Neuroendocrine Tumors

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KEYWORDS

• Neuroendocrine • Tumor • Multimodal • Therapy • Carcinoid • Diagnostics

KEY POINTS

- Neuroendocrine tumors are heterogenous in nature and increasing in incidence.
- Symptoms can develop from secreted bioactive substances or from the mass effect of the tumor.
- Anatomic and functional imaging modalities are helpful in staging disease and assessing tumor biology.
- A range of therapies is available that include surgical, liver directed, and systemic therapies.
- The treatment of neuroendocrine tumors can be multimodal over a patient's disease history.

INTRODUCTION

Neuroendocrine tumors (NETs) of the gastrointestinal tract arise at many different sites, including the pancreas and small bowel, and are heterogeneous in nature with increasing incidence.[1] This review of gastroenteropancreatic (GEP) NETs discusses epidemiology, presentation, diagnosis, and management of primary and secondary sites of disease. Gastroenterologists have traditionally diagnosed and managed these tumors but now have a core role in multidisciplinary tumor board meetings on therapy decisions like surgery and systemic therapies. Significant advances have been made in managing these tumors with new diagnostics techniques and therapies. Many patients are now informed about their condition with information from Web sites and patient support groups with an expectation to access the whole array of diagnostic and therapeutic modalities.

NETs originate from neuroendocrine cells in the pancreatic islet and gastroenteric tissue. Small bowel (sb) and pancreatic (p) NETs have different clinical and genetic signatures and were previously considered to be largely benign in nature. The World Health Organization (WHO) 2010 nomenclature considers all NETs as malignant and classifies them by the cellular proliferation and degree of differentiation.[2] The use of NET rather

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than the historical "carcinoid" tumor is preferred and encouraged for describing gastrointestinal and pNETs. Similarly, classification by primary tumor site rather than embryologic origin (foregut/midgut/hindgut) is the accepted nomenclature. The molecular biology of NETs is still poorly understood, but there are emerging data to suggest that profiling of genetic and molecular signatures may enhance tumor classification and identify potential targets that may be involved in tumor progression[3] (**Table 1**).

Epidemiology

A key problem with NET epidemiology has been changes to classification systems and reliance on registries. International Classification of Diseases for Oncology-10 uses histopathological coding and has been used in most recent registries. It includes all the tumors that were previously classified as benign, which may be partly contributing to the increased incidence since 2000.[4] The largest registry is the Surveillance, Epidemiology, and End Results database that spans more than 5 decades and 15% of the US population from specific states.[5,6] There are national population studies that contribute to defining incidence in the United Kingdom, Norway, Sweden, Ireland, Netherlands, Denmark, and Austria.[7–12] NETs may now be the most common small bowel tumor (37.4%), ahead of adenocarcinoma (36.9%), lymphomas (17.3%), and stromal tumors (8.4%).[13]

There are reported ethnic differences with African Americans having the highest NET incidence at 6.5 per 100,000 persons.[6,14] The overall incidence of NETs in Caucasians in the United States and Norway is 4.44 and 3.24 per 100,000 persons, respectively.[10] The rectum is the commonest site in the United States and Far East, with lung NETs the commonest site in Caucasian US patients.[15,16] The incidence of NETS of the appendix, cecum, and pancreas almost doubled between 1975 and 2005, but these tumors are only a fraction of NETs diagnosed, around 0.1 to 0.2 cases per 100,000 persons. Historical autopsy studies in Sweden described an incidence of 8.4 per 100,000 with a significant number of NET tumors that were not diagnosed antemortem.[17] The prevalence of NET is proportionally much greater than the incidence because of improved survival when compared with other common cancers like gastric and pancreatic adenocarcinomas.[18] Whatever the precise incidence of NETs, it appears that the number of patients presenting with these tumors has been steadily increasing.

Genetics

GEP-NETs may be associated with familial endocrine cancer syndromes, such as pNETs with multiple endocrine neoplasia type 1 (MEN1) and less commonly with von Hippel-Lindau and tuberous sclerosis. The incidence of MEN1 in GEP NETs varies

Table 1
World Health Organization classification of neuroendocrine tumors

WHO (2010) and ENETS Nomenclature	Grade	Mitotic Count	Ki-67 Index (%)	Cell Type
NET	G1	<2 mitoses/10 HPF	≤2	—
NET	G2	2–20 mitoses/10 HPF	3–20	—
Neuroendocrine carcinoma (NEC)	G3	>20 mitoses/10 HPF	>20	Large vs small cell

Abbreviation: ENETS, European Neuroendocrine Tumor Society.
From Bosman F. WHO classification of tumours of the digestive system. Lyon (France): IARC Press; 2010; with permission.