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ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pathology – Diagnosis and Prognostic Stratification

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Abstract
The European Neuroendocrine Tumor Society (ENETS) proposed standard of care guidelines for pathology in 2009. Since then, profound changes in the classification have been made, dividing neuroendocrine neoplasia (NEN) into well-differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC) in the 2010 WHO classification. The 7th edition of the TNM classification (2009) included NEN for the first time, widely adapting ENETS proposals but with some differences for NEC and for NET of the pancreas and the appendix. Therapy guidelines for gastroenteropancreatic NET were updated in 2016. The need for an update of the standards of care prompted the ENETS to organize a consensus conference which was held in Antibes in 2015; a working group was designated to propose pathological standards of care.

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Introduction

The European Neuroendocrine Tumor Society (ENETS) proposed standard of care guidelines for pathology in 2009 [1]. Since then, profound changes in the classification have been made, dividing neuroendocrine neoplasia (NEN) into well-differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC) in the 2010 WHO classification [2]. The 7th edition of the TNM classification (2009) included NEN for the first time, widely adapting ENETS proposals but with some differences for NEC and for NET of the pancreas and the appendix [3]. Therapy guidelines for gastroenteropancreatic NET have recently been updated as well [4]. The need for an update of the standards of care prompted the ENETS to organize a consensus conference which was held in Antibes in 2015; a working group was designated to propose pathological standards of care.

Table 1. Mandatory and optional elements for assessing a biopsy specimen containing a tumor with features of a gastroenteropancreatic NEN

Mandatory
Morphology and differentiation on HE section
Immunostaining for neuroendocrine markers: synaptophysin and chromogranin A
Immunostaining for proliferation marker: Ki-67/MIB1
Optional
Immunostaining for hormones such as insulin, gastrin, serotonin and others: in the context of hormonal symptoms, liver metastases of an unknown primary or follow-up of a tumor with a hormonal syndrome
Immunostaining for transcription factors (TTF1, CDX2, Isl-1): in the context of a carcinoma of unknown primary
Immunostaining for somatostatin receptor (i.e., SSTR2): if not available by in vivo technique such as SRS imaging
Immunostaining for vessel markers: to determine angioinvasion

Gross Analysis and Processing of Tissues

Histopathological analysis of tissue specimens is the gold standard for the diagnosis of NEN. Conventional morphological analysis is completed by immunohistochemistry, required to demonstrate the neuroendocrine phenotype and to evaluate the Ki-67 index. Samples can be obtained by endoscopy, but mini-biopsy is preferred to the classical fine-needle aspiration with smears only [5, 6]. Tissue specimens are gained by biopsy of a primary or secondary tumor, by surgical resection or by endoscopic resection. Tissues are fixed in formalin and embedded in paraffin. Resection specimens require a detailed gross examination to select the proper regions for histological analysis. Gross examination is also crucial to provide data for T and N staging and to select the regions to analyze for establishing resection status.

Diagnostic Standards

Neuroendocrine Phenotype

Table 1 summarizes the mandatory and optional immunohistochemical requirements for a histopathological analysis of a NET biopsy. If by hematoxylin/eosin staining a neuroendocrine phenotype is suspected, immunohistochemical stainings for synaptophysin and chromogranin A are required to definitely confirm this hypothesis [7]. Cytokeratin staining might be useful to confirm the epithelial nature of the tumor and to rule out paraganglioma. In well-differentiated NET, all tumor cells stain diffusely for synaptophysin because of the diffuse presence of small clear vesicles. The expression of chromogranin A is usually more heterogeneous in the cytoplasm of tumor cells, since it depends on the presence of large neurosecretory granules. Rectal NET may frequently stain negative for chromogranin A with most monoclonal antibodies of current use. Otherwise, care must be taken in diagnosing well-differentiated NET without any chromogranin A expression; other entities, such as solid pseudopapillary neoplasia of the pancreas, acinar cell carcinoma or adrenocortical neoplasms, must be ruled out. In poorly differentiated NEC, however, chromogranin A may be lacking. Moreover, in some small cell NEC, synaptophysin may also be focal or absent. In such tumors, the diagnosis of "small cell neuroendocrine carcinoma" is a diagnosis of exclusion. The use of other so-called neuroendocrine markers such as neuron-specific enolase or N-CAM (CD56) is discouraged due to their low specificity [8].

Differentiation

According to the WHO classification, NEN are divided into well-differentiated NET and poorly differentiated NEC. Initially, the assumption was that all G1–G2 tumors were well-differentiated and all G3 tumors were poorly differentiated. However, well-differentiated NET can rarely have proliferation indexes >20%, especially in the pancreas. These patients survive longer than patients

Table 2. Grading of gastroenteropancreatic NEN

Grade	Mitotic count, 10 HPF	Ki-67 index[a], %
G1	≤2	<3[b]
G2	2–20	3–20
G3	>20	>20

HPF, high-power field = 2 cm^2, at least 40 fields evaluated in areas at highest mitotic density. [a] MIB1 antibody; percent of 500–2,000 cells in areas of highest nuclear labeling. If less cells, the number of assessed cells should be noted. [b] <3 could replace ≤2 in the 2010 WHO classification in order to include decimal numbers between 2 and 3.

Table 3. Minimum requirements of pathology reports, given for the example of pancreatic NET, according to CAP guidelines

Type of specimen	excisional biopsy, partial pancreatectomy, Whipple resection, total pancreatectomy
Tumor site	pancreatic head, body, tail, uncinate process
Tumor size	in centimeters and 3 dimensions
Tumor focality	unifocal, multifocal
Tumor functionality	insulinoma, glucagonoma, somatostatinoma, gastrinoma,VIPoma, serotinin producing, other, nonfunctional
Histologic differentiation	well-differentiated, poorly differentiated[a]
Proliferation rate	Ki-67 index and optionally mitotic count
Tumor necrosis	present, absent
Microscopic tumor extension	confined to pancreas, invading peripancreatic soft tissue, invading other organs
Margins	margins uninvolved by tumor, closest margin in centimeters, margins involved by tumor
Lymphovascular invasion	present, absent
Perineural invasion	present, absent
TNM staging (UICC 7th edition)	
Lymph nodes	number of lymph nodes examined, number of lymph nodes involved
Additional features	

[a] Note that for poorly differentiated NEC the TNM system of adenocarcinomas of the pancreas is applied.

with poorly differentiated NEC [9], but shorter than patients with well differentiated NET. This new entity has by some been classified as well-differentiated NET G3 [10]. These well-differentiated NET with a high proliferation index seem to be characterized by a regular network of fine vessels, an organoid growth pattern without expansile growth and absence of geographic necrosis or desmoplastic stroma. Well-differentiated morphology correlates with a Ki-67 index range of 20–50% [9–12]. Therefore, the exact Ki-67 index as well as differentiation needs to be included into pathology reports. For NEC, small cell and large cell morphology should be described.

Grading

Once the neuroendocrine nature of a tumor is demonstrated, the proliferative activity has to be assessed using Ki-67 staining and performing a staining index. The percentage of positive tumor nuclei has to be assessed and reported. Grading is performed as defined in WHO and UICC/AJCC classifications (Table 2). The Ki-67 index seems to be more accurate and reproducible than mitotic count [13, 14] and is the only counting possible on biopsy samples. Therefore, the Ki-67 index is regarded as compulsory and mitotic count as optional. Grading can be performed on primary tumors as well as on metastases, but some heterogeneity exists between both and between different metastases [15–17]; the proliferation index is often higher in metastases. If not enough material for hotspot selection and analysis of 2,000 tumor cells is available, undergrading might occur [18]; this is occurring in EUS-obtained mini-biopsies [5, 19]. Grading is not recommended on smears from fine-needle aspiration, but reliability is increasing in mini-biopsies, also gained by endoscopic procedures [6]. The risk of undergrading decreases between 200 and 2,000 cells examined [19, 20] and was minimal when >2,000 cells were counted [20]. Finally, the amount of tissues needed depends on the purpose of the analysis. Only a limited number of cells is enough for discriminating well-differentiated NET G1/G2 from poorly differentiated NEC G3, but this might not be sufficient for an accurate grading.

Optional Diagnostic Markers

The use of optional or additional markers including hormones or transcription factors may be employed in the setting of neuroendocrine tumor metastases of an unknown primary site: serotonin and CDX2 positivity are in favor of a primary of the small intestine, islet-1 (Isl-1) ex-

pression is found in primaries of the pancreas and duodenum, and TTF1 in primaries of the lung and in medullary thyroid carcinoma [21], the second together with calcitonin. All these markers are of no use in the setting of poorly differentiated NEC [22].

Immunohistochemical detection of somatostatin receptors (SSTR), especially SSTR2, is feasible and indicated in the absence of in vivo somatostatin imaging studies [23, 24]. In the case of questionable vascular invasion, immunohistochemistry for endothelial cell markers such as CD34 or special stains for the visualization of vessel walls might be of help.

Pathological Report

Table 3 summarizes the minimum requirements for pathological reports of resection specimens or biopsy specimens of NEN.

Needs for Research

MGMT (O6-methylguanin-DNA methyltransferase) expression or methylation may serve as a predictive marker of a response to temozolomide-based chemotherapy in PanNET. Clinical trials are on the way to address this issue. In the same regard, translational studies are needed to define biomarkers predicting response to other therapies such as targeted therapies or other chemotherapeutic strategies. The new category of NET G3 needs to be better defined pathologically, possibly by the inclusion of molecular markers in order to have a more solid basis to define the therapeutic consequences of this tumor type. At last, increasing molecular evidence may suggest a grouping of NET according to mutational, expression or methylation profiles, but so far no therapeutic strategies are based on these findings.

Conclusions

The proposed standard procedures for diagnosing NEN should now follow the WHO and TNM classification systems that are under revision. A standardized diagnosis is the basis for a standardized treatment as well as for studies to be comparable.

Appendix

Antibes Consensus Conference Participants

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References

1 Klöppel G, Couvelard A, Perren A, Komminoth P, McNicol AM, Nilsson O, Scarpa A, Scoazec JY, Wiedenmann B, Papotti M, Rindi G, Plockinger U: ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. Neuroendocrinology 2009;90:162–166.

2 Bosman FT, Carneiro F, Hruban R, Theise ND (eds): WHO Classification of Tumors of the Digestive System, ed 4. Geneva, WHO, 2010.

3 Klöppel G, Rindi G, Perren A, Komminoth P, Klimstra DS: The ENETS and AJCC/UICC TNM classifications of the neuroendocrine tumors of the gastrointestinal tract and the pancreas: a statement. Virchows Arch 2010; 456:595–597.

4 O'Toole D, Kianmanesh R, Caplin M: ENETS 2016 consensus guidelines for the management of patients with digestive neuroendocrine tumors: an update. Neuroendocrinology 2016;103:117–118.

5 Larghi A, Capurso G, Carnuccio A, Ricci R, Alfieri S, Galasso D, Lugli F, Bianchi A, Panzuto F, De Marinis L: Ki-67 grading of nonfunctioning pancreatic neuroendocrine tumors on histologic samples obtained by EUS-guided fine-needle tissue acquisition: a prospective study. Gastrointest Endosc 2012; 76:570–577.

6 Vinayek R, Capurso G, Larghi A: Grading of EUS-FNA cytologic specimens from patients with pancreatic neuroendocrine neoplasms: it is time move to tissue core biopsy? Gland Surg 2014;3:222–225.

7 Lloyd RV: Practical markers used in the diagnosis of neuroendocrine tumors. Endocr Pathol 2003;14:293–301.

8 Bussolati G, Volante M, Papotti M: Classic and recent special stains used in differential diagnosis of endocrine tumors. Endocr Pathol 2001;12:379–387.

9 Basturk O, Yang Z, Tang LH, Hruban RH, Adsay V, McCall CM, Krasinskas AM, Jang KT, Frankel WL, Balci S, Sigel C, Klimstra DS: The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. Am J Surg Pathol 2015;39:683–690.

10 Heetfeld M, Chougnet CN, Olsen IH, Rinke A, Borbath I, Crespo G, Barriuso J, Pavel M, O'Toole D, Walter T; other Knowledge Network members: Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer 2015;22:657–664.

11 Tang LH, Untch BR, Reidy DL, O'Reilly E, Dhall D, Jih L, Basturk O, Allen PJ, Klimstra DS: Well-differentiated neuroendocrine tumors with a morphologically apparent high-grade component: a pathway distinct from poorly differentiated neuroendocrine carcinomas. Clin Cancer Res 2016;22:1011–1017.

12 Velayoudom-Cephise FL, Duvillard P, Foucan L, Hadoux J, Chougnet CN, Leboulleux S, Malka D, Guigay J, Goere D, Debaere T, Caramella C, Schlumberger M, Planchard D, Elias D, Ducreux M, Scoazec JY, Baudin E: Are G3 ENETS neuroendocrine neoplasms heterogeneous? Endocr Relat Cancer 2013;20:649–657.

13 Khan M, Luong T, Watkins J, Toumpanakis C, Caplin M, Meyer T: A comparison of Ki-67 and mitotic count as prognostic markers for metastatic pancreatic and midgut neuroendocrine neoplasms. Br J Cancer 2013;108:1838–1845.

14 Dhall D, Mertens R, Bresee C, Parakh R, Wang HL, Li M, Dhall G, Colquhoun SD, Ines D, Chung F, Yu R, Nissen NN, Wolin E: Ki-67 proliferative index predicts progression-free survival of patients with well-differentiated ileal neuroendocrine tumors. Hum Pathol 2012;43:489–495.

15 Grillo F, Albertelli M, Brisigotti MP, Borra T, Boschetti M, Fiocca R, Ferone D, Mastracci L: Grade increases in gastro-entero-pancreatic neuroendocrine tumor metastases compared to the primary tumor. Neuroendocrinology 2015, Epub ahead of print.

16 Couvelard A, Deschamps L, Ravaud P, Baron G, Sauvanet A, Hentic O, Colnot N, Paradis V, Belghiti J, Bedossa P, Ruszniewski P: Heterogeneity of tumor prognostic markers: a reproducibility study applied to liver metastases of pancreatic endocrine tumors. Mod Pathol 2009;22:273–281.

17 Shi C, Gonzalez RS, Zhao Z, Koyama T, Cornish TC, Hande KR, Walker R, Sandler M, Berlin J, Liu EH: Liver metastases of small intestine neuroendocrine tumors: Ki-67 heterogeneity and World Health Organization grade discordance with primary tumors. Am J Clin Pathol 2015;143:398–404.

18 Yang Z, Tang LH, Klimstra DS: Effect of tumor heterogeneity on the assessment of Ki67 labeling index in well-differentiated neuroendocrine tumors metastatic to the liver: implications for prognostic stratification. Am J Surg Pathol 2011;35:853–860.

19 Weynand B, Borbath I, Bernard V, Sempoux C, Gigot JF, Hubert C, Lannoy V, Deprez P, Jouret-Mourin A: Pancreatic neuroendocrine tumour grading on endoscopic ultrasound-guided fine needle aspiration: high reproducibility and inter-observer agreement of the Ki-67 labelling index. Cytopathology 2014;25: 389–395.

20 Hasegawa T, Yamao K, Hijioka S, Bhatia V, Mizuno N, Hara K, Imaoka H, Niwa Y, Tajika M, Kondo S, Tanaka T, Shimizu Y, Kinoshita T, Kohsaki T, Nishimori I, Iwasaki S, Saibara T, Hosoda W, Yatabe Y: Evaluation of Ki-67 index in EUS-FNA specimens for the assessment of malignancy risk in pancreatic neuroendocrine tumors. Endoscopy 2014;46:32–38.

21 Schmitt AM, Riniker F, Anlauf M, Schmid S, Soltermann A, Moch H, Heitz PU, Klöppel G, Komminoth P, Perren A: Islet 1 (Isl1) expression is a reliable marker for pancreatic endocrine tumors and their metastases. Am J Surg Pathol 2008;32:420–425.

22 Agaimy A, Erlenbach-Wünsch K, Konukiewitz B, Schmitt AM, Rieker RJ, Vieth M, Kiesewetter F, Hartmann A, Zamboni G, Perren A: ISL1 expression is not restricted to pancreatic well-differentiated neuroendocrine neoplasms, but is also commonly found in well and poorly differentiated neuroendocrine neoplasms of extrapancreatic origin. Mod Pathol 2013;26:995–1003.

23 Volante M, Brizzi MP, Faggiano A, La Rosa S, Rapa I, Ferrero A, Mansueto G, Righi L, Garancini S, Capella C, De Rosa G, Dogliotti L, Colao A, Papotti M: Somatostatin receptor type 2A immunohistochemistry in neuroendocrine tumors: a proposal of scoring system correlated with somatostatin receptor scintigraphy. Mod Pathol 2007;20:1172–1182.

24 Korner M, Waser B, Schonbrunn A, Perren A, Reubi JC: Somatostatin receptor subtype 2A immunohistochemistry using a new monoclonal antibody selects tumors suitable for in vivo somatostatin receptor targeting. Am J Surg Pathol 2012;36:242–252.