The Pathologic Classification of Neuroendocrine Tumors

A Review of Nomenclature, Grading, and Staging Systems

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Abstract: Neuroendocrine tumors (NETs) arise in most organs of the body and share many common pathologic features. However, a variety of different organ-specific systems have been developed for nomenclature, grading, and staging of NETs, causing much confusion. This review examines issues in the pathologic assessment of NETs that are common among primaries of different sites. The various systems of nomenclature are compared along with new proposal for grading and staging NETs. Although differences persist, there are many common themes, such as the distinction of well-differentiated (low and intermediate-grade) from poorly differentiated (high-grade) NETs and the significance of proliferative rate in prognostic assessment. A recently published minimum pathology data set is presented to help standardize the information in pathology reports. Although an ultimate goal of standardizing the pathologic classification of all NETs, irrespective of primary site, remains elusive, an understanding of the common themes among the different current systems will permit easier translation of information relevant to prognosis and treatment.

Key Words: neuroendocrine tumor, NET, pathology, classification, grade, stage

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Neuroendocrine neoplasms, defined as epithelial neoplasms with predominant neuroendocrine differentiation, arise in most organs of the body.[21,22] Some of the clinical and pathologic features of these tumors are characteristic of the organ of origin, but other attributes are shared by neuroendocrine neoplasms irrespective of their anatomic site. In general, studies of neuroendocrine neoplasms have concentrated on tumors of a specific organ system such as the lung, the pancreas, or the gastrointestinal tract. For this reason, various proposals have appeared regarding the classification and nomenclature of neuroendocrine tumors (NETs), and many of these differ somewhat in the use of specific terminology and criteria for grading and staging.[1] Most proposed systems have indeed proven useful to stratify prognostic subgroups of NETs. However, the differences in criteria have resulted in much confusion, especially because morphologically similar tumors may be designated differently depending on the site of origin, and some of the terminology used in one system suggests markedly different tumor biology based on another system. It would be of great benefit for the prediction of outcome and the determination of therapy if a single system of nomenclature, grading, and staging could be developed for NETs of all anatomic sites, and there are many similarities among NETs throughout the body. However, a number of the systems that have arisen independently are now firmly established and recognized by organizations charged with standardizing terminology, such as the World Health Organization (WHO). Also, compelling clinical data favoring one system over another do not exist. Thus, abandoning some of the current systems in favor of a single, uniform proposal has proven impractical. On the other hand, careful examination of the existing proposals reveals many common features that underlie the classification and form the basis for grading and staging.[17] Features such as the proliferative rate of the tumor and the extent of local spread (assessed based on similar parameters used for non-neuroendocrine carcinomas of the same anatomic sites) are shared by most systems. Therefore, it is recommended that these basic data elements used to stratify NETs be specified and documented in pathology reports, in addition to the use of a specified system of nomenclature, grading, and staging. By doing this, we assure that the fundamental data necessary for prognostic assessment and therapy determination are recorded, allowing retrospective comparison of the characteristics of NETs irrespective of the specific classification system that may currently be in vogue. Recently, a multidisciplinary consensus group of experts in the field of NETs has recommended such an approach and has developed a *minimum pathology data set* (Table 1) of features to be included in pathology reports.[17] The College of American Pathologists (CAP) has also developed similar *tumor checklists* for NETs that specify many of the same parameters.[36–39]

NOMENCLATURE ISSUES

One semantic issue relates to the use of the term *endocrine* versus *neuroendocrine*. Originally, the concept of *neuroendocrine* neoplasia reflected the hypothesis that the cells from which these tumors were derived originated from the embryonic neural crest. This concept was disproved years ago, causing some authorities to advocate abandoning the term *neuroendocrine* in favor of *endocrine*, to reflect that most of these epithelial neoplasms recapitulated cells of endodermal origin. However, the neoplastic cells also possess features of neural and epithelial cells, and for this reason, the most recent edition of the WHO classification of tumors of the digestive system has once again recommended the use of *neuroendocrine*.[3] Although there may be arguments favoring either term, it must be recognized that they are essentially synonymous, and both are widely understood. For the sake of uniformity, *neuroendocrine* will be used throughout this manuscript. Another debated terminological issue relates to the use of *tumor* instead of *neoplasm*. Certainly, all of the entities under discussion are neoplastic, and *neoplasm* is therefore a more accurate term than *tumor*, which means only a mass. However, *neuroendocrine tumor (NET)* has achieved

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TABLE 1. Minimum Pathology Data Set: Information to be Included in Pathology Reports on NETs (from Klimstra et al 2010)[17]

For resection of primary tumors:
Anatomic site of tumor
Diagnosis (functional status need not be included in the pathology report)
Size (3 dimensions)
Presence of unusual histologic features (oncocytic, clear cell, gland-forming, and other features)
Presence of multicentric disease
[OPTIONAL: immunohistochemical staining for general neuroendocrine markers]
Chromogranin
Synaptophysin
Peptide hormones, IF a specific clinical situation suggests that the correlation with a functional syndrome may be helpful
Grade (specify grading system used)
Mitotic rate (number of mitoses per 10 high-power fields or 2 mm^2; count 50 high-power fields in the most mitotically active regions, count multiple regions)
[OPTIONAL: Ki67 labeling index (count multiple regions with highest labeling density, report mean percentage; *eyeballed* estimate is adequate)]
Presence of nonischemic tumor necrosis
Presence of other pathological components (eg, non-neuroendocrine components)
Extent of invasion (use anatomic landmarks for the AJCC T staging of analogous carcinomas of the same anatomic sites)
Stomach: depth of invasion into/through gastric wall
Small bowel: depth of invasion into/through bowel wall
Large bowel: depth of invasion into/through bowel wall
Appendix: depth of invasion into/through appendiceal wall; presence and extent of mesoappendiceal invasion
Pancreas: presence of extrapancreatic invasion or invasion of bile duct, duodenum, or ampulla
All sites: involvement of serosal/peritoneal surfaces; invasion of adjacent organs or structures
Presence of vascular invasion [OPTIONAL: perform immunohistochemical stains for endothelial markers if needed]
Presence of perineural invasion
Lymph node metastases
Number of positive nodes
Total number of nodes examined
TNM staging (specify staging system used)
Resection margins (positive/negative/close) [OPTIONAL: measure distance from margin if within 0.5 cm]
Proliferative changes or other abnormalities in non-neoplastic neuroendocrine cells
For biopsy of primary tumors:
Anatomic site of tumor
Diagnosis (functional status need not be included in the pathology report)
Presence of unusual histologic features (oncocytic, clear cell, gland forming, and other features)
[OPTIONAL: immunohistochemical staining for general neuroendocrine markers]
Chromogranin
Synaptophysin
Peptide hormones, IF a specific clinical situation suggests that the correlation with a functional syndrome may be helpful
Grade (specify grading system used)
Mitotic rate (number of mitoses per 10 high-power fields or 2 mm^2; count up to 50 high-power fields)
Ki67 labeling index, for biopsies in which a diagnosis of high-grade neuroendocrine carcinoma cannot be excluded (count multiple regions with highest labeling density, report mean percentage; eyeballed estimate is adequate)
Presence of nonischemic tumor necrosis
Presence of other pathological components (eg, non-neuroendocrine components)
For resection of metastatic tumors:
Location of metastasis(es)
Diagnosis (functional status need not be included in the pathology report)
Number of metastases resected
Extent of involvement of resected tissue (percentage)
Greatest dimension of largest metastasis
Presence of unusual histologic features (oncocytic, clear cell, gland-forming, and other features)
[OPTIONAL: immunohistochemical staining for general neuroendocrine markers]
Chromogranin
Synaptophysin
Peptide hormones, IF a specific clinical situation suggests the correlation with a functional syndrome may be useful
Grade (specify grading system used)
Mitotic rate (number of mitoses per 10 high-power fields or 2 mm^2; count 50 high-power fields in the most mitotically active regions and provide separate mitotic rate for each major separate site of disease)
[OPTIONAL: Ki67 labeling index (count multiple regions with highest labeling density, report mean percentage; eyeballed estimate is adequate)]
Presence of nonischemic tumor necrosis
Presence of other pathological components
Resection margins (positive/negative/close) [OPTIONAL measure distance from margin if within 0.5 cm]
Identification of primary site
Immunohistochemistry for CDX2 and TTF1
For biopsy of metastatic tumors:
Location of metastasis
Diagnosis (functional status need not be included in the pathology report)
Presence of unusual histologic features (oncocytic, clear cell, gland-forming, and other features)
Immunohistochemical staining for general neuroendocrine markers
Chromogranin
Synaptophysin
[OPTIONAL: peptide hormones, IF a specific clinical situation suggests the correlation with a functional syndrome may be useful]
Grade for adequate biopsy specimens; fine needle aspiration specimens may not be adequate (specify grading system used)
Mitotic rate (number of mitoses per 10 high-power fields or 2 mm^2; count up to 50 high-power fields)
Ki67 labeling index (count multiple regions with highest labeling density, report mean percentage; eyeballed estimate is adequate)
Presence of nonischemic tumor necrosis
Presence of other pathological components (eg, non-neuroendocrine components)
Identification of primary site
Immunohistochemistry for CDX2 and TTF1

widespread acceptance in many systems and will be used here in lieu of the more correct but less accepted alternative, *neuroendocrine neoplasm*.

The terminology for NETs varies by anatomic site. The use of the term *carcinoid tumor* has been repeatedly criticized[8,32] because of concerns that the term does not adequately convey the potential for malignant behavior that accompanies many of these neoplasms. However, *carcinoid tumor* remains in use, both in the official WHO classification of NETs of the lung[34] and as a synonym for NETs of other sites that retains widespread colloquial usage.[17]

In general, neuroendocrine neoplasms are divided into well-differentiated and poorly differentiated categories. The concept of differentiation is linked to the grade of the tumors, but

TABLE 2. Grade Versus Differentiation in Neuroendocrine Tumors

Differentiation	Grade
Well differentiated	Low grade (ENETS G1)
	Intermediate grade (ENETS G2)
Poorly differentiated	High grade (ENETS G3)

there are subtle differences between the concepts of differentiation and grade. Differentiation refers to the extent to which the neoplastic cells resemble their non-neoplastic counterparts. In NETs, well-differentiated examples have characteristic *organoid* arrangements of the tumor cells, with nesting, trabecular, or gyriform patterns. The cells are relatively uniform and produce abundant neurosecretory granules, reflected in the strong and diffuse immunoexpression of neuroendocrine markers such as chromogranin A and synaptophysin. Poorly differentiated NETs less closely resemble non-neoplastic neuroendocrine cells and have a more sheetlike or diffuse architecture, irregular nuclei, and less cytoplasmic granularity. Immunoexpression of neuroendocrine markers is usually more limited. Grade, on the other hand, refers to the inherent biologic aggressiveness of the tumor. Low-grade NETs are relatively indolent, high-grade tumors are extremely aggressive, and intermediate grade examples have a less predictable, moderately aggressive course. In general, well-differentiated NETs are either low or intermediate grade, and poorly differentiated NETs are considered high grade in all cases (Table 2). The concept that some well-differentiated tumors could nonetheless be biologically high grade has been proposed but is controversial.[33]

The systems of nomenclature reflect differentiation and grading features of NETs. In essentially all systems, a sharp division is made between well-differentiated and poorly differentiated tumors, with the latter group being clearly designated as high-grade neuroendocrine carcinomas (neuroendocrine carcinoma, grade 3), including small-cell carcinoma and large-cell neuroendocrine carcinoma variants. Combined (mixed) forms with elements of non-neuroendocrine carcinoma (usually adenocarcinoma or squamous cell carcinoma) are also well recognized. The distinction of well-differentiated from poorly differentiated NETs is probably one of the most important pathologic assessments related to these neoplasms, as the biologic behavior of the well-differentiated group is often rather indolent, whereas poorly differentiated neuroendocrine carcinomas are very highly aggressive; therapy also differs significantly between these 2 categories of tumors. The term *carcinoma* also has been applied to well-differentiated tumors, however. In some systems (particularly the prior 2001 and 2004 versions of the WHO classifications of digestive and pancreatic NETs[5,13,18]), *carcinoma* was used in the place of *tumor* for neoplasms with obvious evidence of malignant behavior, such as vascular invasion, gross local invasion, or metastases. Others have argued to use the term *carcinoma* for all NETs to specify that all are regarded to be malignant.[23] However, the use of the same term for all grades of NETs implies a relationship between the well-differentiated and poorly differentiated groups that does not exist in most instances. It is most 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.

Well-differentiated (low and intermediate grade) NETs have been variably termed *carcinoid tumor* (typical and atypical), *neuroendocrine tumor* (grade 1 and grade 2), or *neuroendocrine carcinoma* (low grade and intermediate grade), among other options. Table 3 displays a comparison of the various systems of nomenclature currently in use for NETs, along with the organ systems most commonly using each system. Although the criteria that define each category do not perfectly match among the various systems, there are several common themes. Each system recognizes 3 grades. In each, the low and intermediate grades are closely related, well differentiated, and distinguished largely by proliferative rate (or necrosis). Finally, each system generally recognizes that individual tumors rarely display hybrid well-differentiated and poorly differentiated features.

The issue of functionality of NETs also impacts on nomenclature. Functioning NETs are defined based on the

TABLE 3. Systems of Nomenclature for Neuroendocrine Tumors

Grade	Lung and Thymus (WHO)[34]	GEP-NETs (ENETS)[28,29]	GEP-NETs (WHO 2010)[3]	Lung and Thymus (Moran et al)[23]	Pancreas (Hochwald et al)[14]
Low grade	Carcinoid tumor	Neuroendocrine tumor, grade 1 (G1)	Neuroendocrine neoplasm, grade 1	Neuroendocrine carcinoma, grade 1	Well-differentiated pancreatic endocrine neoplasm, low grade
Intermediate grade	Atypical carcinoid tumor	Neuroendocrine tumor, grade 2 (G2)	Neuroendocrine neoplasm, grade 2	Neuroendocrine carcinoma, grade 2	Well-differentiated pancreatic endocrine neoplasm, intermediate grade
High grade	Small cell carcinoma	Neuroendocrine carcinoma, grade 3 (G3), small cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell carcinoma	Poorly differentiated pancreatic endocrine carcinoma, small cell carcinoma
	Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma grade 3 (G3), large cell neuroendocrine	Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma	Poorly differentiated pancreatic endocrine carcinoma, large cell neuroendocrine carcinoma

The grade of the tumor MUST be included in the pathology report, along with a reference to the specific grading system being used. Unqualified terms such as *neuroendocrine tumor* or *neuroendocrine carcinoma* without reference to grade do not provide adequate pathology information.

presence of clinical symptoms due to excess hormone secretion by the tumor and include functioning carcinoid tumors and a variety of other functioning NETs arising in the pancreas or elsewhere. Terms reflecting the clinical syndromes may be applied to these NETs, such as insulinoma, glucagonoma, and gastrinoma, although the term *carcinoid tumor* is used for tumors with or without the carcinoid syndrome. Although there are prognostic implications to some of the functional categories (eg, insulinomas are generally very indolent), the biologic behavior of most functioning NETs is still defined by the grade and stage of the tumor (although the clinical consequences of the hormone hypersecretion can be significant). Furthermore, the functional status of the tumor is defined by the clinical findings, not by the pathologic appearance or immunohistochemical profile. 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.

GRADING ISSUES

The proliferative rate has been repeatedly shown to provide significant prognostic information for NETs,[2,12,16,19,24,26,35] and most systems of grading rely extensively on the proliferative rate to separate low-, intermediate-, and high-grade tumors. Some systems (such as the WHO classification for lung and thymus) include the presence of necrosis as a feature to distinguish intermediate grade from low grade within the well-differentiated group.[34] The proliferative rate can be assessed as the number of mitoses per unit area of tumor (usually expressed as mitoses per 10 high-power microscopic fields or per 2 mm^2) or as the percentage of neoplastic cells immunolabeling for the proliferation marker Ki67.[28,29] The WHO classification of lung and thymus tumors relies only on the mitotic rate,[34] whereas the system recently proposed for gastroenteropancreatic NETs by the European Neuroendocrine Tumor Society (ENETS) and also now recommended by the WHO uses either mitotic rate or Ki67 labeling index.[3,29] A comparison of the most widely used grading systems is shown in Table 4. As can be seen, the cut-points to distinguish the 3 grades vary somewhat among the different systems, and definitive clinical data to determine the optimal cut-points do not exist. In fact, some studies suggest that the optimal cut-points may differ between organ systems.[9,11,12,14] For these reasons, it is recommended to specify the actual proliferative rate in the pathology report, in addition to designating a grade based on a system that is specifically referenced.

The use of mitotic counts versus Ki67 index is controversial. In Europe, where the ENETS system is already in widespread use, Ki67 labeling indices are commonly reported for all NETs. When the amount of tumor tissue is limited (eg, in a biopsy from a primary tumor or a metastatic focus), it may not be possible to perform an accurate mitotic count because it is recommended to count 40 to 50 high-power fields—more than most biopsy samples contain. In these cases, Ki67 staining provides a more accurate assessment of proliferative rate, and it is particularly helpful to separate well-differentiated (low or intermediate grade) tumors from poorly differentiated (high grade) neuroendocrine carcinomas, which usually have dramatically different Ki67 labeling rates.[7,20,27] However, when adequate tissue is present to perform an accurate mitotic count, there are no data to demonstrate that the Ki67 labeling index adds important additional information, and in some cases, the 2 measures of proliferative rate may provide conflicting information about grading.

STAGING ISSUES

A few years ago, no formal TNM-based staging systems existed for NETs. Data submitted to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute separated tumors into localized, regional, and distant stages based on the presence of lymph node or distant metastases, but substratification of the extent of the primary tumor was not performed.[40] Recently, TNM staging systems have been proposed. The American Joint Committee on Cancer has recently published a new TNM staging manual that includes NETs of all anatomic sites,[10] and the ENETS has previously published recommendations for TNM staging of gastroenteropancreatic NETs.[25,28,29] There are some differences between these systems, particularly for primary tumors of the pancreas and the appendix, but there is also considerable overlap. Additionally, the staging criteria for both systems rely predominantly on the size of the tumor and the extent of invasion into similar landmarks as used for the staging of non-neuroendocrine carcinomas of the same sites. It is recommended that the extent of involvement of these structures be specifically indicated in the pathology reports in addition to providing a TNM stage using a system that is specifically referenced.

Until very recently, the WHO classifications for NETs of the tubular gastrointestinal tract (2000) and pancreas (2004) used a hybrid classification system that incorporated both staging information (size and extent of tumor—limited to the primary site versus having metastases) and grading information (proliferative rate) into a single prognostic prediction system, with a different name being applied to the tumors in each prognostic group.[4–6,13] Although this system did allow prognostic stratification of NETs, it did not allow for grading information to be applied to advanced stages of disease, preventing prognostication once metastases occurred and therefore limiting information

TABLE 4. Grading Systems for Neuroendocrine Tumors

Grade	Lung and Thymus (WHO)[34]	GEP-NETs (ENETS, WHO)[3,28,29]	Lung and Thymus (Moran et al)[23]	Pancreas (Hochwald et al)[14]
Low grade	<2 mitoses / 10 hpf AND no necrosis	<2 mitoses / 10 hpf AND <3% Ki67 index	≤3 mitoses / 10 hpf AND no necrosis	<2 mitoses / 50 hpf AND no necrosis
Intermediate grade	2–10 mitoses / 10 hpf OR foci of necrosis	2–20 mitoses / 10 hpf OR 3%–20% Ki67 index	4–10 mitoses / 10 hpf OR foci of necrosis	2–50 mitoses / 50 hpf OR foci of necrosis
High grade	>10 mitoses / 10 hpf	>20 mitoses / 10 hpf OR >20% Ki67 index	>10 mitoses / 10 hpf, Necrosis present	>50 mitoses / 50 hpf

In the pathology report, the actual proliferative rate (mitotic count and/or Ki67 index) should be specified, and a grade should be provided, with the specific grading system used to be specified in the report.

for therapeutic decision making.[12] Furthermore, the implications of this classification were that the name for a NET limited to the primary site was different than that to be used for the same tumor once metastases occurred in the future, a relatively common occurrence for some NETs. Because of these limitations, the most recent WHO classification that applies to all gastroenteropancreatic NET has abandoned the hybrid classification system in favor of separately grading and staging the tumors (Tables 3 and 4).[3] This will bring the WHO system more closely in line with other widely used systems.

OTHER PATHOLOGY INFORMATION

A variety of other pathologic findings may be of use in the prognostication and management of patients with NETs (Table 1). Immunolabeling for general neuroendocrine markers (chromogranin A and synaptophysin) may not be needed in histologically typical resected primary tumors,[17] but it is very useful to confirm the nature of the tumor based on biopsy specimens in many cases. Immunolabeling for specific peptide hormones is only useful in highly defined circumstances, however. Adverse prognostic factors not included in grading and staging, such as vascular or perineural invasion, should be documented. Adequacy of surgical resection should be indicated, and the number of involved lymph nodes (and the total number of nodes examined) should also be stated. Histologic abnormalities of the neuroendocrine cells in the surrounding tissues (such as neuroendocrine hyperplasia in the lung or stomach) should be described. A variety of prognostic or treatment-related biomarkers has been investigated, and some may have significant utility in the future, but currently, none is recommended to be routinely used outside of specific research settings. Finally, markers of primary origin now exist for metastatic NETs of unknown origin. For well-differentiated NETs, thyroid transcription factor-1 (TTF1) labeling favors pulmonary origin, CDX2 expression is typical of intestinal or pancreatic primaries, and PDX1 or Isl1 are most commonly expressed in pancreatic NETs.[15,30,31]

CONCLUSIONS

Despite the inability to establish a single system of nomenclature, grading, and staging for NETs of all sites, there are common features to form the basis of most systems. Documentation of these features will allow greater reliability in the pathology reporting of these neoplasms. Hopefully, future clinicopathologic studies will help further define the optimal criteria to subclassify NETs.

Bullet Points

- Neuroendocrine tumors (NETs) arise throughout the body and share certain basic characteristics.
- Tumor differentiation refers to the extent of resemblance to the normal cellular counterpart.
- Tumor grade refers to the degree of biologic aggressiveness and is related to differentiation but different.
- Tumor stage refers to the extent of spread of the tumor.
- A number of different systems exist to classify, grade, and stage NETs.
- Although the criteria differ among systems, the underlying basic data are similar.
- The proliferative rate (mitotic index or Ki67 labeling rate) is a critical factor.
- The extent of invasion into the organ of origin and involvement of nodes or distant sites are critical factors.
- Basic information should be included in the pathology reports, including a grade and stage along with a reference to the specific systems being used to define these parameters.

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