WHO 2010 Classification of the Neuroendocrine Tumors of the Gastrointestinal Tract and Pancreas

Historically, neuroendocrine tumors are categorized, graded and staged by the organ system. Over the years, different schemas underwent multiple revisions. As a result, discrepancy, inconsistency and confusions inevitably emerged and eroded the quality of reporting data. Efforts have been made by World Health Organization (WHO) and European Neuroendocrine Tumor Society (ENETS) in attempts to improve the standardization and clarify some key issues. This episode summarizes the key points of the 2010 WHO classification.

In this new classification schema, digestive neuroendocrine tumors are classified into three main histological categories: neuroendocrine tumors grade 1, neuroendocrine tumors grade 2, and neuroendocrine carcinomas which are grade G3. Neuroendocrine carcinomas are subdivided into large and small cell types. This new classification parallels well with the WHO classification for pulmonary neuroendocrine tumors. Two other categories include mixed adenoneuroendocrine carcinomas and hyperplastic and preneoplastic lesions. Mixed adenoneuroendocrine carcinomas have both an endocrine and an exocrine glandular phenotype. At least 30% of each component must be identified for this definition. This definition is the same as before, but the previous term, “mixed endocrine exocrine tumor”, is no longer favored.

To strengthen the validity of morphological classification, measurement of tumor cell proliferation activity by mitotic count and Ki-67 index is incorporated in the classification. The cut-points of mitotic count in 50 high power fields for G1, G2 and G3 neoplasms are less than 3, 3 to 20 and greater than 20 per 10 high power fields, respectively. However, assessment of mitotic count may be problematic when the biopsy sample is small, where evaluation of the Ki-67 index using the MIB antibody should be performed. The cut-points of Ki-67 index for G1, G2 and G3 are <3%, 3 to 20% and >20% of 500 to 2000 tumor cells, respectively. If grade differs by the mitotic count and Ki-67 index, it is suggested that the higher grade be endorsed. Several additional changes are also specified or inferred.

First, this new classification eliminates the terms “benign” and “malignant” to indicate that neuroendocrine neoplasms as a category are potentially malignant. This also highlights that morphology alone is not sufficient to predict biologic behavior or clinical outcomes of these neoplasms. The term “atypical carcinoid” is not recommended in the WHO 2010; it cannot be used for G2 neuroendocrine tumor. Although “endocrine” and “neuroendocrine” are essentially synonymous, the most recent edition of the WHO classification of tumors of the digestive system has once again recommended the use of neuroendocrine.

Second, neuroendocrine carcinoma is NOT defined by local vascular invasion or metastasis but by tumor histology and the grading (G3, mitoses >20 per 10 HPF and/or Ki-67 > 20%). By 2010 WHO definition, a neuroendocrine carcinoma is poorly-differentiated high grade malignant neoplasm composed of small or of large cells, expressing the neuroendocrine markers chromogranin-A and synaptophysin. There is no “well differentiated neuroendocrine carcinoma” in the current ENETS and 2010 WHO classifications.

Third, tumor size is NOT the only staging criterion. Tumor topographic extent is also a staging attribute in both TNM systems (by AJCC and ENETS) currently. It is recommended that the extent of involvement of landmark anatomic structures be specifically indicated in the pathology reports in addition to a TNM stage designation.
It is important to recognize that AJCC TNM and ENETS TNM classifications are two parallel systems, each of which uses identical TNM terminology but may refer to different types and extents of disease for certain neuroendocrine neoplasms. To minimize confusion caused by the existence of different staging schemas, it is recommended to note which classification is used (e.g. WHO 2010, WHO 2000, AJCC and ENETS TNM classifications, etc.).

In practice, because of the recent modifications in nomenclature, grading and staging and because the classifications are different (particularly the TNM by AJCC vs. TNM by ENETS for the pancreas), the actual proliferative rate (mitotic count and/or Ki67 index) should be specified to make comparison possible, and a grade should be provided, with the specific grading system used in the pathology report. It is important to recognize that the unqualified terms "neuroendocrine carcinoma" and "neuroendocrine tumor", without reference to grade or differentiation, are inadequate for prognostication or therapy and considered inappropriate in pathology reports.

This new WHO classification has abandoned the hybrid classification system in favor of separately grading and staging the tumors. This will bring the WHO system more closely in line with other widely used systems. Thus, the pathologic diagnosis of functioning NETs should be the same as for analogous nonfunctioning NETs of the same anatomic site, with the descriptive functional designation appended to the diagnosis when there is knowledge of a clinical syndrome.

====== Summary ======

- The neuroendocrine tumors are defined by morphology & neuroendocrine markers.
- They are classified by morphology & proliferative activity.
  - Grade-1: mitotic figure <3 per 10 high power field, or Ki-67 <3%.
  - Grade-2: mitotic figure 3 to 20 per 10 high power field, or Ki-67 3 to 20%.
  - Grade-3: mitotic figure > 20 per 10 high power field, or Ki-67 >20%.
    - (Grade 3 = large and small cell carcinomas).
- Do not use "atypical carcinoid", "well differentiated neuroendocrine carcinoma".
- TNM staging systems by AJCC and ENETS are different.
- Grading attributes and TNM system should be specified in report.

Reference / Suggested Readings