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National Rise of Primary Pancreatic Carcinoid Tumors: Comparison to Functional and Non-Functional Pancreatic Neuroendocrine Tumors

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Abstract

Background—New guidelines recommend differentiating between carcinoid and pancreatic neuroendocrine tumors (PNETs) during clinical trials. However, little is known about the behavior and incidence of primary pancreatic carcinoid tumors.

Study Design—Retrospective cohort study utilizing the National Cancer Data Base (NCDB) to identify adults with primary PNETs diagnosed between 2004 and 2013. The Kaplan-Meier method was used to evaluate overall survival and multivariate Cox proportional hazards model was used to assess the hazard of death in resected patients.

Results—Of 10,752 patients, 12.7% were diagnosed with carcinoid tumors, 84.7% with non-functional and 2.6% with functional PNETs. While the number of functional PNETs has remained relatively constant over time, rates of non-functional and carcinoid tumors have risen dramatically. Only 36 (5.7%) carcinoid tumors were diagnosed in 2004, which increased to 497 (27.7%) in 2013. Overall survival was significantly longer for carcinoid compared to functional and non-functional tumors (log-rank $p < 0.0001$); with 5 year survival rates of 63.1%, 58.3%, and 52.6%, respectively. For resected patients, overall survival further improved for carcinoid tumors relative to functional (log-rank $p = 0.0011$) and non-functional (log-rank $p < 0.0001$) tumors, but the survival difference between functional and non-function tumors disappeared (log-rank $p = 0.4579$); 5 year survival rates were 89.2%, 76.6%, and 78.7%, respectively. On multivariate Cox regression of the resected cohort, mortality was significantly higher for patients with functional (HR 1.81) and non-functional (HR 1.40) PNETs compared to carcinoid tumors.

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Conclusions—Primary pancreatic carcinoid tumors are increasingly diagnosed. Differentiating PNET subtypes plays an important role in prognostication. Resection remains a critical component of care.

Background

Neuroendocrine tumors (NETs) have historically had varied and complex classifications, including embryologic origin (foregut, midgut, hindgut), anatomic origin (pancreas, lung, gastrointestinal tract), and type of hormonal secretion. More recently, the anatomic site of origin, specifically pancreatic versus non-pancreatic subgroups, has become a critical feature in treatment selection (1). Pancreatic neuroendocrine tumors (PNETs), traditionally referred to as islet cell tumors, are also further divided into functional (those that secrete bioactive substance, including insulin, vasoactive intestinal peptide [VIP], glucagon, gastrinoma and somatostatin) and non-functional subtypes, with over 85% of cases being non-functional (1). However, little information exists regarding primary pancreatic carcinoid – serotonin producing – tumors.

While primary serotonin producing NETs of the pancreas have only rarely been reported (2–4), there has been an increased incidence of all carcinoid tumors, with estimates of primary pancreatic carcinoid tumors around 1% from data assessed through the 1990s (5). However, it has been suggested that the incidence of primary carcinoid tumors may have been underestimated, as serotonin production is not typically evaluated and few patients manifest clinical signs of carcinoid syndrome (4). Furthermore, recent recommendations from the National Cancer Institute Neuroendocrine Tumor Taskforce Clinical Trials Planning Meeting encourage that carcinoid tumors and PNETs be assessed separately in clinical trials (6).

The current study aims to evaluate patient and tumor characteristics at presentation, as well as treatment strategies and outcomes, of primary pancreatic carcinoid tumors relative to other functional and non-functional PNETs. Secondarily, trends in the national annual incidence of PNET types are assessed.

Methods

Population

The National Cancer Data Base (NCDB) participant user files were queried for adult patients aged 18–90+ who were diagnosed with primary pancreatic neuroendocrine tumors between 2004 and 2013. Neuroendocrine tumors were identified by the following International Classification of Disease (ICD-O-3) histology codes: 8150, 8151, 8152, 8153, 8155, 8156, 8240, 8246, 8013, and 8574. The NCDB is a joint venture between the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons founded in 1989. It is a nationwide oncologic database that encompasses over 1,500 CoC hospitals and captures approximately 70% of all newly diagnosed malignancies in the United States (7–9). The NCDB collects de-identified data from state tumor registries regarding patient demographics, tumor characteristics, treatment regimens, including receipt of surgery, chemotherapy, and radiation, and longitudinal outcomes.

A total of 14,856 patients with neuroendocrine tumors were identified. Patients were excluded if they received treatment at a facility other than the reporting center (N=1,485) and/or if they had more than one cancer type (N=2,910), for a final cohort consisting of 10,752.

Variable Definitions

The ICD-O-3 histology codes were used to define functional, non-functional, and carcinoid tumor subtypes. Functional PNETs consisted of insuloma, glucagonoma, gastrinoma, VIPoma and somatostatinoma. Tumor location was grouped according to the Collaborative Staging Task Force for pancreas into: head (C25.0), body/tail (C25.1, C25.2), and other (C25.3, C25.4, C25.7, C25.8, C25.9). Clinical stage was defined based on the American Joint Committee on Cancer (AJCC) guidelines as reported via variables available through the NCDB. For those patients missing clinical stage, individual clinical T, N, and M variables were used to define a stage according to the 7th edition AJCC guidelines for pancreatic cancer (10). Resection was defined as any definitive surgical procedure on the primary site. Chemotherapy included drugs resulting in the inhibition of tumor growth and did not include hormone therapy or immunotherapy. Patients with unknown receipt of chemotherapy and no chemotherapy administered had similar overall survival and were therefore grouped together.

Statistical Analysis

Univariate analyses of categorical variables were performed using chi-square tests. Age and tumor size were originally reported as continuous variables, but were divided into categories for analysis. Survival analyses were performed using the Kaplan-Meier method and compared by log-rank tests for overall survival. Only patients diagnosed through 2012 were included in the survival analysis due to limited follow up. Unadjusted survival analyses were performed for all patients by tumor type and for a subset of resected patients by tumor type (N=4,902). Five year survival rates are reported as not all subgroups reached median survival.

Cox proportional hazards models were generated to assess the impact of tumor type on overall survival for resected patients (N=4,902). Covariates of interest were tested by the Kaplan-Meier method and those with significant p-values in log-rank tests were included in the final Cox model. Proportional hazards assumptions were tested and stratification was used for variables that violated proportional hazards assumptions. The final Cox model was adjusted for sex, age, tumor grade, tumor size, nodal status, tumor location, clinical stage, facility type, Charlson-Deyo comorbidity status, insurance status, and stratified by receipt of chemotherapy. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA). *P*-values of less than 0.05 were considered statistically significant.

Results

Patient and Tumor Characteristics

Of the 10,753 patients identified with pancreatic neuroendocrine tumors over a 10-year period, 9,107 (84.7%) had non-functional tumors, 1,369 (12.7%) had carcinoid, and 276 (2.6%) had functional tumors. The majority of patients presenting with a PNET were male (53.0%). Females were more likely to have functional tumors (52.9%), while males were more likely to have non-functional PNETs (53.7%) ($p=0.0016$). Most patients were between 51 and 65 years of age (40.6%), white (81.5%), had no comorbidities (73.2%), and were privately insured (52.7%). The majority of PNETs were treated at academic centers (59.8%); carcinoid tumors were more likely to be treated at an academic center (67.8%) compared to functional (58.0%) and non-functional (58.7%) tumors ($p<0.0001$). All tumors most commonly arose in the body/tail of the pancreas (42.8%). Nearly one third of all PNETs were 21–40mm in size (30.3%); but carcinoid tumors were more likely to be ≥ 20 mm in size (38.1%) compared to functional (31.9%) and non-functional (20.1%) tumors ($p<0.0001$). Carcinoid tumors were more commonly well-differentiated (60.6%) relative to functional (41.3%) and non-functional (40.3%) tumors ($p<0.0001$). Carcinoid tumors were also significantly more likely to have negative regional lymph nodes (42.7%), present with clinical stage I/II disease (50.3%), and undergo resection (68.7%) (Table 1). Less than a quarter of patients presenting with PNETs received systemic chemotherapy.

Trends

Between 2004 and 2013 there was a near tripling in the number of PNETs diagnosed annually, from 629 to 1,793, respectively. The number of functional PNETs has remained stable over time; however, both carcinoid and non-functional PNETs have been rising. The number of annual carcinoid tumors increased over 13-fold between 2004 and 2013 with the proportion of carcinoid tumors increasing from 5.7% to 27.7%; while the number of non-functional PNETs doubled (Figure 1).

Outcomes

Comparing overall survival for all patients and treatments by tumor type, there was a significant difference (log-rank $p<0.0001$) (Figure 2A). Five-year survival rates were higher for carcinoid tumors (63.1%) compared to functional (58.3%) and non-functional (52.6%) tumors. Subset analysis of only resected patients demonstrated a similarly significant difference in overall survival (log-rank $p<0.0001$) (Figure 2B); however, 5 year survival rates were higher for carcinoid tumors (89.2%), but comparable for functional (76.6%) and non-functional (78.7%) tumors.

After multivariate Cox proportional hazards modeling, tumor type remained a significant predictor of mortality in resected patients, with higher hazard ratio of death for functional (HR: 1.81; $p=0.0097$) and non-functional (HR: 1.40; $p=0.0322$) tumors compared to carcinoid tumors. Male sex, age over 50, Medicare, Charlson-Deyo score of 2+, tumor location other than head of the pancreas, community center, moderate-undifferentiated and unknown tumor grade, increasing and unknown tumor size, node positivity, and advanced or unknown disease stages were also independent predictors of mortality (Figure 3).

Discussion

The incidence of PNETs has been rising steadily over the past decade. While the number of non-functional tumors diagnosed annually has nearly doubled, there has been a greater than 13-fold increase in the incidence of primary pancreatic carcinoid tumors. Significant differences in outcomes were noted between the various neuroendocrine tumor subtypes, with the highest 5-year survival rates for carcinoid tumors (63.1%) followed by other functional (58.3%) and non-functional (52.6%) tumors. Resection further improved survival rates for all subtypes; however, there was no longer a difference in survival between functional and non-functional tumors (log-rank $p=0.4579$), but a significant survival advantage remained for carcinoid tumors with 5-year survival of almost 90%. Furthermore, the survival advantage for carcinoid tumors persisted after multivariate Cox modeling, adjusting for available patient and tumor characteristics, compared to other functional (HR 1.81, 95% CI: 1.15–2.83) and non-functional (HR 1.40, 95% CI: 1.03–1.89) tumors.

Previous work has similarly noted an increasing incidence of neuroendocrine tumors in recent years (1). The rising incidence, particularly of small and nonfunctional PNETs, has in part been attributed to the widespread adoption of high resolution imaging and, consequently, the increased detection of incidentalomas (11). A review of 5 decades of data utilizing the Surveillance Epidemiology and End Results (SEER) database through 1999 also noted a steady increase in all types of carcinoid tumors (5). The review estimated the incidence of primary pancreatic carcinoid tumors in SEER to be 0.7%, with the majority presenting with non-localized disease (5). The 5 year survival rate was calculated to be 37.5%, significantly higher than pancreatic adenocarcinoma, and the authors suggested that carcinoid tumors may have an indolent course and potentially the best outcomes amongst pancreatic malignancies (5). Additionally, at the time of the study, immunohistochemical techniques for staining of carcinoid tumors had only briefly been introduced (5). In a European study by La Rosa *et al.* (4), immunohistochemical staining for serotonin production was routinely performed on all suspected PNETs and carcinoid tumors were found to occur at a rate of 4%, which is similar to the rate of 5.7% that we found in the 2004 cohort. The authors did, however, believe this to be an underestimation and suggested the need for immunohistochemical staining with anti-serotonin antibodies in all non-functional PNETs that do not express other hormonal activity (4). While the method used to establish a histologic diagnosis cannot be determined in the NCDB, the current consensus does recommend immunohistochemical staining in the majority of cases (12), which may in part explain the observed rise in incidence.

This study's results are consistent with previous work demonstrating the presence of a survival advantage for functional versus non-functional tumors; however, carcinoid tumors were included in the subset of functional tumors and not evaluated separately (13). Similarly to our findings, surgical resection has been shown to prolong survival for all stages of PNETs including metastatic disease (14–16), as well as in patients with small PNET (< 2cm) tumors (17–19). While previous work suggests that non-functional PNETs have an indolent course (20), we noted that patients with non-functional tumors had the worst overall prognosis relative to functional tumors. The administration of systemic chemotherapy has also been shown to result in improved outcomes for patients with PNETs (21). However, in

our cohort of resected patients, those who received chemotherapy had significantly worse overall survival than those who did not (log-rank $p < 0.0001$); with 5 year survival rates of 51.5% vs 82.8%, respectively, likely reflecting selection bias in the administration of chemotherapy.

While previous studies evaluating PNETs at times divided functional and non-functional subtypes, no study has yet characterized the outcomes of primary pancreatic carcinoid tumors. The 2010 World Health Organization (WHO) classification does not take into account differences between functional and non-functional tumors and defines tumor versus carcinoma based on tumor differentiation, mitotic count, and Ki-67 index (22). However, the latest recommendations from the Neuroendocrine Tumor Clinical Trials Planning Meeting state that carcinoid tumors and PNETs should be assessed separately in clinical trials with consideration of stratification by primary site of origin for carcinoid tumors (6). Our findings provide further justification for this recommendation.

There are several limitations to our work due to its retrospective nature. As with all large database work, this study is limited by the predefined variables available through the NCDB. Due to the heterogeneity of NETs a consensus was reached for the minimum pathologic data set to be provided, which included recommended immunohistochemical staining for general neuroendocrine makers, Ki-67 index, mitotic rate, and tumor grade (12). Unfortunately, data regarding immunohistochemistry, Ki-67 index, and mitotic rate are absent in the NCDB. Nevertheless, tumor grade, distant metastases (13) and lymph node status (23, 24) have also been demonstrated to be of significant prognostic value and were adjusted for in our multivariate modeling. In addition, the NCDB provides de-identified data and does not have any information regarding clinical presentation and symptomatology, which are pertinent to differentiating functional and non-functional tumors; instead this was determined solely based on histologic classification (9).

This is the first study, to our knowledge, that has specifically evaluated outcomes for primary pancreatic carcinoid tumors. It is the largest, first national, and most comprehensive study to date to demonstrate a survival advantage in pancreatic carcinoid tumors that persists after resection relative to other PNET subtypes. These results suggest that carcinoid tumors are in fact different from other functional PNETs and further support the latest stratification guidelines for clinical trials (6). Additionally, this study demonstrates a rapid rise in recent years in the number of carcinoid tumors being diagnosed, which may in part be a reflection of advances in immunohistochemical techniques and practices. The results also highlight the importance of appropriate tumor subtype identification with significant resulting differences in prognostication, which may serve as a crucial source of information during treatment planning for physicians and patients.

In summary, primary pancreatic carcinoid tumors are a rapidly emerging subtype of PNETs, which demonstrate distinct outcomes. Similar to other functional and non-functional PNETs, carcinoid tumors drastically benefit from surgical resection. As recommended by current guidelines, any clinical trials should differentiate carcinoid tumors from other pancreatic NETs.

Future clinical trials evaluating pancreatic carcinoid and other neuroendocrine tumors will be essential for further characterization of treatment options and outcomes. Surgical resection remains a key component of care in the management of patients with all types of pancreatic neuroendocrine tumors.

Conclusions

The incidence of primary pancreatic carcinoid tumors is rapidly increasing. Differentiating PNET subtypes plays an important role in prognostication; with carcinoid tumors demonstrating significantly better overall outcomes relative to other functional and non-functional tumors. Surgical resection remains the mainstay of treatment for all PNETs. Future clinical trials should stratify treatment by tumor subtype to further characterize and establish the best treatment options.

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Precis

The incidence of primary pancreatic carcinoid tumors is rapidly increasing. Differentiating pancreatic neuroendocrine tumor (PNET) subtypes plays an important role in prognostication, with surgical resection remaining the mainstay of treatment for all PNETs.

Figure 1.
Total number of pancreatic neuroendocrine tumors diagnosed (logarithmic scale) per year of diagnosis by histology type. PNET, pancreatic neuroendocrine tumor.

Figure 2.
 (A) Unadjusted overall survival by histology type for all treatments and all stages. (B) Unadjusted overall survival by histology type for resected patients only. PNET, pancreatic neuroendocrine tumor; Dx, diagnosis.

Figure 3.

Adjusted hazard ratios of death in resected patients. HR, hazard ratio; 95% LCL, lower confidence limit; 95% UCL, upper confidence limit.

Table 1

Patient and Tumor Characteristics by Pancreatic Neuroendocrine Tumor Type

Characteristic	Functional PNET		Carcinoid		Non-functional PNET		Total (%)	p Value
	N	%	N	%	N	%		
Sex								
Male	130	47.1	676	49.4	4891	53.7	53.0	0.0016
Female	146	52.9	693	50.6	4216	46.3	47.0	
Age, y								
50	88	31.9	378	27.6	2437	26.8	27.0	0.4236
51 to 65	105	38.0	551	40.3	3707	40.7	40.6	
>65	83	30.1	440	32.1	2963	32.5	32.4	
Race								
White	233	84.4	1094	79.9	7439	81.7	81.5	0.2461
Black	28	10.1	189	13.8	1189	13.1	13.1	
Other/unknown	15	5.4	86	6.3	479	5.3	5.4	
Charlson-Deyo score								
0	208	75.4	1009	73.7	6657	73.1	73.2	0.7001
1	50	18.1	272	19.9	1903	20.9	20.7	
2+	18	6.5	88	6.4	547	6.0	6.1	
Insurance								
Private	157	56.9	731	53.4	4778	52.5	52.7	0.0003
Medicare	88	31.9	485	35.4	2935	32.2	32.6	
Uninsured/Medicaid/unknown	31	11.2	153	11.2	1394	15.3	14.7	
Facility type*								
Academic	138	58.0	848	67.8	4872	58.7	59.8	<0.0001
Community	100	42.0	402	32.2	3430	41.3	40.2	
Tumor location								
Head	66	23.9	403	29.4	2863	31.4	31.0	<0.0001
Body/tail	107	38.8	653	47.7	3839	42.2	42.8	

Characteristic	Functional PNET		Carcinoid		Non-functional PNET		Total (%)	p Value
	N	%	N	%	N	%		
Other	103	37.3	313	22.9	2405	26.4	26.2	
Tumor size, mm								
20	88	31.9	522	38.1	1827	20.1	22.7	<0.0001
21 to 40	71	25.7	403	29.4	2784	30.6	30.3	
41 to 69	48	17.4	184	13.4	1948	21.4	20.3	
70	25	9.1	128	9.4	1286	14.1	13.4	
Unknown	44	15.9	132	9.6	1262	13.9	13.4	
Grade								
Well-differentiated	114	41.3	829	60.6	3669	40.3	42.9	<0.0001
Moderately/poor/undifferentiated	19	6.9	119	8.7	1795	19.7	18.0	
Unknown	143	51.8	421	30.7	3643	40.0	39.1	
Regional lymph nodes								
Positive	78	28.3	196	14.3	2000	22.0	21.2	<0.0001
Negative	65	23.6	584	42.7	2423	26.6	28.6	
Unknown	133	48.2	589	43.0	4684	51.4	50.2	
AJCC clinical stage								
I/II	72	26.1	688	50.3	2901	31.9	34.1	<0.0001
III/IV	42	15.2	210	15.3	3225	35.4	32.3	
Unknown	162	58.7	471	34.4	2981	32.7	33.6	
Resected [†]								
Yes	178	64.5	938	68.7	4966	54.6	56.7	<0.0001
No	98	35.5	428	31.3	4127	45.4	43.3	
Chemotherapy								
Yes	49	17.7	157	11.5	2376	26.1	24.0	<0.0001
No/unknown	227	82.3	1212	88.5	6731	73.9	76.0	

* 962 missing

[†] 17 missing

AJCC, American Joint Committee on Cancer