal tract. *Endocr Pathol.* 2014;25(4):390-6.
- Koehler JA, Baggio LL, Yusta B, Longuet C, Rowland KJ, Cao X, et al. GLP-1R agonists promote normal and neoplastic intestinal growth through mechanisms requiring Fgf7. *Cell Metab.* 2015;21(3):379-91.

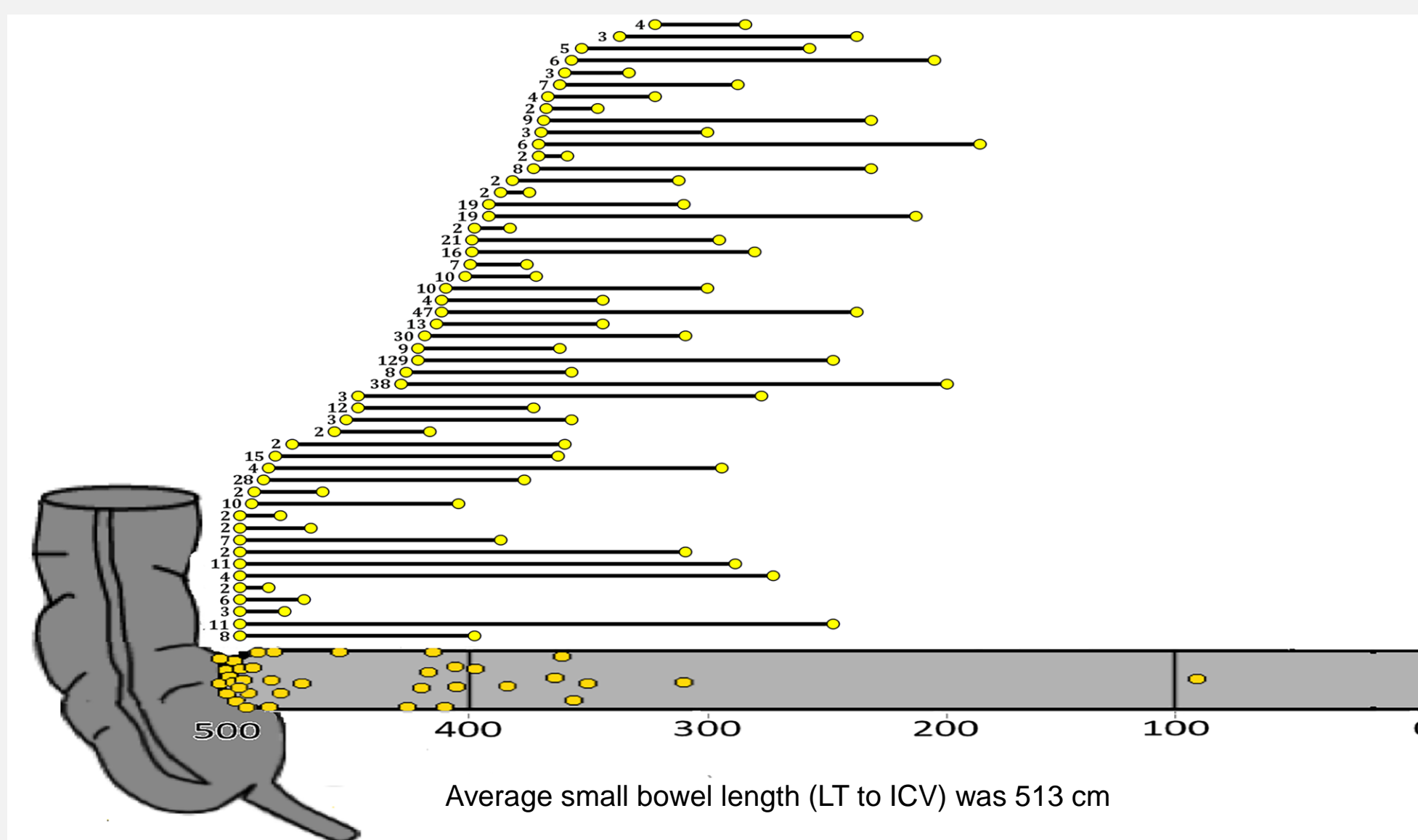


Figure 1: Locations of Unifocal and Multifocal SBNETs: Unifocal tumors are shown in rectangle, multifocal tumors are shown above with number to the left indicating the number of tumors and the length of the line indicating the span.

Average small bowel length (LT to ICV) was 513 cm