# Increasing incidence of duodenal neuroendocrine tumors: Incidental discovery of indolent disease?

**Timothy L. Fitzgerald, MD, Samuel O. Dennis, BS, Swapnil D. Kachare, MD, Nasreen A. Vohra, MD,** *and* **Emmanuel E. Zervos, MD,** *Greenville, NC*

***Background.*** *There has been a marked increase in the recognized incidence of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Studies have often combined duodenal neuroendocrine tumors (D-NETs) with other small bowel GEP-NETs. As a result, the natural history and clinical ramifications of these D-NETs is poorly understood.*

***Methods.*** *Patients diagnosed with duodenal "carcinoid" tumors from 1983 to 2010 were identified in the Surveillance Epidemiology and End Results tumor registry.*

***Results.*** *A total of 1,258 patients were identified. The mean age was 64 years. The majority of patients were male (55.6%), white (55.6%), and had stage I disease (66.2%). Patients meeting inclusion criteria were divided into 2 cohorts: (i) era 1 patients diagnosed with GEP-NETs from 1983 to 2005, and (ii) era 2 those diagnosed from 2005 to 2010. There was a clear increase in the incidence rate of D-NETs from 0.27 per 100,000 in 1983 to 1.1 per 100,000 in 2010 (*$P < .001$*). Comparison of patients from the different eras revealed that those in era 2 were more likely than era 1 to present with stage I disease (69.9 vs 57.5%;* $P < .01$*) and less likely to present with late-stage disease. The 5-year, disease-specific survival improved for era 2 patients compared with era 1 (89.3 vs 85.2%;* $P = .05$*); however, multivariate analysis demonstrated that stage but not era was associated with disease-specific survival.*

***Conclusion.*** *Prognosis for D-NETs, in contrast with other small bowel NETs, is excellent. There has been a steady increase in the recognized incidence of D-NETs, coincident with the migration to earlier disease stage and improved disease-specific survival. (Surgery 2015;158:466-71.)*

*From the Brody School of Medicine, Division of Surgical Oncology, East Carolina University, Greenville, NC*

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), commonly known as carcinoid tumors, are a heterogeneous group of neoplasms. Their origin is from the neuroendocrine cells of the embryologic gut, most often with the primary lesion located in the gastric mucosa, the small and large intestine, the rectum, or the pancreas, and because of our ability to diagnose them, these GEP-NETs are of increasing clinical relevance. Neuroendocrine neoplasms can occur anywhere in the gastrointestinal tract, but are most common in the stomach, duodenum, ileum, pancreas, appendix, and rectum.[1-4] Although these neoplasms may be of high or low grade, the focus of this study is on low-grade neoplasms, because they represent the majority of GEP-NETs and are most amenable to operative intervention.[3,5-7] Although these neoplasms most often seem to be histologically bland, GEP-NETs have a capricious malignant potential predicated on factors such as location, size, and depth of invasion.[8]

GEP-NETs have been increasing in both incidence and prevalence.[1,4,9,10] Over the last 3 decades, multiple investigators from the United States, South America, Europe, and Australasia have documented this epidemiologic change for GEP-NETs.[2-5,10-12] Since the 1970s, GEP-NETs have increased by 720% in incidence and 213–286% in prevalence in the United States.[13] Mocellin and Nitti[11] reported that this increase in GEP-NETs is greater than any other cancer in the United States. In this study, the authors reported data from 1973 to 2009, during which there was an average annual increase of 4.4 per year. The increase in GEP-NETs was greatest for stomach and rectum; the only site noted with a

Presented at the Academic Surgical Congress, Las Vegas, Nevada, February 2015.

Accepted for publication March 13, 2015.

Reprint requests: Timothy L. Fitzgerald, MD, Brody School of Medicine, 4S24, 600 Moye Boulevard, Greenville, NC 27834. E-mail: fitzgeraldt@ecu.edu.

0039-6060/$ - see front matter



http://dx.doi.org/10.1016/j.surg.2015.03.042

decreased incidence of GEP-NETs was appendiceal. The 5-year survival of 60% for small bowel GEP-NETs has changed little over this period of time.[13] As a result, there has been a corresponding increase in mortality from small bowel GEP-NETs of 3.5 per year from 1973 onward.[11]

The etiologic factors behind the increasing incidence and mortality for GEP-NETs are unclear. The increase has been attributed to screening and diagnostic endoscopy, the more ready use of cross-sectional imaging, physician awareness, and possible environmental factors such as proton pump inhibitors.[1,2,4,14] A Swedish autopsy study from 1958 to 1968 demonstrated a 8.4 per 100,000 incidence of carcinoid tumors, most of which were incidental and discovered asymptomatically at the autopsy a rate of about 7 times of that in the population of Sweden.[15] These data imply that at least a portion of the increased number of cases diagnosed in the modern era could be the result of an incidental discovery of clinically occult disease.

The population trends for D-NETs are not documented clearly. An understanding of the epidemiology of D-NETs has been hindered by the pervasive tendency to report the incidence along with other small bowel NETs.[1-3,11,16] It is inappropriate to combine D-NETs with ileal NETs because D-NETs can be diagnosed more easily during routine endoscopy and have a more indolent clinical course.[8] As a result of such differences, our group has proposed a modification of the current American Joint Committee on Cancer (AJCC) staging system to reflect the distinct biology of D-NETs that is dictated by the tumor size and depth of invasion.

Given the epidemiologic trends for GEP-NETs and the paucity of research available currently to guide the care of patients with D-NETs, further investigation is imperative. To better define the true incidence, mortality, and refine treatment paradigms, we analyzed data the Surveillance Epidemiology and End Results (SEER) tumor registry from a large, national cancer registry. We hypothesized that, similar to other small bowel NETs, the incidence of D-NETs is increasing, and this increase will be associated with an increased mortality.

## MATERIALS AND METHODS

**Data source.** The SEER tumor registry was used to gather patient data. The National Cancer Institute's SEER program collects data on patient demographics, site, morphology, stage, and treatment. This registry also provides information on cancer incidence and survival for approximately 28% of the US population.[17]

**Patient selection.** A query of the SEER registry from 1983 to 2010 using SEER*Stat 7.0 was performed to identify patients with "carcinoid tumor" of the duodenum. Patient demographics included age, race, sex, survival time in months, and vital status. The tumor characteristics were coded using the staging systems of SEER for historic stage, collaborative stage, and extent of disease. The characteristics included extent of the disease (local, regional, or distant), size of the primary tumor, and nodal status. The patients were staged using a modification of the AJCC 7th *Edition Neuroendocrine Tumors: Duodenum, Ampulla, Jejunum and Ileum*, as previously reported by our group.[8] In this modified staging system, a new T category named T1b was created to represent patients with tumors 1–2 cm in size and not involving the muscularis propria. Patients were excluded if staging data were incomplete or if the tumor emanated from a site other than the duodenum.

**Statistical analysis.** Data were reported as mean values and ranges to summarize continuous variable and as frequency and proportions for categorical data. A univariate statistical analysis was performed using the Student *t* test or Chi-square test as indicated. Kaplan–Meier and log-rank tests were used for univariate survival analysis, and the Cox regression hazard model was used for the multivariate survival analysis. The data were analyzed using the SAS platform JMP Pro version 10.0.0 (2012, SAS Institute Inc., Cary, NC).

## RESULTS

**Demographics.** A total of 1,258 patients with D-NETs were identified (Table I). The mean age was 64 years. A majority of the patients were white (55.6%) and male (68.8%). The majority of patients (883; 66.2%) had stage I disease. The remainder of the patients were distributed fairly evenly between different stage disease. There were 129 (10.3%) stage II, 158 (12.6%) stage III, and 88 (11%) stage IV disease patients.

For comparison, 2 groups were created: (i) 1983–2005 (era 1) and (ii) 2006–2010 (era 2). On comparing era 2 with era 1 using the univariate analysis (Table I), patients in era 2 were more likely to present with stage I disease (69% vs 57.5%; $P \leq .001$) and less likely to present with higher stage metastatic disease (7.3% vs 19.8%; $P \leq .001$). Patients were otherwise similar in age, sex, and race. There was a 70% decrease in patients presenting with stage IV disease (odds ratio, 0.304; $P < .001$).