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Localized high-grade gastroenteropancreatic neuroendocrine tumors: Defining prognostic and therapeutic factors for a disease of increasing clinical significance☆

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Abstract

Background: Due to the limited sample size in the existing series, the natural history and management of high-grade gastroenteropancreatic neuroendocrine tumors (GEP-NET) is poorly understood. In order to better understand high-grade GEP-NET, a large cohort study was undertaken.
Objective: To determine the prognostic factors associated with high-grade GEP-NET.
Methods: Patients diagnosed with non-metastatic high-grade GEP-NET from 1988 to 2010 were identified in SEER.
Results: Incidence of high-grade GEP-NETs increased from 0.03 to 0.19/100,000 over the study period. The median age was 65 years, and the majority of the patients were white and females. The most common primary site was colorectal, and the most frequent T classification was T3. Surgical resection was performed in 89% of patients that varied by site ($p < 0.0001$). Nodal involvement was frequent and varied by site ($p = 0.0002$). The 5-year disease-specific survival was 63.3% and was the greatest for small bowel ($p = 0.0003$). Survival was associated with age, node status and surgery ($p < 0.05$). On multivariate analysis, the node status, surgery, and site continued to be associated with survival ($p < 0.05$); however, age ($p = 0.08$) no longer influenced the patient's survival.
Conclusion: High-grade GEP-NETs are neoplasms with exponentially increasing in incidence. Tumor location and nodal status are predictors of survival. Surgery is associated with a survival advantage and could be considered for localized disease.

Keywords: Survival; High-grade gastroenteropancreatic neuroendocrine tumors; Prognostic factors; Incidence

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms, a majority of which originate in the gastrointestinal tract and are designated as gastro-enteropancreatic-NET (GEP-NET).[1] Although GEP-NETs were once rarely observed, multiple recent reports have documented an increase in the incidence of this disease.[1–4] Fraenkel recently reported a 3.65-fold incidence increase in the last four decades in the US.[5]

The natural history of localized GEP-NETs varies depending largely on the primary location and grade. The well-differentiated (low to intermediate grade) neoplasms are often found to be slow-growing and asymptomatic and can often be treated with limited resection or observation if diagnosed at an early stage. However, poorly differentiated (high-grade) neoplasms have a proclivity to metastatic dissemination and poor prognosis and may require more aggressive medical or surgical therapy.[6] In the case of GEP-NET, the grading system seems to be one of the most important determinates of clinical behavior.[3,7–9] The prognosis of poorly differentiated GEP-NETs is more similar to small bowel carcinoma than to the well-differentiated GEP-NET.[10]

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A multitude of studies have been done on GEP-NETs. Unfortunately, most of these are retrospective single-centered[8,11,12] or large dataset studies.[1,3] These studies are often inclusive of all grades of neuroendocrine neoplasms analyzed as a single entity. Given the clinical significance of tumor grade, the further extrapolation of treatment paradigms is problematic. However, only a few retrospective series have reported prognostic factors exclusive to high-grade GEP-NET.[7]

The lack of sufficient data specific to high-grade GEP-NETs has resulted in no clear consensus on its treatment. Extrapolation of therapeutic paradigms from the low-grade GEP-NET would indicate that surgery is the primary curative therapy.[13] Pape reported surgery to be associated with improved long-term outcomes for a group of patients with mixed grade GEP-NETs.[8] Similarly, in a comprehensive review of carcinoid tumors, Schinirer (2011) recommended surgery to be the primary treatment option for all patients with loco-regional diseases.[13] The optimal surgical treatment was predicated solely on the stage of presentation.[8,13–17]

The recommendations are contradictory when data was inferred from high-grade pulmonary NETs. In this setting, surgery was not considered as the primary therapy. In fact, surgery alone is rarely curative. The benefits of surgery following neoadjuvant chemotherapy, even in localized disease, are unknown. Given the aggressive metastatic potential of this disease, the platinum-based regimens are considered for primary therapy.[18,19] The National Comprehensive Cancer Network (NCCN) provides the therapeutic guidelines for poorly differentiated high-grade neuroendocrine tumors. The guidelines are based on the (WHO G3) NORDIC NEC study[7] and therapeutic guidelines for small cell lung cancer.[20] The (WHO G3) NORDIC NEC study presents factors associated with the treatment of advanced GEP-NETs (patients with metastatic disease at diagnosis or patients with localized unresectable disease), with little guidance for those with localized disease. As guidelines are inferred from data that is not specific to localized high-grade GEP-NETs, the applicability of the (WHO G3) NORDIC NEC study for these patients is debatable.[21] Indeed, the data obtained from contemporary studies suggested different prognosis and response to therapy for extra-pulmonary NET when compared to the pulmonary small-cell cancers.

Given the rarity of data and the controversy regarding the optimal treatment paradigms that are largely based on inference, additional studies on high-grade GEP-NET are imperative for distinguishing the low- and high-grade GEP-NETs. The rationale for the present study was to analyze the outcomes from a large national dataset to better determine the prognostic factors associated with high-grade GEP-NET and also define the treatment algorithms unique to this entity.

Materials and methods

Data source

The SEER tumor registry was used to extract the patient's data. The National Cancer Institute SEER program collected the data on patient demographics, tumor characteristics, and treatment methods. The registry also provided information on cancer incidence and survival for around 28% of the US population.[22]

A SEER registry query was performed from 1988 to 2010 to identify the patients with high-grade GEP-NET. ICD-0-3 histologic codes were used to identify the patients. These codes included: (8150) islet cell carcinoma, (8151) insulinoma malignant, (8152) glucagonoma malignant, (8153) gastrinoma malignant, (8154) mixed islet cell and exocrine adenocarcinoma, (8155) vipoma, (8156) somatostatinoma malignant, (8240) carcinoid tumor, (8240) carcinoid tumor malignant, (8241) enterochromaffin cell carcinoid, (8242) enterochromaffin-like cell tumor malignant, (8243) goblet cell carcinoid, (8244) composite carcinoid, (8246) neuroendocrine carcinoma, (8249) atypical carcinoid tumor, and (8238) apudoma. The sites with five or fewer patients (gallbladder, ampulla of Vater and anus) were excluded. Only poorly differentiated and anaplastic (grade 3/4) neoplasms were included. High-grade GEP-NET incidence and survival analysis were performed for the overall population as well as independently by grade.

The survival analysis censor was determined based on the "SEER cause-specific death classification" and "COD to site recode." The patients categorized as "N/A not first tumor" in SEER cause-specific death classification were further analyzed. If the "site category" was the same as the primary site, the patients were classified as "dead from the specific disease". If the death was attributable to other causes, then the patients were classified as "dead of other cause" for the purpose of disease-specific survival. Our main interest was the impact of surgical therapy on high-grade GEP-NET; cases recognized as stage IV (metastatic) were excluded from the study (48.2% in the anaplastic group and 41.8% in the poorly differentiated group).

The patient demographics included age, gender, and race. The tumor characteristics were coded using a combination of the SEER staging systems: historic, collaborative, and extent of disease, and included the location of the primary tumor, size, and nodal status. Treatment was classified as a binomial variable based on the use or non-use of surgery. The patients with unknown surgical intervention were excluded from the study. As these data are de-identified the IRB at the Brody School of Medicine, East Carolina University does not consider this human subjects research requiring IRB approval.