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Recurrence Patterns Following Surgical Resection of Gastroenteropancreatic Neuroendocrine Tumors: Analysis from the National Comprehensive Cancer Network Oncology Outcomes Database

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Abstract

Objective: Current National Comprehensive Cancer Network guidelines for gastroenteropancreatic neuroendocrine tumors (GEPNETs) recommend complete (R0) surgical resection of the primary tumor and metastases, if feasible. However, large multicenter studies of recurrence patterns of GEPNETs following resection have not been performed.

Methods: Patients ≥18 years who presented to seven participating National Comprehensive Cancer Network institutions between 2004 and 2008 with a new diagnosis of a small bowel, pancreas, or colon/rectum NET and underwent R0 resection of the primary tumor and synchronous metastases, if present, were included in this analysis. Descriptive statistics and Kaplan-Meier estimates were used to calculate recurrence rates and time-associated endpoints, respectively.

Results: Of 294 patients with GEPNETs, 50% were male, 88% were White, and 99% had Eastern Cooperative Oncology Group Performance Status 0–1. Median age was 55 years (range, 20–90). Median follow-up time from R0 resection was 62.1 months. Recurrence rates were 18% in small bowel NETs (n = 110), 26% in pancreatic NETs (n = 141), and 10% in colon/rectum NETs (n = 50). Frequency of surveillance imaging was highly variable.

Conclusions: R0 resection was associated with variable risk of recurrence across subtypes. Further research to inform refinement of guidelines for the appropriate duration of surveillance following R0 resection is needed.

Keywords

neuroendocrine tumors; recurrence; surveillance; guidelines

INTRODUCTION

While the natural history of gastroenteropancreatic neuroendocrine tumors (GEPNETs) is poorly understood, it has been previously described that resection prolongs patient survival. A retrospective analysis of patients with pancreatic neuroendocrine tumors (NETs) from the Surveillance, Epidemiology and End Results (SEER) database demonstrated that patients with a pancreatic NET have a median survival of 9.5 years after primary pancreatic resection, compared with 2.9 years when resection was recommended but declined by the patient.[1] Similarly, another report estimated that median disease-free survival (DFS) ranges from 4.8 to 9.0 years after resection of primary gastrointestinal carcinoid tumors.[2] Even in patients with liver metastases, median overall survival (OS) is prolonged in patients who undergo resection versus those who do not.[3–5]

Current guidelines from the National Comprehensive Cancer Network (NCCN) for GEPNETs recommend that complete surgical resection of the primary tumor and metastases

with curative intent should be performed whenever feasible;[6] however, many patients develop disease recurrence following resection. The probability of recurrence varies depending upon the site, aggressiveness of the tumor, and extent of metastases. Guidelines for surveillance imaging following resection vary widely, reflecting the absence of data and lack of standardization in clinical practice.[5,7,8]

In addition, NCCN guidelines, which represent a *de facto* standard, do not recommend adjuvant therapy for patients who undergo complete resection of a NET, regardless of subtype or grade.[5,7,8] The design and completion of definitive studies evaluating adjuvant regimens in patients with fully resected NETs is challenging, and no controlled studies have been conducted. In particular, a lack of data regarding recurrence rates and median time to tumor recurrence following surgical resection remains a major obstacle to designing studies, precluding evidence-based estimation of the power and duration of such trials.[9–12] Furthermore, there are limited data to inform guidelines regarding standard surveillance intervals or imaging modalities.

This study aimed to utilize data from the NCCN NET Outcomes Project Database to report recurrence rates, disease-free survival (DFS), and overall survival (OS) for patients with GEPNETs who underwent surgical resection with curative intent. Moreover, we aimed to identify patient subgroups at particularly high risk of recurrence following surgical resection of GEPNETs and to characterize surveillance practices at the participating NCCN institutions as they impact detection of recurrences.

MATERIALS AND METHODS

Data Collection

The NCCN NET Outcomes Project Database collected data from seven participating NCCN member institutions. The participant institutions identified patients ≥18 years who received care for a NET on or after January 1, 2004 and before December 31, 2008. Patients were required to have a second visit at the participant institution within six months of initial presentation for inclusion in the database. Data collection and storage policies underwent institutional review board review and approval at each participating institution. Inclusion in the database did not require participant consent given minimal risk to patient safety.

A data manager at each institution abstracted data from medical records of eligible patients. Clinical and treatment data were collected retrospectively and/or concurrently via review of existing medical records dating from the time of first presentation and then at annual reassessment intervals. Extensive detail regarding baseline sociodemographic factors, tumor staging, symptoms, and cancer-directed treatments, including all treatments delivered at NCCN and outside institutions (e.g., surgeries, radiation therapy, systemic therapy) were included in the chart abstraction process.

Data were subject to rigorous data quality assurance procedures required for institutional participation in the NCCN Oncology Outcomes Database, including training for data managers, online edit-checking during web-based data entry, programmed logic checks against the pooled data repository, and generation of routine quality assurance reports to

each institution for data managers to rectify. Disease status (alive/dead) was updated at six-month intervals. Follow-up data was collected until database closure in March 31, 2013.

Study Population

Patients included in this analysis were limited to those with a new diagnosis of a small bowel, pancreas, or colon/rectum NET who underwent a complete (R0) resection of the primary tumor, with resection of metastases if present, without gross residual disease following surgical procedure(s) between 2004 and 2008 (see Fig. 1). Patients with NETs reported as high-grade or poorly differentiated tumors in pathology reports were excluded from the analysis. Because poorly differentiated neuroendocrine carcinomas (NECs) are typically characterized by a much more aggressive disease biology (akin to small cell lung cancer) which often precludes surgical resection, they were excluded from analysis.[6] R0 resection was defined as any resection of the primary tumor and/or synchronous metastases which resulted in change in the patient's disease status from "with disease" to "no evidence of disease." For patients who underwent a staged metastectomy, the R0 resection date was the date of the final surgery which rendered the patient disease-free. Complex cases were adjudicated by two investigators to determine the R0 resection date.

Charlson scores, a predictor of mortality based on medical comorbidities, were grouped into four previously established indices: 0 points (none), 1–2 points (low), 3–4 points (moderate), and > or =5 points (high).[13,14] Stage for each patient was determined according to the American Joint Committee on Cancer (AJCC), 7th edition, based upon interpretation of nodal status reported at time of resection.[15] Tumors were staged as localized disease with primary tumor involvement, regional disease with lymph node or adjacent organ involvement, and metastatic disease with distant metastases. Staging classifications for regional lymph nodes were defined according each primary site of origin. Two investigators (K.V.L., E.B.) reviewed each case independently, and adjudication was performed in cases of disagreement.

Statistical Methods

Descriptive statistics were used to determine recurrence rates across sites and stages. The primary clinical outcome of this retrospective study was DFS, which was calculated from the date of primary tumor resection and, if metastases present, complete metastasectomy to the date of local recurrence, development of distant metastases, or death from any cause. The secondary clinical outcome of this study was OS, which was calculated as the date of diagnosis to the date of death or censoring. Date of diagnosis was defined as the date of the first pathology or cytology report documenting invasive cancer in either a primary tumor or metastatic site. Kaplan-Meier estimates were used to calculate time-associated endpoints stratified by sites and disease stages, and comparisons were assessed by the log-rank test. The intervals for patients remaining alive were censored at the last known contact date. All analyses were performed using R software (Version 3.1.2, R Core Team, Vienna, Austria).[16] Differences were considered statistically significant with P value <0.05.

RESULTS

Patient and Tumor Characteristics

A total of 294 patients were identified who underwent R0 resection for well or moderately differentiated GEPNETs that were newly diagnosed at participating NCCN institutions. Patient and tumor characteristics are summarized in Table 1.

Of these, 51% were male, 85% were reported as White, and the median age was 55 years (range, 20–90 years). The subset with primary tumors of the colon/rectum was notable for a younger median age at diagnosis of 44 years (range, 20–76 years) ($P < 0.001$) and higher proportion of patients without comorbidities compared to patients with small bowel and pancreatic NETs (85% with Charlson score of 0) ($P = 0.001$). While each participating institution contributed between 25 and 54 patients, there were significant differences in types of primary tumors which received care at different institutions ($P < 0.001$).

Of the 110 small bowel primary tumors, 80% were reported as non-functional, 20% had localized disease based upon available data, 55% had regional disease, and 25% had metastatic disease. Of the 138 primary pancreatic tumors, 75% were reported as non-functional, 67% had localized disease, 20% had regional disease, and 12% had metastatic disease. Of the 46 patients with colon/rectum primary tumors, 100% were reported as non-functional, 61% had localized disease, 35% had regional disease, and 4% had metastatic disease.

Recurrence Rates and Survival

Median follow-up time from R0 resection date was 62.1 months (range, 0.2–101.6 months). Among patients with small bowel NET (n = 110), 18% recurred. Among patients with pancreatic NET (n = 141), 26% recurred. Among patients with colon/rectum NET (n = 50), 10% recurred.

Median DFS was 97.4 months among patients with pancreatic NETs. Median DFS was not reached in colon/rectum NETs or small bowel NETs. Among patients with small bowel NETs, median DFS was 56.3 months for patients with metastatic disease and was not reached for patients with localized or regional disease stage. Among pancreatic NETs, median DFS was 52.1 months in patients with metastatic disease and 97.4 months in patients with regional disease; median DFS was not reached in patients with localized disease. Among colon/rectum NETs, median DFS was 18.6 months in patients with metastatic disease; median DFS was not reached among patients with localized or regional disease stage. When stratified by stage and primary disease site, differences in median DFS were significant in small bowel NETs ($P = 0.001$), pancreatic NETs ($P = 0.002$), colon/rectum NETs ($P = 0.05$).

Median OS was 29.3 months in patients with metastatic NETs of the colon/rectum. Median OS was not reached for any other group due to insufficient follow-up time. DFS and OS according to primary disease site, stratified by stage are displayed in Figures 2A and 2B, respectively.

At five-year follow-up, 76% of patients with small bowel NETs were without recurrence, and 92% were alive; 69% of patients with a pancreas NETs were without recurrence, and 94% were alive; and 88% of patients with colon/rectum NETs were without recurrence, and 96% were alive.

Surveillance

In terms of surveillance imaging within 1 year after R0 section, which included abdominal cross-sectional and radio-isotope imaging, 27% had no imaging, 35% had 1 image procedure, 27% had 2 imaging procedures, and 12% had greater than 2 imaging procedures. In terms of chest imaging within 1 year after R0 resection, 52% had no imaging, 29% had 1 imaging procedure, 14% had 2 imaging procedures, and 5% had greater than 2 imaging procedures. Percentage of patients undergoing surveillance abdominal imaging and chest imaging over time from R0 resection are displayed in Figures 3A and 3B, respectively.

Among the 61 patients who developed recurrent disease, the most common sites of recurrence were liver (36.1%), unknown (29.5%), and distant site NOS (16.4%). Least common sites of recurrence were bone, (1.6%), lung (1.6%), and peritoneum (4.9%).

DISCUSSION

In this study, we discovered that among all patients with a GEPNET who underwent an R0 resection, greater than 90% of patients were alive at five-year follow-up, regardless of primary site; this finding is consistent with prior studies.[2] 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 in pancreatic and small bowel NETs. Furthermore, stratification by stage did demonstrate a difference in both DFS and OS in colon/rectum NETs. As such, the presence of metastatic disease should not deter an attempt at resection, when feasible.[17,18] Outcomes of patients with GEPNETs after R0 resection is an area that merits further exploration as recommendations for surveillance imaging according to NCCN guidelines rely on clinical suspicion, and frequency and duration of imaging in clinical practice is largely due to provider discretion.

Current NCCN guidelines for surveillance following resection are summarized in Figure 4, with recommendations to obtain abdominal imaging every 1–2 years for at least 10 years in small bowel and colon/rectum NETs and to “consider” interval follow up in pancreatic NETs.[19] The guidance for surveillance intensity is intentionally permissive, based upon existing gaps in knowledge regarding optimal surveillance strategies. Our data demonstrate that recurrences were detected beyond five years, suggesting NCCN recommendation for 10 years of follow-up is appropriate. Recommendations from an international expert panel by the Commonwealth Neuroendocrine Tumour Collaboration and the North American Neuroendocrine Tumor Society (NANETS) propose cross-sectional imaging annually for the first three years after complete resection of a GEPNET, followed by cross-sectional imaging every 12 to 24 months for the following three to ten years.[20] A similar review of the SEER database suggested that surveillance imaging should be tailored based on clinicopathologic data but could be avoided beyond five years in elderly patients.[21] Based upon our analysis,

surveillance practices among NCCN institutions are variable, reflecting inadequate data allowing more evidence-based practice.

In addition, our findings regarding the low frequency of recurrence in the form of lung metastases (<2%) raise questions regarding the utility of chest imaging as part of surveillance. According to current NCCN guidelines, chest imaging for GEPNETs is only recommended, if clinically indicated, twelve months after resection. Furthermore, according to the European Neuroendocrine Tumor Society (ENETS) chest imaging is not specifically recommended as part of routine surveillance in completely resected GEPNETs.[7,22] Nonetheless, chest imaging was performed for 20–30% of patients beyond 12 months, which likely reflects that the guidance to restrict to abdominal imaging only was not specified in the NCCN Guidelines at the time this data was collected.[23] Our data supports the omission of chest imaging from current surveillance guidelines, particularly in consideration of the risk of long term sequalae from cumulative radiation exposure.[24]

Limitations

There are notable limitations of this study. First, the analysis was limited by incompleteness of follow-up data in the database, including stage, test results, and site of recurrence with nearly half of the sites of recurrences recorded as unknown or not otherwise specified. Notably, a major limitation was the lack of pathology data including histologic grade, mitotic rate, and differentiation. This is particularly important given the utility of these markers, such as the Ki-67 proliferation index, in risk stratifying patients and as a prognostic indicator of DFS and OS.[9,25]

Second, median follow-up time was limited by database closure in 2013, limiting our ability to calculate median DFS and OS for most groups. Based upon previous reports that the majority of patients who undergo resection of liver metastases from NETs recur within 10 years, this data may not reflect late recurrence patterns and longer-term outcomes for GEPNETs.[3,4] Furthermore, analyses of time-associated endpoints were limited by our reliance upon surveillance imaging as documentation of recurrence, and we acknowledge the possibility that recurrence may actually have occurred earlier than it was detected.

Third, our study was conducted at seven NCCN institutions, which may be subject to referral bias, resulting in a greater proportion of complex cases and a lack of racial diversity in our patient population. Nearly 90% of our patient population identified as White. When benchmarked with demographic data on racial differences in NET incidence, White patients are over-represented and African Americans are under-represented in this cohort of patients who received care at participating NCCN institutions during the study period. This under-representation of African Americans may be due to a variety of social determinants, including access to a NCCN institution, and may limit the generalizability of our findings among African American patients who are known to have worse NET outcomes.[26]

Lastly, since the closure of this database, ^{68}Gallium DOTA-TOC/TATE imaging and peptide receptor radionuclide therapy (PRRT) have played a greater role in management of patients with NETs.[27] With the increasing use of DOTA-TOC/TATE imaging for staging of NETs, patients may have been under-staged relative to imaging modalities present between 2004

and 2008.[28] In addition, while PRRT applies only to patients with low- or intermediate-grade GEPNETs that have progressed on a first-line somatostatin analog, a trend towards longer overall survival may not have been captured in our database.

Future Directions

In this study, we detected recurrences beyond five years in patients with GEPNETs who have underwent complete surgical resection and highlighted the variability in surveillance patterns at participating NCCN institutions. Further inquiry into appropriate frequency, imaging modality, and duration of surveillance is needed. Prospective database design and clinical trials evaluating adjuvant therapy following complete resection of GEPNETs should include annotation and long duration of follow-up data.

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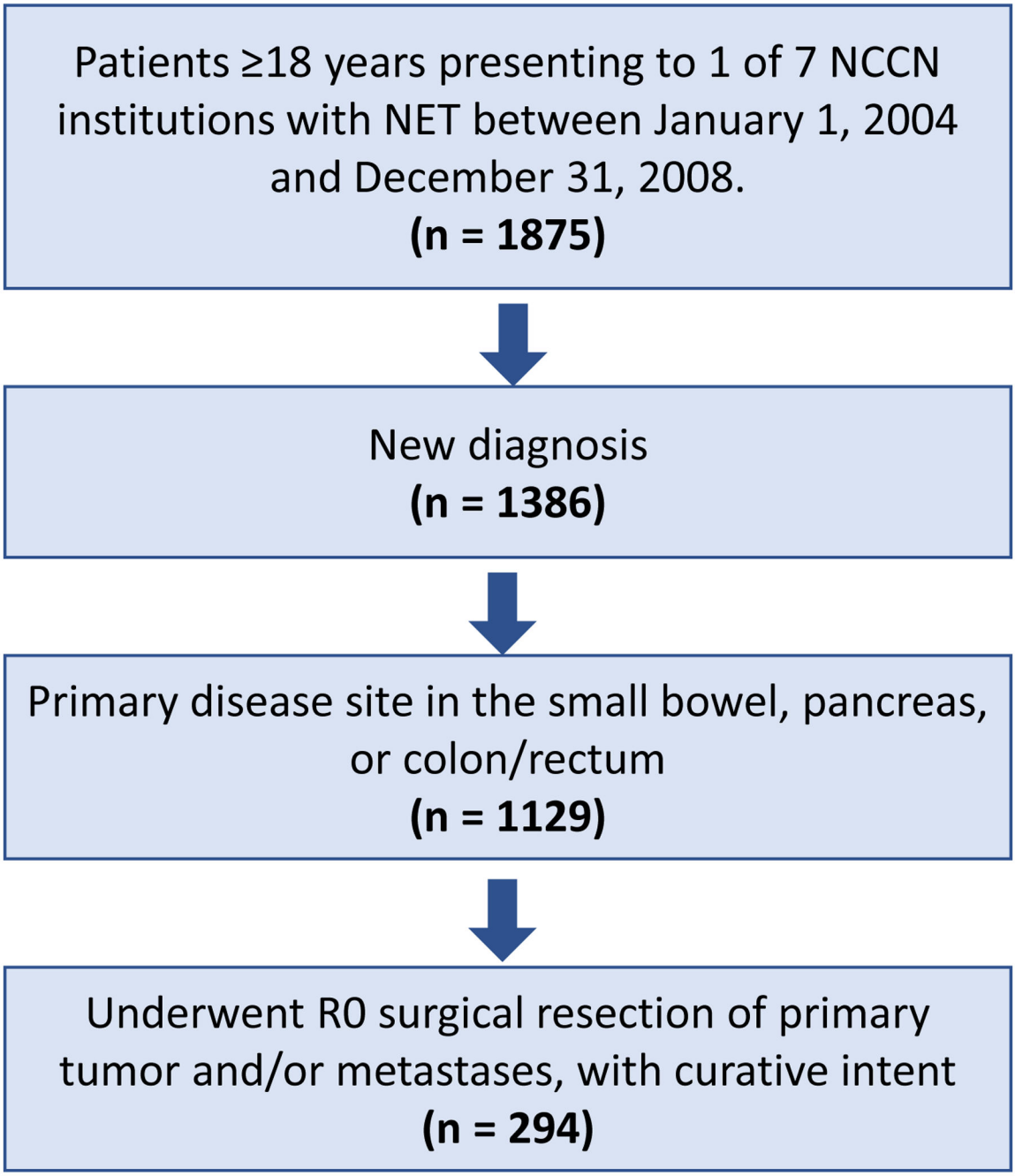

FIGURE 1.
Derivation of study cohort.

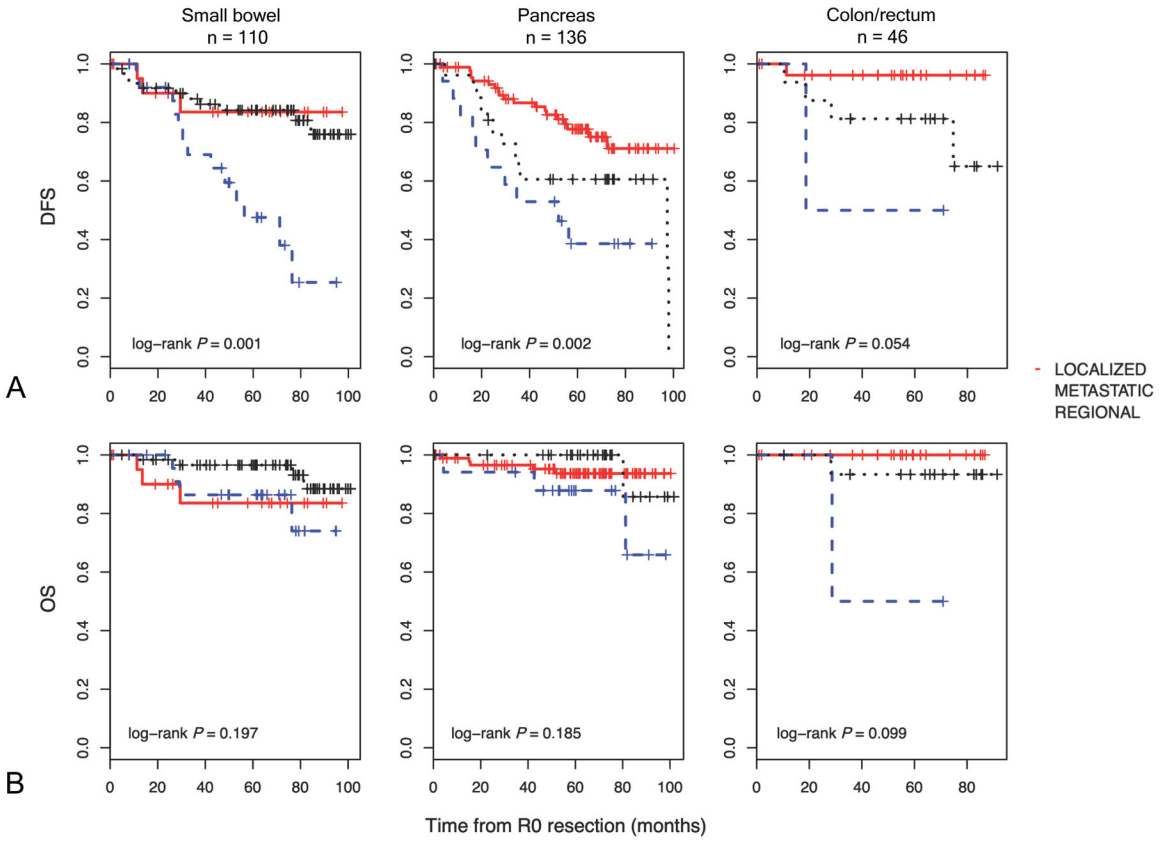

FIGURE 2.

A, Disease-free survival (DFS) according to primary site, stratified by stage. B, Overall survival (OS) according to primary site, stratified by stage.

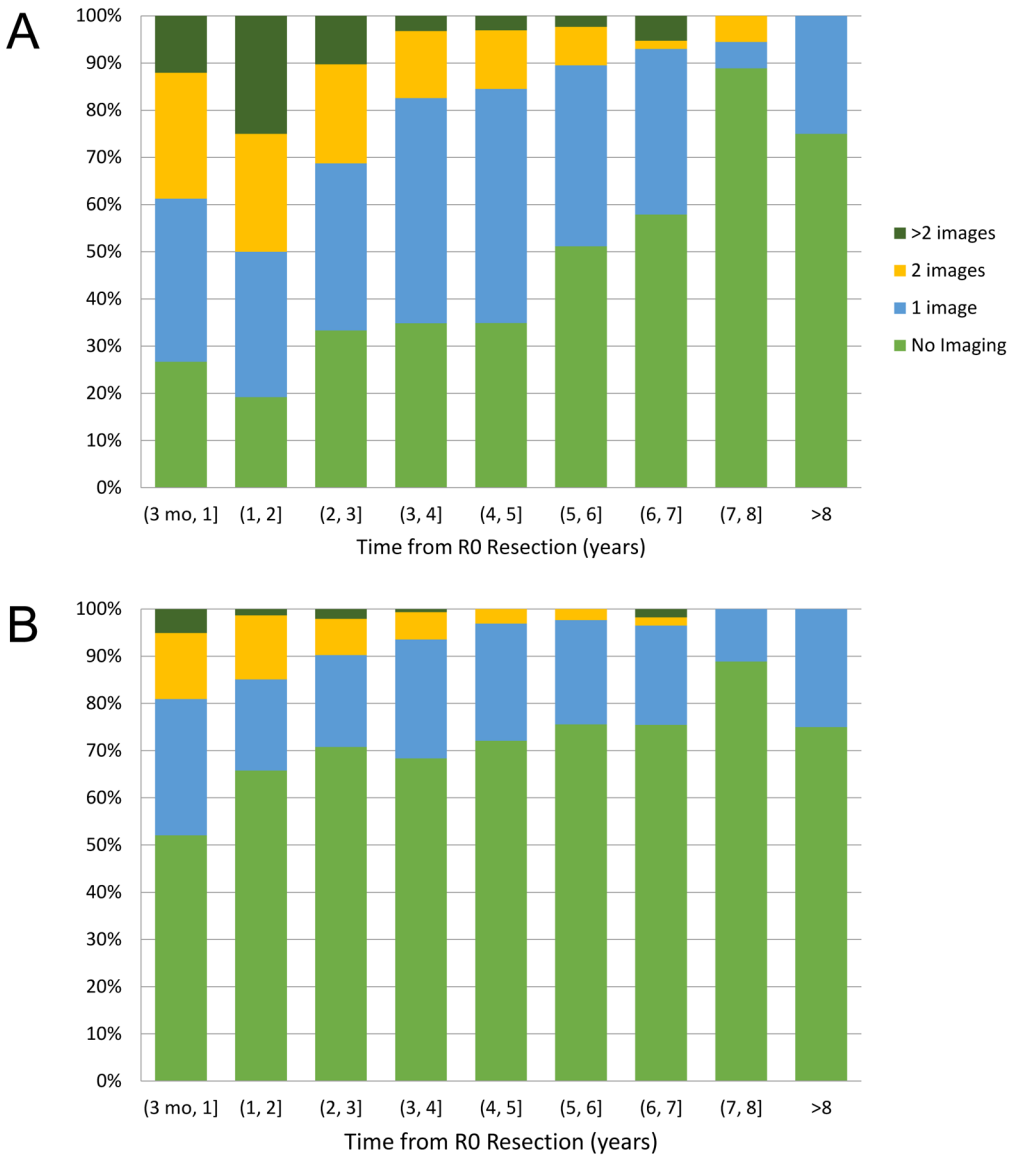

FIGURE 3.

A Surveillance imaging by cross-sectional and/or radio-isotope imaging, stratified by quantity of images per year, over time. B, Surveillance imaging by chest imaging, stratified by quantity of images per year, over time.

NCCN Guidelines for Surveillance Imaging following Resection

	3-12 months post-resection	>1-10 years post resection
Pancreas	Abdominal multiphasic CT or MRI and chests CT **as clinically indicated**	**Consider** abdominal multiphasic CT or MRI and chest CT every 6-12 months
Small bowel and colon/rectum	Abdominal +/- pelvic multiphasic CT or MRI **as clinically indicated**	Abdominal +/- pelvic multiphasic CT or MRI every 12-24 months; Chest CT every 12-24 months **as clinically indicated**

REF: NCCN Guidelines Version 2.2020

FIGURE 4.
Summary of NCCN Guidelines for Surveillance Imaging following Resection.

TABLE 1.

Characteristics of Patients in the NCCN NET Database Who Underwent R0 Resection

	Small Intestine, n (%) n = 110	Pancreas, n (%) n = 138	Colon/rectum, n (%) n = 46	TOTAL n = 294	*P*[*]
Age at diagnosis, median (range), y	56 (36–82)	55 (24–90)	44 (20–76)	55 (20–90)	<0.001
Sex					
Male	62 (56)	68 (49)	19 (41)	149 (51)	0.207
Female	48 (44)	70 (51)	27 (59)	145 (49)	
Ethnicity					
White	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)	
Functional status of tumor					
No	88 (80)	103 (75)	46 (100)	237 (81)	<0.001[†]
Carcinoid syndrome	19 (17)	3 (2)	0 (0)	22 (7)	
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)	0 (0)	7 (2)	
Disease stage at resection[‡]					<0.001
Localized	22 (20)	93 (67)	28 (61)	143 (49)	
Regional disease	61 (55)	28 (20)	16 (35)	105 (36)	
Distant metastases	27 (25)	17 (12)	2 (4)	46 (16)	
Institution					<0.001
DFCI	26 (24)	7 (5)	14 (30)	47 (16)	
Johns Hopkins University	16 (15)	2 (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)	

	Small Intestine, n (%)	Pancreas, n (%)	Colon/rectum, n (%)	TOTAL	
	n = 110	n = 138	n = 46	n = 294	*P*[*]
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

P value calculation comparing functional and non-functional NETs across sub-groups

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