The New World Health Organization Classification for Pancreatic Neuroendocrine Neoplasia

Frediano Inzani, MD, PhD[a,b,c], Gianluigi Petrone, MD, PhD[a,b,d], Guido Rindi, MD, PhD[a,b,d,e,*]

KEYWORDS

• Neuroendocrine neoplasm • Neuroendocrine tumor • Neuroendocrine carcinoma • Ki67 • World Health Organization • American Joint Cancer Committee

KEY POINTS

- The World Health Organization (WHO) in 2017 classification emphasizes the concept of separate neuroendocrine tumor (NET) and neuroendocrine carcinoma (NEC) families for pancreatic neuroendocrine neoplasms (panNENs).
- NENs comprise both NET and NEC.
- NETs are G1-G3 with increasingly aggressive behavior.
- NEC are by default G3 with highly aggressive behavior.
- The American Joint Cancer Committee in 2017 applied this classification to NENs of the entire gastro-enteric tract and pancreas.

INTRODUCTION

Neuroendocrine neoplasms (NENs) are found throughout the body in all organs, although they are more common in the lung, the digestive tract, and the pancreas.[1,2] By definition the neuroendocrine neoplasm is made by cancer cells expressing

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[a] Department of Anatomic Pathology, IRCCS Fondazione Policlinico Universitario A. Gemelli, Largo A. Gemelli, 8, Roma I-00168, Italy; [b] Roma ENETS Center of Excellence, IRCCS Fondazione Policlinico Universitario A. Gemelli, Largo A. Gemelli, 8, Roma I-00168, Italy; [c] Gynecological and Breast Pathology Unit, IRCCS Fondazione Policlinico Universitario A. Gemelli, Largo A. Gemelli, 8, Roma I-00168, Italy; [d] Anatomic Pathology Unit, IRCCS Fondazione Policlinico Universitario A. Gemelli, Largo A. Gemelli, 8, Roma I-00168, Italy; [e] Institute of Pathology, Università Cattolica-IRCCS Fondazione Policlinico Universitario A. Gemelli, Largo A. Gemelli, 8, Roma I-00168, Italy
* Corresponding author. Institute of Anatomic Pathology, Università Cattolica-IRCCS Fondazione Policlinico Universitario A. Gemelli, Largo A. Gemelli, 8, Roma I-00168, Italy.
E-mail address: guido.rindi@unicatt.it

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markers of neuroendocrine differentiation including chromogranin A and synaptophysin (also called general markers of neuroendocrine differentiation), as well as hormones (also called [organ] specific markers of neuroendocrine differentiation), and transcription factors, which are tissue-specific and assimilate the cancer cell to its normal neuroendocrine cell counterpart.[3]

THE PATIENT OUTCOME

Predicting outcome for patients with NENs is usually difficult, with the notable exception of the high-grade carcinomas comprising the small cell carcinoma of the lung (SCLC) and the poorly differentiated neuroendocrine carcinoma (NEC) of the digestive tract and pancreas.[4–6] These aggressive cancers are usually diagnosed when at a high stage and drive patients to death at a rapid pace not comparable to any other epithelial cancer of both the respiratory and the digestive systems. On the contrary, the behavior of well-differentiated neuroendocrine neoplasms has always been considered as poorly predictable. This fact is embedded in the iconic definition of carcinoid, coined in 1907 by Siegfried Oberndorfer for the well-differentiated neuroendocrine neoplasm of the digestive tract to indicate the "sort of cancer" morphology of such rare epithelial neoplasms.[7] This "sort of" concept applies for the clinical behavior of carcinoids too, in the sense that such patients may show a slow, deceptive pace, resulting in multisite deposits and unexpectedly long survival in spite of the diffuse cancer burden. Indeed, the definition of "quiet cancer"effectively describes the clinical behavior of carcinoids.[8]

CLASSIFICATION TOOLS

The World Health Organization (WHO) set order into the neuroendocrine cancer world of the digestive system with the classifications devised in 2000 and 2004.[4,5] Such classifications introduced the differentiation status of cancer cells (as defined by traditional morphology) as the main tool for the diagnosis of 2 separate neuroendocrine cancer entities with significantly different behaviors, well differentiated versus poorly differentiated (**Fig. 1**). In addition, the WHO 2000/2004 classification introduced multiparametric clinical-pathological correlations utilizing grading and staging variables to predict the survival of neuroendocrine cancer patients.[4] In particular, the presence of metastases was defined as the only parameter capable of defining as malignant the well-differentiated neuroendocrine neoplasm, associated with a change of neoplasm definition from tumor to carcinoma. Such classifications were broadly effective in predicting patients' survival, but would work only once the neuroendocrine neoplasm's malignant pace was overt, a condition rarely seen at many anatomic sites such as the stomach, the pancreas, and the large intestine, for which an early diagnosis is frequent.

In 2010, under the auspices of the European Neuroendocrine Tumor Society (ENETS) proposals,[9,10] the WHO introduced both grading and staging tools for the stratification of patients with digestive neuroendocrine cancer.[11,12] The American Joint Cancer Committee (AJCC) staging manual, seventh edition rapidly followed.[13] The 2010 WHO/AJCC classifications introduced several principles:

- The term neoplasm was adopted as a unifying concept definition embracing both low- and high-grade neuroendocrine cancer.
- The neuroendocrine neoplasm was by default considered malignant
- A three-tier grading tool was devised based on proliferation markers (either mitotic count or Ki-67).