Recurrence Patterns following Surgical Resection of Gastroenteropancreatic Neuroendocrine Tumors: An Analysis from the NCCN Oncology Outcomes Database

Katherine Van Loon, MD, MPH[1]; Li Zhang, PhD[1]; Jennifer Creasman[1]; Sarah Bobiak, PhD[2]; Carrie C. Zornosa[2]; Michael A. Choti, MD, MBA[3]; Matthew Kulke, MD[4]; James C. Yao, MD[5]; Eric K. Nakakura, MD, PhD[1]; Mark Bloomston, MD[6]; Al B. Benson, MD[7]; Manisha H. Shah, MD[6]; Jonathan R. Strosberg, MD[8]; Emily K. Bergsland, MD[1]

[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco; [2]National Comprehensive Cancer Network; [3]University of Texas Southwestern Medical Center; [4]Dana-Farber Cancer Institute; [5]University of Texas MD Anderson Cancer Center; [6]The Ohio State University; [7]Northwestern University; [8]H. Lee Moffitt Cancer Center

Introduction

- Resection of gastroenteropancreatic neuroendocrine tumors (NETs) is known to prolong survival.[1-4]
- Current National Comprehensive Cancer Network (NCCN) guidelines recommend that complete surgical resection of the primary tumor and metastases with curative intent should be performed whenever possible.[5]
- However, risk and patterns of recurrence are not well defined following resection of gastroenteropancreatic NETs.

Aims

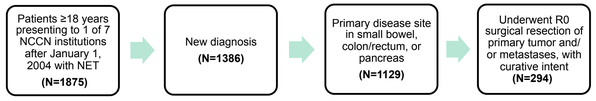
To utilize data from the NCCN's NET Outcomes Project database to:

- 1) Report recurrence rates, disease-free survival (DFS), and overall survival (OS) for patients with gastroenteropancreatic NETs, who undergo surgical resection with curative intent.
- 2) Identify patient subgroups at particularly high risk of recurrence following surgical resection of gastroenteropancreatic NETs.

Methods

- The NCCN NET Outcomes Project Database was comprised of data collected from 7 participating NCCN member institutions
- The study cohort consisted of patients ≥18 years who received care at a participating institution for a new diagnosis of a small bowel, pancreas, or colorectal NET on or after January 1, 2004 and before December 31, 2008. All underwent a complete (R0) resection of the primary tumor, with resection of metastases if present, without gross residual disease following surgical procedure(s) (see **Figure 1**).
- Follow-up data was collected until database closure in 2012. Median follow-up time from R0 resection date was 62.1 months.
- Descriptive statistics were used to determine recurrence rates across sites and stages.
- Kaplan-Meier estimates were used to calculate time-associated endpoints. Comparisons were assessed by the log-rank test.

Figure 1. Inclusion criteria and determination of sample size.



Results

Table 1. Characteristics of patients in the NCCN NET database who underwent R0 resection

	Small intestine n=110		Pancreas n=138		Colon/rectum n=46		TOTAL n=294		p-value
Median age at diagnosis (years) (range)	56 (36-82)		55 (24-90)		44 (20-76)		55 (20-90)		<0.001
	n	%	n	%	n	%	n	%	
Gender									
Male	62	56%	68	49%	19	41%	149	51%	0.207
Female	48	44%	70	51%	27	59%	145	49%	
Ethnicity									
Caucasian	98	89%	112	81%	41	89%	251	85%	0.212
African-American	10	9%	7	5%	2	4%	19	6%	
Asian/Pacific Islander	2	2%	10	7%	1	2%	13	4%	
American Indian	0	0%	1	1%	0	0%	1	0%	
Other/Unknown	0	0%	8	6%	2	4%	10	3%	
ECOG performance status									
0	39	35%	46	33%	18	39%	103	35%	0.263
1	11	10%	20	14%	2	4%	33	11%	
2	0	0%	1	1%	0	0%	1	0%	
Unknown	60	55%	71	51%	26	57%	157	53%	
Charlson score									
0 (None)	80	73%	73	53%	39	85%	192	65%	0.001
1-2 (Low)	25	23%	58	42%	6	13%	89	30%	
3-4 (Moderate)	4	4%	6	4%	0	0%	10	3%	
≥5 (High)	1	1%	1	1%	1	2%	3	1%	
Histology									
Carcinoid	107	97%	0	0%	34	74%	141	48%	<0.001
Pancreatic endocrine tumor	0	0%	134	97%	0	0%	134	46%	
Adenocarcinoid/goblet cell carcinoid/composite carcinoid	0	0%	0	0%	11	24%	11	4%	
Mixed histology	1	1%	1	1%	0	0%	2	1%	
Other	2	2%	3	2%	1	2%	6	2%	
Functional status of tumor									
No	88	80%	103	75%	30	65%	221	75%	<0.001
Carcinoid syndrome	19	17%	3	2%	4	9%	26	9%	
Insulinoma	0	0%	17	12%	0	0%	17	6%	
Gastrinoma	0	0%	6	4%	0	0%	6	2%	
Glucagonoma	0	0%	2	1%	0	0%	2	1%	
VIPoma	0	0%	2	1%	0	0%	2	1%	
Other functional PNET	0	0%	1	1%	0	0%	1	0%	
Missing	3	3%	4	3%	12	26%	19	6%	
Disease stage at resection*									
Localized	22	20%	93	67%	28	61%	143	49%	<0.001
Regional disease	61	55%	28	20%	16	35%	105	36%	
Distant metastases	27	25%	17	12%	2	4%	46	16%	
Unknown									
Institution									
DFCI	26	24%	7	5%	14	30%	47	16%	<0.001
Johns Hopkins University	16	15%	27	20%	5	11%	48	16%	
MD Anderson	11	10%	37	27%	1	2%	49	17%	
Moffitt Cancer Center	15	14%	18	13%	5	11%	38	13%	
Northwestern University	8	7%	12	9%	5	11%	25	9%	
The Ohio State University	14	13%	9	7%	10	22%	33	11%	
UCSF	20	18%	28	20%	6	13%	54	18%	

p-value calculations did not include data with missing values

* Stage for each primary tumor site was defined according AJCC Cancer Staging Manual, 7th Edition.

Figure 2. DFS and OS according to primary site, stratified by stage.

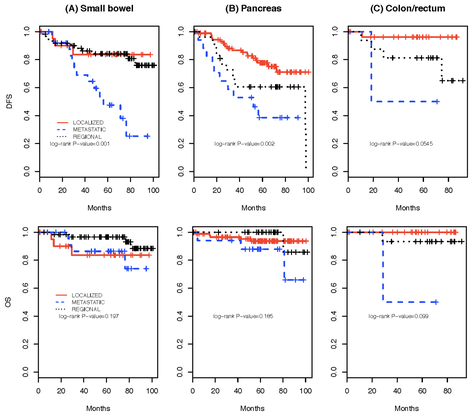


Table 2. Recurrence events according to stage and primary site.

	Small intestine N=110		Pancreas N=138		Colon/Rectum N=46		Overall Cohort N=294	
	Events/N	%	Events/N	%	Events/N	%	Events/N	%
Localized	0/22	0%	14/93	15%	1/28	4%	15/143	10%
Regional	10/61	16%	12/28	43%	3/16	19%	25/105	24%
Distant metastases	10/27	37%	10/17	59%	1/2	50%	21/46	46%
TOTAL	20/110	18%	36/138	26%	5/46	11%	61/294	21%

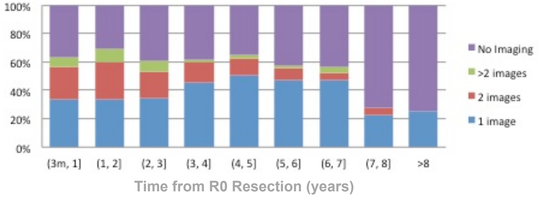
NCCN Guidelines for Surveillance Imaging following Resection

	3-12 months post-resection	>1 - 10 years post-resection
Pancreas	Multiphase CT or MRI 3-12 months post-resection	**Consider** CT or MRI every 6-12 months until 10 years post-resection
Small bowel and colon/rectum	**Consider** multiphase CT or MRI 3-12 months post-resection	**Consider** CT or MRI every 6-12 months until 10 years post-resection

REF: NCCN Guidelines Version 1.2015

Figure 3. Average number of tests performed over time, including cross-sectional of abdomen or radio-isotope imaging, following R0 resection.

Figure 4. Proportion of patients who underwent one or more cross-sectional or radio-isotope imaging studies following R0 resection.



Conclusions

- Among all patients with a gastroenteropancreatic NET who underwent an R0 resection, >90% of patients were alive at five-year follow-up, regardless of primary site.
- While stratification according to stage revealed differences in DFS for patients with pancreatic and small bowel NETs, a statistically significant difference in OS was not detected.
- The presence of metastatic disease should not deter an attempt at R0 resection, when feasible.
- Recurrences were detected beyond five years, suggesting NCCN recommendations for 10 years of follow-up may be appropriate.
- Chest imaging as surveillance may be of limited utility.
- Surveillance practices among NCCN institutions are variable, suggesting need for refinement of guidelines.

Limitations

- Analysis was limited by incompleteness of follow-up data in the database, including stage, test results, and site of recurrence.
- Median follow-up time was limited by database closure in 2012.
- Based upon previous reports that nearly all patients who undergo resection of liver metastases from NETs recur within 10 years,[6-7] this data may not reflect late recurrence patterns and longer-term outcomes for gastroenteropancreatic NETs.

Future Directions

- Further inquiry into appropriate frequency, type, and duration of surveillance is needed.
- Prospective database design and construction should include annotation and long duration of follow-up data.

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