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The Impact of Failure to Achieve Symptom Control After Resection of Functional Neuroendocrine Tumors: An 8-Institution Study from the US Neuroendocrine Tumor Study Group

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Synopsis: Using a multi-institutional database, this study found that for patients with functional neuroendocrine tumors, the failure to achieve symptom improvement after resection is associated with earlier disease recurrence even when accounting for histologic type, presence of genetic syndromes, R1 resection margin, and lymph node involvement.

Abstract:

Background: The goals of resection of functional neuroendocrine tumors (NETs) are two-fold: oncologic benefit and symptom control. The interaction between the two is not well understood.

Methods: All patients with functional NETs of the pancreas, duodenum, and ampulla who underwent curative-intent resection between 2000 and 2016 were identified. Using Cox regression analysis, factors associated with reduced recurrence-free survival (RFS) were identified.

Results: 230 patients underwent curative-intent resection. 53% were insulinomas, 35% gastrinomas, and 12% were other types. 21% had a known genetic syndrome, 23% had lymph node (LN) positivity, 80% underwent an R0 resection, and 14% had no postoperative symptom improvement (SI). Factors associated with reduced RFS included non-insulinoma histology, presence of a known genetic syndrome, LN positivity, R1 margin, and lack of SI. On multivariable analysis, only the failure to achieve SI following resection was associated with reduced RFS. Considering only those patients with an R0 resection, failure to achieve SI was associated with worse 3-year RFS compared to patients with SI (36% vs 80%; p=0.006).

Conclusions: Failure to achieve symptomatic improvement after resection of functional NETs is associated with worse recurrence-free survival. These patients may benefit from short-interval surveillance imaging postoperatively to assess for earlier radiographic disease recurrence.

Introduction

Neuroendocrine tumors (NETs) consist of a heterogeneous group of tumors with distinct molecular, histologic, and clinical features with complex and often challenging management strategies.(1) These tumors are traditionally divided as either functional or nonfunctional: functional NETs produce peptide hormones which cause symptoms, while nonfunctional NETs are typically clinically silent until they produce mass effect or bleed. Functional NETs are comprised of several histologic types. In sporadic cases, the most common type is insulinoma, followed by gastrinoma and other types including glucagonoma, VIPoma, and somatostatinoma.(2) Each type is characterized by a discrete

secretory phenotype and a predictable clinical syndrome. (3) The otherwise distinguishable clinical syndromes, however, can become muddied when functional NETs occur in the background of a hereditary tumor syndrome. These tumor syndromes, the most common being multiple endocrine neoplasia-I (MEN-I), provide unique challenges in the management of these patients.(4-10)

For both sporadic and hereditary functional NETs, surgical resection provides the only potential for cure in patients with locoregional disease. Although NETs are generally indolent tumors, many patients undergo resection to relieve the clinical symptoms associated with functional NETs.(11) Aside from insulinomas which are commonly treated with enucleation, most functional NETs require a wide oncologic resection with regional lymphadenectomy to achieve cure.(12, 13) Curative oncologic resection, however, is not always possible, as many patients present with distant disease due to the propensity of these tumors to metastasize to the liver. Yet even in the metastatic setting, multiple groups have demonstrated that resection of liver metastases, cytoreductive surgery, and local ablative therapy may be associated with improved survival and alleviate symptoms of functional NETs.(14-16) These findings suggest a potential interaction between the relief of clinical symptoms of functional NETs, known oncologic parameters, disease recurrence, and survival.

Little information is available regarding the relationship between the achievement of hormone-specific symptom control and oncologic benefit after surgery for functional neuroendocrine tumors. The aim of this study is to use a large, multi-institutional database to define the association between the failure to achieve symptom improvement after surgical resection for functional neuroendocrine tumors and clinical outcomes. We

also aimed to determine other clinicopathologic factors associated with worse outcomes for functional NETs. Lastly, we aimed to establish the prognostic value of symptom improvement compared to other known oncologic parameters.

Methods

Patients were identified using the United States Neuroendocrine Tumor Study Group (US-NETSG), a collaborative of 8 US-based institutions (Emory University, The Ohio State University, Stanford University, Virginia Mason University, Vanderbilt University, University of Michigan, University of Wisconsin, and Washington University in St. Louis). Institutional Review Board (IRB) approval was obtained at each institution. All patients who underwent curative-intent surgical resection of a functional NET of the pancreas, duodenum, or ampulla between 2000 and 2016 were included. Functional tumor status was defined by clinical and histopathologic diagnoses of insulinoma, gastrinoma, glucagonoma, somatostatinoma, or VIPoma. Symptomatic non-functional NETs with a carcinoid syndrome were excluded. Patients with genetic tumor syndromes were included, specifically MEN-I, Von Hippel-Lindau disease, neurofibromatosis 1, and tuberous sclerosis. Final resection status was defined as R0 (complete gross tumor clearance with negative microscopic margins), R1 (complete gross tumor clearance with positive microscopic margins), and R2 (incomplete gross tumor clearance). Patients with mortality less than 30 days after surgery were excluded.

Data on demographics, perioperative conditions, and histopathology were collected. Pathology was reviewed by expert GI pathologists at each institution. Staging was based on the American Committee on Cancer (AJCC) 7th edition guidelines. (17)

Recurrence-free survival (RFS) data were collected from the electronic medical record. Disease-recurrence was defined strictly as the radiographic recurrence of disease.

The primary aim was to assess the association between clinicopathologic variables and decreased RFS. The failure of symptom improvement, defined as the patient-reported lack of clinical symptom improvement after surgery, was of particular interest. Symptoms were specifically related to the secretory phenotype of the resected functional tumor, as recorded in post-operative visit documentation in the electronic medical record.

All statistical analysis was conducted using SPSS 22.0 software (IBM Inc., Armonk, NY). Chi-squared analysis was used to compare categorical variables, and Student's t-test was used for continuous variables. Univariate and multivariable Cox regression analyses were used to determine the association of the variables of interest with reduced RFS. All variables which correlated with reduced RFS at statistical significance of $p<0.1$ on univariate analysis were included in the multivariable model. Kaplan-Meier survival plots for RFS were constructed to compare patients with and without symptom improvement after surgery. Statistical significance was defined as $p<0.05$.

Results

Demographics

Of 2,181 total patients within the US-NETSG database, 230 patients underwent curative-intent resection of a functional NET. Demographic characteristics are listed in Table 1. Average age was 52.4 (±15.3) years and 110 (47.8%) patients were male. Forty-eight (20.9%) patients had functional tumors associated with a hereditary tumor

syndrome, the most common being MEN-I. The majority of the functional tumors were insulinomas (122, 53%), followed by gastrinomas (80, 34.8%), and glucagonomas (11, 4.8%).

Perioperative Data and Pathology

The most frequent location for a functional NET in this cohort was in the pancreas (194, 84.3%), followed by the duodenum (26, 11.3%). Perioperative and pathologic characteristics are listed in Table 2. One-hundred and two (44%) patients underwent enucleation of their tumors, 26 of whom had lymph node retrieval with enucleation, and 128 (56%) patients underwent anatomic resection. There was no difference in recurrence-free survival between patients who underwent enucleation versus those who underwent anatomic resection (p=0.152). The majority of patients had well-differentiated tumors (181 patients, 78.7%) with a Ki-67 of less than 3% (92, 40%). Final resection status was R0 for 184 (80%) patients and R1 for 46 (20%) patients. Radiographic surveillance strategies varied among patients with 35 (15%) patients undergoing cross-sectional imaging at every 3-4 months, 73 (32%) patients at every 6 months-1 year, 2 (1%) patients at greater than once per year, and 120 (52%) patients undergoing no set surveillance strategy or an unknown surveillance strategy. Postoperatively, 108 (47%) patients experienced symptom improvement, 17 (7.4%) did not experience symptom improvement, and 105 (45.7%) of patients had unknown symptom improvement following surgery. Median follow-up time was 29.4 months. Of patients with disease recurrence, 12 (32.4%) had locoregional recurrence, 19 (51.4%) had distant recurrence, and 6 (16.2%) patients had both locoregional and distant recurrences. Seventeen patients without symptom improvement after surgery experienced disease recurrence (Table 3).

Relationship between Symptom Improvement and Preoperative and Pathologic Factors

Patients who experienced symptom improvement after surgery were more likely to not have a genetic tumor syndrome (p=0.001), have insulinoma tumor histology (p=0.014), and have an R0 resection (p=0.007), as seen in Table 4. Multifocality, tumor differentiation, Ki-67 index, lymph node positivity, and lymphovascular/perineural invasion status were not associated with symptom improvement after surgery.

Symptom Improvement and Recurrence-free Survival

On univariable analysis, factors associated with reduced RFS were non-insulinoma tumor histology (gastrinoma: HR 2.8, 95% CI 1.3-6.1,p=0.006, other: HR 2.7, 95% CI 1.0-7.2 p=0.042), having a known genetic tumor syndrome (HR 1.8, 95% CI 0.9-3.5, p=0.077), lymph node positivity (HR 1.8, 95% CI 0.9-3.6, p=0.080), R1 resection margin (HR 2, 95% CI 1.0-3.9, p=0.052) and failure of symptom improvement after surgery (HR 3.1, 95% CI 1.3-7.2, p=0.008) (Table 5). Tumor location, multifocality, and tumor differentiation were not associated with decreased RFS. On multivariable analysis however, only the failure of symptom improvement was associated with decreased RFS (HR 4.7, 95% CI 1.3-16.6, p=0.016).

For this entire cohort, patients without symptom improvement had a lower 3-year RFS than patients who did experience symptom improvement (49.9% vs 80.3%, p=0.005, Figure 1a). When considering only patients with R0 resections, patients without symptom improvement continued to have a decreased 3-year RFS compared to patients with symptom improvement after surgery (36% vs 80%, p=0.006, Figure 1b).

Discussion

Functional neuroendocrine tumors are surgically resected for both oncologic benefit and for symptom control, but the interaction between the two is not clear. This study found that patients who fail to experience hormone-specific symptom improvement after surgical resection tend to have worse RFS than those who do experience symptom improvement, even in patients who received an R0 resection. When evaluating other variables associated with worse RFS, the failure of symptom improvement persisted as the only factor associated with decreased RFS when considering resection status, lymph node positivity, the presence of a hereditary tumor syndrome and histologic type of tumor. Thus, the failure of symptom improvement after resection may serve as an important clinical indicator for worse prognosis and earlier radiographic recurrence of disease.

NETs tend to be more indolent tumors with a better prognosis compared to other malignancies within the gastrointestinal tract.(18) Compared to nonfunctional NETs, functional NETs are described to carry a better prognosis as they are more likely to present earlier in their disease course with identifiable clinical manifestations.(19-21) Even with generally favorable outcomes, certain subtypes of functional NETs are aggressive, particularly those with non-insulinoma histology. Gastrinomas cause clinical symptoms leading to significant morbidity, and many patients with gastrinomas have metastatic disease at the time of presentation.(2) Even with this more aggressive histopathologic tumor type, patients may benefit from surgery with improvement in symptom control and increased survival.(22) Patients with functional NETs in the background of hereditary tumor syndromes have also been described to have worse

prognoses, due to the presence of multifocal tumors which occur earlier in age. Multiple groups have previously demonstrated that in well-selected patients, surgical resection can both alleviate symptoms and increase survival.(4, 23, 24) Our study confirmed previous findings that patients with non-insulinoma histology and genetic tumor syndromes have lower RFS. However when examining these variables together in a multivariable model with failure of symptom improvement after surgery, only the failure of symptom improvement persisted as being associated with decreased RFS.

In this cohort of functional NETs, symptom control likely serves as a perceptible measure for oncologic control. Symptom persistence may represent a manifestation of other oncologic parameters, such as micro-metastatic disease. This is supported by a mouse study performed by Li et al. in which micrometastases of pancreatic β-cell tumors express insulin even at distant sites such as the lung and spleen.(25) In our cohort of patients who underwent R0 resections however, there was no radiographic, pathologic or surgical evidence which would suggest these patients had residual disease. These findings suggest that symptom persistence after surgery may serve as a strong surrogate marker for persistence of tumor cells within the body. Although there is no current standard adjuvant therapy for patients with functional NETs, as the therapeutic armamentarium grows, it is feasible that symptom persistence after surgery may be a reasonable selection criterion for patients in future clinical trials. (26, 27) Even more importantly however, this study demonstrates that patients with symptom persistence may warrant more frequent radiographic surveillance to detect earlier disease recurrence.(28)

The retrospective design and multi-institutional nature of this study pose certain limitations. Capturing complete recurrence data in a retrospective design presented some

challenges, as some patients were lost to follow-up. Also, surgical conduct and pathologic examination was not standardized across institutions, which may lead to variability in reporting. Further, surveillance strategies were not standardized in this retrospective study which may impact our recurrence rates and timing. Despite these limitations, this study serves as one of the largest in the literature focusing on functional neuroendocrine tumors, as well as symptom control after surgery. Furthermore, the multi-institutional model captures several institutions and patient populations from a diverse set of geographic regions in the United States.

Conclusion

Patients with functional neuroendocrine tumors who fail to experience hormone-specific symptom improvement after curative-intent surgical resection have worse recurrence-free survival than those patients who do experience symptom improvement. The failure of symptom improvement likely serves as a perceptible measure of sub-radiographic residual disease. Patients who fail to have symptom improvement after curative-intent resection may be well-suited to undergo short-interval radiographic surveillance in order to detect earlier radiographic recurrence of disease.

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Figure

Figure 1:

Kaplan-Meier plots assessing the association between symptom improvement and recurrence-free survival. For all patients within the study cohort (a), the failure to achieve postoperative symptom improvement was associated with a significantly reduced recurrence-free survival. This remained true when examining only patients with R0 resection status on final pathologic assessment (b).

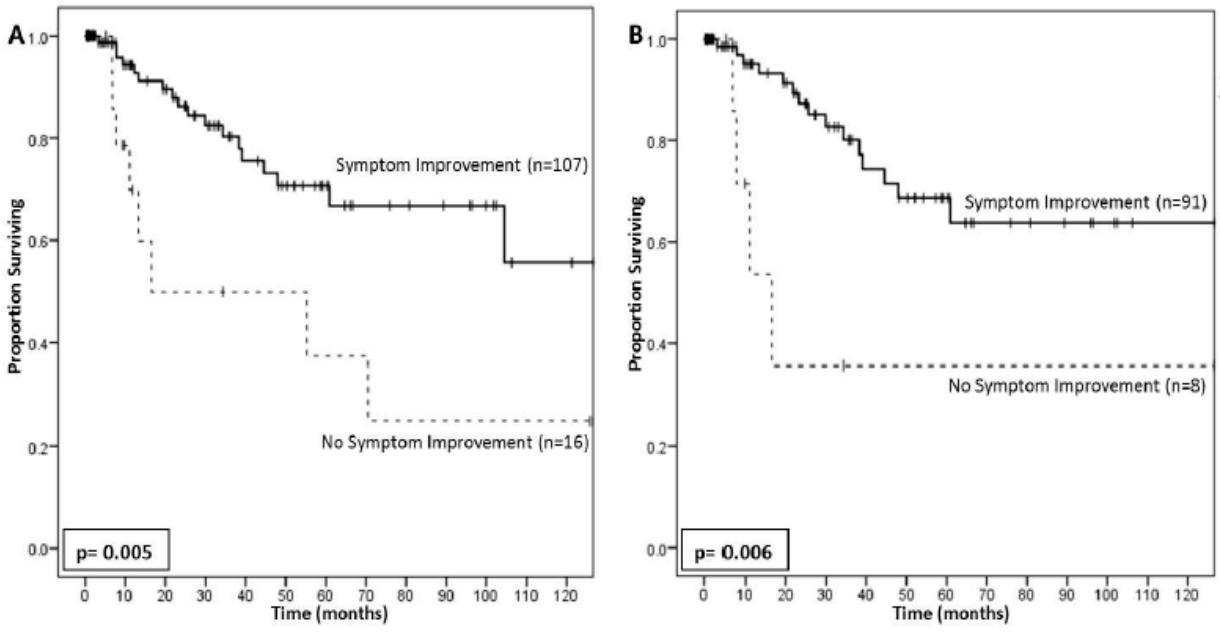

Table 1: Demographic characteristics of patients with functional neuroendocrine tumors within the US- Neuroendocrine Tumor Study Group database.

Baseline Variable	n (%)
Age (years), mean, ± STD	52.4 ± 15.3
Male	110 (47.8)
BMI, mean, ± STD	29.1 ± 6.9
Race	
White	173 (75.2)
Black	21 (9.1)
Latino	11 (4.8)
Functional Status	
Independent	184 (80.0)
Partially Dependent	11 (4.8)
Genetic Syndrome	48 (20.9)
MEN-I	41 (17.8)
Neurofibromatosis-1	1 (0.4)
Other	6 (2.6)
Type of Functional Tumor	
Insulinoma	122 (53.0)
Gastrinoma	80 (34.8)

Glucagonoma	11 (4.8)
VIPoma	10 (4.3)
Somatostatinoma	3 (1.3)
Other	4 (1.7)

Abbreviations: MEN-I, multiple endocrine neoplasia type 1.

Table 2: Perioperative and pathologic characteristics of patients with functional neuroendocrine tumors within the US- Neuroendocrine Tumor Study Group database.

Pathologic Variable	n (%)
Operative Intent	
Curative	230 (100.0)
Type of Resection	
Enucleation alone	76 (33.0)
Enucleation with lymph node retrieval	26 (11.3)
Anatomic Resection	128 (55.7)
Multifocal Tumors	31 (16.1)
Tumor Size (cm), median (IQR)	1.7 (1.2-2.5)
Tumor Location	
Pancreas	194 (84.3)

Duodenum	26 (11.3)
Liver	5 (2.2)
Ampulla	5 (2.2)
# Tumors, median (IQR)	1 (1-1)
Tumor Differentiation	
Well	181 (78.7)
Moderate	9 (3.9)
Ki-67	
<3%	92 (40.0)
3-20%	40 (17.4)
>20%	3 (1.3)
Unknown	113 (43.5)
LVI	48 (20.9)
PNI	16 (7.0)
Lymph Node Positive	52 (22.6)
# Lymph Nodes Positive, median (IQR)	0 (0-1)
Final Resection Status	
R0	184 (80.0)
R1	46 (20.0)

Postoperative Variable	n (%)
Any Complication	118 (51.3)
Clavien-Dindo 1	26 (11.3)
Clavien-Dindo 2	33 (14.3)
Clavien Dindo ≥3	59 (25.7)
Symptom Improvement	
Yes	108 (47.0)
No	17 (7.4)
Unknown	105 (45.7)
Reoperation	11 (4.8)
Readmission	46 (20.0)
Recurrence	38 (16.5)

Abbreviations: LVI, lymphovascular invasion; PNI, perineural invasion

Table 3: Preoperative and postoperative characteristics of patients without symptom improvement who experienced disease recurrence.

Pt #	Age (yrs)	Sex	Type of Tumor	Genetic Syndrome	Type of Resection	Size (cm)	Tumor Location	R0/R1	Multifocal Recurrence	Region of Recurrence
1	59	F	VIPoma	None	Anatomic	1.7	Liver	R0	Yes	Distant
2	70	M	VIPoma	None	Anatomic	2	Pancreas	R0	No	Distant
3	47	M	Gastrinoma	Other	Anatomic	9.1	Pancreas	R0	Yes	Distant
4	52	F	Gastrinoma	None	Anatomic	1.3	Pancreas	R0	Yes	-
5	33	M	Gastrinoma	MEN-1	Anatomic	11.5	Pancreas	R0	Yes	Distant
6	45	F	Glucagonoma	None	Anatomic	15.2	Pancreas	R0	Yes	Locoregional + Distant
7	52	F	Insulinoma	MEN-1	Anatomic	2.0	Pancreas	R0	No	Locoregional
8	38	M	Insulinoma	None	Anatomic	4.6	Pancreas	R0	No	Distant
9	63	M	Insulinoma	None	Anatomic	12.9	Pancreas	R0	No	Locoregional + Distant
10	66	F	Gastrinoma	None	Enucleation	1.8	Pancreas	R1	Yes	Locoregional
11	48	M	Gastrinoma	MEN-1	Enucleation	2.0	Pancreas	R1	-	Locoregional
12	44	F	Gastrinoma	None	Enucleation	1.3	Duodenum	R0	Yes	Locoregional
13	73	F	Gastrinoma	None	Enucleation	5.5	Pancreas	R0	No	Distant

14	38	F	Gastrinoma	MEN-1	Enucleation	1.4	Duodenum	-	Yes	Locoregional
15	42	M	Glucagonoma	None	Enucleation	7.5	Pancreas	R0	No	Distant
16	39	F	Insulinoma	None	Enucleation	1.0	Pancreas	R0	No	Distant
17	91	F	Insulinoma	None	Enucleation	7.5	Pancreas	R0	Yes	Distant

Table 4: Relationship between clinicopathologic factors of patients with functional neuroendocrine tumors and post-operative symptom improvement.

	Symptom Improvement		
Variable	**No, n (%)**	**Yes, n (%)**	**p value**
Known Genetic Syndrome	9 (52.9%)	16 (14.8%)	**0.001**
Type of Functional Tumor			**0.014**
Insulinoma	5 (29.4%)	63 (58.3%)	
Gastrinoma	11 (64.7%)	30 (27.8%)	
Other	1 (5.9%)	15 (13.9%)	
Multifocal	6 (35.3%)	22 (20.4%)	0.290
Tumor Location			**0.091**
Pancreas	12 (70.6%)	88 (81.5%)	
Duodenum	4 (23.5%)	12 (11.1%)	
Liver	0 (0%)	4 (3.7%)	
Ampulla	0 (0%)	4 (3.7%)	
Tumor Differentiation			0.601

Well	13 (100%)	88 (98.9%)	
Moderate	0 (0%)	1 (1.1%)	
Ki67			0.652
<3%	6 (54.5%)	41 (65.1%)	
3-20%	5 (45.5%)	21 (33.3%)	
>20%	0 (0%)	1 (1.6%)	
LVI	4 (50.0%)	24 (27.0%)	0.332
PNI	1 (20.0%)	8 (9.9%)	1.0
Lymph Node Positive	7 (50.0%)	20 (27.8%)	0.185
Resection Status			**0.007**
R0	9 (52.9%)	91 (84.3%)	
R1	8 (47.1%)	17 (15.7%)	

Abbreviations: LVI, lymphovascular invasion; PNI, perineural invasion

Table 5: Univariable and multivariable cox regression analysis examining clinical and pathologic factors associated with reduced recurrence-free survival in patients with functional neuroendocrine tumors.

	Univariable			Multivariable		
Variable	**HR**	**95%CI**	**p-value**	**HR**	**95%CI**	**p-value**
Type of Functional Tumor						
Insulinoma	Ref	--	--	Ref	--	--
Gastrinoma	2.8	(1.3-6.1)	0.006	1.1	(0.6-2.0)	0.75
Other (including glucagonoma, somatostatinoma, VIPoma)	2.7	(1.0-7.2)	0.042	--	--	--
Known Genetic Syndrome	1.8	(0.9-3.5)	0.077	0.68	(0.2-2.0)	0.49
Lymph Node Positive	1.8	(0.9-3.6)	0.080	1.6	(0.6-4.6)	0.35
R1 Resection Margin	2	(1.0-3.9)	0.052	0.45	(0.1-1.8)	0.25
Failure of Symptom Improvement	**3.1**	**(1.3-7.2)**	**0.008**	**4.7**	**(1.3-16.6)**	**0.016**