Malignant Neuroendocrine Neoplasms

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I. Introduction

Neuroendocrine cells are nerve cells that respond to signals from other nerve cells by releasing hormones into the blood. They are distributed widely throughout the body and may undergo malignant transformation to give rise to neuroendocrine neoplasms.

Neuroendocrine neoplasms are commonly defined as epithelial neoplasms with a predominant presence of scattered neuroendocrine cells singly or in small nests (neuroendocrine differentiation).[1] Many neuroendocrine neoplasms traditionally have been called "carcinoids," but this term does not accurately account for their variable biology, histologic differentiation, and secretory potential.[2] The WTC Health Program uses the term “malignant neuroendocrine neoplasm” to refer to the family of solid malignant tumors that are believed to originate from neuroendocrine cells found throughout the body, including “carcinoid tumors.”

II. Anatomic Distribution

Neuroendocrine neoplasms arise in a variety of anatomic locations, including the lung, stomach, small intestine, pancreas, colon, rectum, breast, prostate and ovary.[3,4]

[1] The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) is based on the World Health Organization's Ninth Revision, International Classification of Diseases (ICD-9). ICD-9-CM is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

[2] Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S [2012]. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading and staging systems. *Pancreas* 39(6):707-712.

[3] Modlin IM, Oberg K, Chung DC, Jensen RT, deHerder WW, Thakker RV, Caplin M, Delle Fave G, Kaltsas GA, Krenning EP, Moss SF, Nilsson O, Rindi G, Salazar R, Ruszniewski, Sundin A [2008]. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 9:61-72.

[4] Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, Corrie P, Davar J, Davies AH, Lewington V, Meyer T, Newell-Price J, Poston G, Reed N, Rockall A, Steward W, Thakker RV, Toubanakis C, Valle J, Verbeke C, Grossman

The majority of neuroendocrine tumors occur in the gastrointestinal tract (67.5%) and the bronchopulmonary tree (25.3%).[5]

Within the gastrointestinal tract, most neuroendocrine tumors occur in the small intestine (41.8%), rectum (27.4%), and stomach (8.7%), and less than 1% of neuroendocrine neoplasms occur in the pancreas.[6] Other anatomical sites where neuroendocrine neoplasms also arise—but very rarely—include the uterus, ovary, testis, breast and larynx.[7]

III. Clinical and Pathologic Features

Some of the clinical and pathologic features of neuroendocrine neoplasms are characteristic of the anatomic site of origin, but, more frequently, neuroendocrine neoplasms have more in common with each other than they do with the anatomic site where they arise. For example, some functioning neuroendocrine neoplasms produce polypeptide hormones that are not commonly produced by normal cells within the same anatomic site, such as gastrin, vasoactive intestinal polypeptide, or adrenocorticotropic hormone production by neuroendocrine neoplasms in the pancreas.[8] A hypersecretory syndrome may be the first indication of the presence of a neuroendocrine neoplasm.[4] Other neuroendocrine neoplasms may be non-functioning and exhibit no hormone-related clinical features. Neuroendocrine neoplasms, then, are said to "involve" a particular organ, but they are not "specific" to that particular organ.

IV. Classification

Neuroendocrine neoplasms do not have a single unified system of nomenclature, grading or staging. However, both the World Health Organization (WHO), and the International Classification of Diseases (ICD) coding system, classify neuroendocrine neoplasms as a *unified* group, distinct from other neoplasms.[9,10,11]

AB [2012] . Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut* 61:6-32. "*Gastroenteropancreatic NETs may be classified into non-functioning tumours, which have no hormone-related clinical features, and functioning tumours, which cause symptoms due to peptide and hormone release."* See p. 9, Clinical features.

[5] Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB [2008]. One hundred years after 'carcinoid:' epidemiology of and prognostic factors for neuroendocrine tumours in 35,825 cases in the United States. *J Clin Oncol* 26(18):3063-3072.

[6] Modlin IM, Lye KD, Kidd M [2008]. A 5-decade analysis of 13,715 carcinoid tumours. *Cancer* 97(4):943-959.

[7] Modlin IM, Shapiro MD, Kidd M [2005]. An analysis of rare carcinoid tumors: clarifying these clinical conundrums. *World J Surg* 29(1):92-101.

[8] Klimstra D, Perren A, Oberg K [2004]. Pancreatic endocrine tumours: non-functioning tumours and microadenomas. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C eds. Pathology and genetics of tumours of endocrine organs. IARC Press, Lyon, pp. 201-204.

[9] International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM).

A. World Health Organization

The 2010 *World Health Organization's Classification of Tumours of the Digestive System* is the guidance most commonly used to classify the malignant potential of different types neuroendocrine neoplasms.[11] The WHO classification guidelines categorize neuroendocrine neoplasms as a whole into 2 groups based on clinical behavior: (1) well-differentiated neoplasms (which can be further sub-divided into grade 1 (G1) and grade 2 (G2))—these are less aggressive; and (2) poorly differentiated (grade 3 (G3)) neuroendocrine neoplasms—these are the most aggressive.

B. International Classification of Diseases.

The ICD, Ninth Revision, Clinical Modification (ICD-9-CM) is based on the WHO's Ninth Revision, ICD-9. ICD-9-CM is the official system of assigning codes to diagnoses and health care procedures in the United States.[12] The replacement for the ICD-9-CM is the ICD, Tenth Revision, Clinical Modification (ICD-10-CM). Both the ICD-9-CM and ICD-10-CM Coding Systems are used by the WTC Health Program for classifying neoplasms and making certification decisions. Neuroendocrine tumors are classified under several distinct codes in the ICD-9-CM and ICD-10-CM coding systems.

V. Incidence and Prevalence of Neuroendocine Neoplasms

Even though the incidence rate for nearly all types of gastrointestinal neuroendocrine neoplasms increased between 1975 and 2008, the age-adjusted incidence rate for neuroendocrine tumors is below 1.4 cases per 100,000 persons.[13] Furthermore, the annual incidence rate per 100,000 persons of malignant neuroendocrine tumors *involving* the pancreas is about 0.2 per 100,000 persons.[14]

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[10] International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM).

[11] Rindi G., Arnold R., Bosman FT, Capella C, Klimstra DS, Klöppel G, and Solcia E [2010]. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carniero F, Hruban Rh, Theise ND eds. WHO Classification of Tumours of the Digestive System. IARC Press, Lyon 4:3-14.

[12] See http://www.cdc.gov/nchs/icd/icd9cm.htm. Accessed on October 2, 2013.

[13] Tsikitis VL, Wertheim BC, Guerrero MA [2012]. Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: A SEER analysis. *Cancer* 3:292-302.

[14] Halfdananson TR, Rabe KG, Rubin J, Petersen GM [2008]. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis, and recent trends toward improved survival. *Ann Oncol* 19(10):1-7.

In 2004, the prevalence of neuroendocrine tumors in the United States is estimated to be 103,312 cases or 35 cases per 100,000 persons.[5] The prevalence rate of 35 cases per 100,000 persons reflects the number of people alive on January 1, 2004 who were diagnosed with neuroendocrine tumors during the preceding 31 years (SEER Data, 1973-2004).[15]

VI. Summary of Evidence

Neuroendocrine neoplasms are distributed in widely different anatomical sites throughout the body, but share common histologic and biological features. They are identified by authoritative disease coding systems as a separate class of neoplasms.

VII. Certification

When a physician from the Clinical Center of Excellence, or the Nationwide Provider Network, determines a neoplasm to be a "malignant neuroendocrine neoplasm" under ICD-9-CM code system, the WTC Health Program will consider the malignant neuroendocrine neoplasm for possible certification as a "rare cancer," regardless of the anatomic site where identified.

Each determination of any malignant neoplasm must be considered for certification as a WTC-related health condition under the minimum latency requirements for solid cancers,[16] and the exposure requirements specified by the WTC Health Program in the WTC-3 Certification Request form.

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[15] The prevalence of neuroendocrine tumors as a group meets the current WTC Health Program's definition for "rare cancers" found at 42 C.F.R. § 88.1.(4)(Table 1)—"any type of cancer affecting populations smaller than 200,000 individuals in the United States, i.e., occurring at an incidence rate less 0.08 percent of the U.S. population."

[16] WTC Health Program. *Minimum Latency & Types or Categories of Cancer* (May 1, 2013). http://www.cdc.gov/wtc/pdfs/wtchpminlatcancer2013-05-01.pdf