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

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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: We performed a retrospective cohort study using 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 nonfunctional and 2.6% with functional PNETs. Although the number of functional PNETs has remained relatively constant over time, rates of nonfunctional and carcinoid tumors have risen dramatically. Only 36 (5.7%) carcinoid tumors were diagnosed in 2004; this increased to 497 (27.7%) in 2013. Overall survival was significantly longer for carcinoid compared with functional and nonfunctional tumors (log-rank $p < 0.0001$), with 5-year survival rates of 63.1%, 58.3%, and 52.6%, respectively. For patients having resection, overall survival further improved for carcinoid tumors relative to functional (log-rank $p = 0.0011$) and nonfunctional (log-rank $p < 0.0001$) tumors, but the survival difference between functional and nonfunctional 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 (hazard ratio [HR] 1.81) and nonfunctional (HR 1.40) PNETs compared with carcinoid tumors.

CONCLUSIONS: Primary pancreatic carcinoid tumors are increasingly being diagnosed. Differentiating PNET subtypes plays an important role in prognostication. Resection remains a critical component of care. (J Am Coll Surg 2017;224:1057−1064. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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 vs nonpancreatic 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 nonfunctional subtypes, with more than 85% of cases being nonfunctional.[1] However, little information exists regarding primary pancreatic carcinoid (serotonin-producing) tumors.

Although primary serotonin-producing NETs of the pancreas have only rarely been reported,[2-4] there has

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Abbreviations and Acronyms

HR = hazard ratio
NCDB = National Cancer Data Base
NET = neuroendocrine tumor
PNET = pancreatic neuroendocrine tumor

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 because 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 recommend that carcinoid tumors and PNETs be assessed separately in clinical trials.[6]

This study aimed 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 nonfunctional PNETs. Secondarily, trends in the national annual incidence of PNET types were assessed.

METHOD

Population

The National Cancer Data Base (NCDB) participant user files were queried for adult patients aged 18 to 90+ years, who were diagnosed with primary PNETs between 2004 and 2013. Neuroendocrine tumors were identified by the following 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 of the American College of Surgeons founded in 1989. It is a nationwide oncologic database that encompasses more than 1,500 Commission on Cancer hospitals and captures approximately 70% of all newly diagnosed malignancies in the US.[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 NETs 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 1 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, nonfunctional, and carcinoid tumor subtypes. Functional PNETs consisted of insulinoma, 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 patients missing a 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 because not all subgroups reached median survival.

Cox proportional hazards models were generated to assess the impact of tumor type on overall survival for patients having resection (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). Values of $p < 0.05$ were considered statistically significant.