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ORIGINAL ARTICLE

TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system

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Abstract The need for standards in the management of patients with endocrine tumors of the digestive system prompted the European Neuroendocrine Tumor Society (ENETS) to organize a first Consensus Conference, which

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was held in Frascati (Rome) and was based on the recently published ENETS guidelines on the diagnosis and treatment of digestive neuroendocrine tumors (NET). Here, we report the tumor–node–metastasis proposal for foregut NETs of the stomach, duodenum, and pancreas that was designed, discussed, and consensually approved at this conference. In addition, we report the proposal for a working formulation for the grading of digestive NETs based on mitotic count and Ki-67 index. This proposal, which needs to be validated, is meant to help clinicians in the stratification, treatment, and follow-up of patients.

Keywords Neuroendocrine tumors · Gut · Pancreas · Staging · TNM · Grading · Mitotic index · Ki-67 index

Background

It has been known for a long time, and was finally defined within the World Health Organization (WHO) classification of endocrine and digestive tumors, that neuroendocrine tumors (NET) arising at different anatomical sites of the digestive system represent tumor entities that differ in their biology [5, 7, 9, 31]. Several recent publications focused on the application of the "new" WHO classification and proved its effectiveness, supporting the concept that the different endocrine tumor types also differ in their clinical behavior [3, 4, 19, 20, 27, 32].

Malignant gastroenteropancreatic NETs may be fatal, though at a significantly slower pace than their exocrine counterparts. A number of retrospective papers and epidemiological data solidly support such statements [8, 9, 12–14, 21, 24, 25, 32]. This peculiar clinical feature attracted the interest of pathologists very early and was the reason for the special designation of such tumors as "carcinoid" by Oberndorfer [15].

As gastroenteropancreatic NETs are rare [9, 13, 14], it is tempting to lump them together and equate all digestive "carcinoids" with the appendiceal "carcinoid," probably the best known NET with the most benign behavior [28]. However, in recent years it has become clear that gastroenteropancreatic NETs, especially foregut NETs, are heterogeneous in their morphological and biological features. In the last two decades efforts were therefore made by the WHO to define NET features that discriminate true benign behavior (low risk) from low-grade malignant well-differentiated NETs in the different parts of the digestive system. Although the new WHO classification is an important step toward defining the diverse tumor biology of NETs, further efforts are necessary to improve the prognostic assessment of the individual NET.

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The demand for standards in the stratification and treatment of patients with gastroenteropancreatic NETs prompted the recently established European Neuroendocrine Tumor Society (ENETS) to define guidelines [22, 33]. Such guidelines underwent scrutiny for consensus in the first of two meetings entitled "Consensus Conference on the ENETS Guidelines for the Diagnosis and Treatment of Neuroendocrine Gastrointestinal Tumors, Part 1: Foregut Tumors" held in Frascati (Rome, Italy) from November 2–5, 2005. During this meeting the clinical need for a tumor–node–metastasis (TNM) classification of gastroenteropancreatic NETs was felt. Here we report the TNM staging classification proposal for foregut NETs that was approved at this consensus conference. In addition, we suggest a simple grading system with some pointers that may help to standardize the prognostic assessment of gastroenteropancreatic NETs.

Materials and methods

Sixty-two experts in the field of digestive endocrine tumors from 20 different countries attended the Consensus Conference. The attendees represented all medical branches involved in managing patients with gastroenteropancreatic NETs. They formed four working groups according to their specific clinical expertise: (1) pathology and genetics (11 participants, all listed as authors and G. Klöppel), (2) surgery (10 participants, including the coauthors H. Alhman and M. Falconi), (3) imaging and radiology (10 participants), (4) medicine and clinical pathology (31 participants, including the coauthors M. Caplin, W.W. de Herder, B. Erikssson, and B. Wiedenmann).

The Conference was divided sequentially into eight sessions devoted to specific topics on an anatomical basis (gastric NET sessions 1–2, duodenal NET, pancreatic NET sessions 1–4, and poorly differentiated endocrine carcinomas). A working booklet with the ENETS guidelines and specific queries had been prepared in advance by the Organizing Committee. The work was organized such that, after a short case presentation in a plenary session, each working group gathered separately to discuss group-specific questions. Once agreement was reached within each group, consensus statements were discussed and approved or rejected by all participants gathered in the plenary session. This procedure was followed for all eight sessions. The TNM staging proposal was made by the

Table 1 Proposal for a TNM classification and disease staging for gastric endocrine tumors

TNM			
T—primary tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	In situ tumor/dysplasia (<0.5 mm)		
T1	Tumor invades lamina propria or submucosa and ≤1 cm		
T2	Tumor invades muscularis propria or subserosa or >1 cm		
T3	Tumor penetrates serosa		
T4	Tumor invades adjacent structures		
	For any T, add (m) for multiple tumors		
N—regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M—distant metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastases		
M1[a]	Distant metastasis		
Stage			
Disease stages			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
IIIb	Any T	N1	M0
Stage IV	Any T	Any N	M1

[a]M1 specific sites defined according to Sobin and Wittekind [29]

Pathology and Genetics working group and amended and approved by the plenary session of the consensus conference. The grading system was discussed and defined by the Pathology and Genetics working group only.

Results and discussion

The consensus guidelines are reported elsewhere. Here, we report the TNM staging proposal for gastroenteropancreatic NETs of the foregut together with a grading system that may be relevant for the prognostic assessment by the pathologist. The foregut NETs were separated into gastric, duodenal (including ampulla and proximal jejunum), and pancreatic NETs, but were not distinguished according to specific functional activity, main tumor cell type, and specific genetic background.

TNM staging proposal (see Tables 1, 2 and 3)

The currently published TNM format was adopted as working template [29].

Tumor The proposed definition of tumor in situ applies to the stomach only and adheres to the literature [30]. No definition is given for the duodenum and pancreas because none has been agreed upon in spite of recent working proposals [1, 2]. The size limits indicated for T1 are those defined by the WHO for tumors with "benign behavior" according to site-specific clinicopathological correlations [5, 7, 31]. Similarly, for T2 of the stomach and duodenum, the sizes are those indicated for tumors of "uncertain behavior." In the pancreas the size limit given for T2 needs to be validated [5]. Deeply invasive tumors are included under the T3 and T4 definitions, taking into account site-specific features.

Nodes N1 indicates the presence of any single or multiple metastases in regional lymph nodes, according to TNM rules. Although the presence of regional lymph-node metastases is, per se, a negative prognostic factor in gastroenteropancreatic NETs [11], the prognostic significance of the number of metastatic nodes is not known. In light of this, stage 3B of Tables 1, 2 and 3 is proposed to mark the N1 status for future validation.

Distant metastasis M1 indicates the presence of any single or multiple metastases at any distant anatomical site (including nonregional nodes). Because there is evidence that extrahepatic bone metastases are a particularly ominous

Table 2 Proposal for a TNM classification and disease staging for endocrine tumors of the duodenum/ampulla/proximal jejunum

TNM			
T—primary tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor invades lamina propria or submucosa and size ≤1 cm[a]		
T2	Tumor invades muscularis propria or size >1 cm		
T3	Tumor invades pancreas or retroperitoneum		
T4	Tumor invades peritoneum or other organs		
	For any T, add (m) for multiple tumors		
N—regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M—distant metastases			
MX	Distant metastasis cannot be assessed		
M0	No distant metastases		
M1[b]	Distant metastasis		
Stage			
Disease stages			
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
IIIb	Any T	N1	M0
Stage IV	Any T	Any N	M1

[a]Tumor limited to ampulla of Vater for ampullary gangliocytic paraganglioma
[b]M1 specific sites defined according to Sobin and Wittekind [29]

Table 3 Proposal for a TNM classification and disease staging for endocrine tumors of the pancreas

TNM			
T—primary tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor limited to the pancreas and size <2 cm		
T2	Tumor limited to the pancreas and size 2–4 cm		
T3	Tumor limited to the pancreas and size >4 cm or invading duodenum or bile duct		
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery)		
	For any T, add (m) for multiple tumors		
N—regional lymph nodes			
NX	Regional lymph node cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M—distant metastases			
MX	Distant metastasis cannot be assessed		
M0	No distant metastases		
M1[a]	Distant metastasis		
Stage			
Disease stages			
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
IIIb	Any T	N1	M0
Stage IV	Any T	Any N	M1

[a] M1 specific sites defined according to Sobin and Wittekind [29]

sign [6, 20], it is recommended to specify the anatomical site of the metastasis according to the TNM classification rules (PUL, pulmonary; HEP, hepatic; OSS, osseous; etc.) [29].

Staging The proposed staging system lists stage 0 only for the stomach because this is the only anatomical site where Tis is defined. Stage I encompasses the T1 NETs with limited growth. Stage II identifies tumors that are larger in size or more invasive, either T2 or T3, though always in the absence of metastasis. At stage III the increased malignancy refers either to invasion into surrounding structures (stage IIIa) or to the presence of regional node metastasis (stage IIIb). Stage IV always implies the presence of distant metastasis.

Table 4 Grading proposal for foregut (neuro)endocrine tumors

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

[a] 10 HPF: high power field=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density

[b] MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

Grading proposal (see Table 4)

Grading It has been widely discussed and generally accepted that no histological grading system effectively predicts the behavior of well-differentiated endocrine tumors. The major obstacle to developing a practically effective grading system is the fact that severe cytological atypia, as, for instance, in pheochromocytomas, has no impact on the clinical behavior and malignancy of such tumors. However, recent studies in well differentiated NETs of the foregut, including the pancreas, and of the midgut have shown the usefulness of a grading system [10, 25, 32]. Thus, well-differentiated endocrine tumors with a more solid appearance and distinct proliferative activity, which also lead to difficulties in the differential diagnosis vs poorly differentiated endocrine carcinomas, seem to have a worse prognosis than NETs without these features [16–18, 22, 23]. It was therefore decided to introduce a grading system that could be of help in distinguishing the well-differentiated NETs into G1 and G2 categories.

As a working suggestion, we propose to apply to foregut NETs a grading system modified from that adopted by the WHO for endocrine tumors of the lung, though exclusively referring to the proliferation status. In brief (see Table 4), three tumor categories are identified: G1, <2 mitosis per

2 mm^2 [10 high power fields (HPF) 40× magnification] and/or Ki-67 index ≤2%; G2, 2–20 mitosis per 2 mm^2 and/or Ki-67 index between 3 and 20%; G3 with 21 or more mitosis per 2 mm^2 and Ki-67 index >20%.

In general, G1 and G2 should refer to well-differentiated NETs displaying diffuse and intense expression of the two general immunohistochemical neuroendocrine markers, chromogranin A and synaptophysin [26]. Punctate necrosis is, per se, indicative of a more aggressive tumor, pointing to a G2 status, which, however, has to be confirmed by the mitotic count. G3 indicates a poorly differentiated neuroendocrine carcinoma. It has high mitotic counts/Ki-67 index, is often associated with fields of necrosis, and shows significantly reduced chromogranin A expression, while maintaining intense staining for synaptophysin. It is relevant to remind here that the diagnosis of G3 carcinoma is based on a specific histologic pattern according to the current WHO criteria [5, 7, 31]. In addition, the clinical behavior of G3 poorly differentiated neuroendocrine carcinomas of the gastroenteropancreatic tract does not necessarily correspond to that of small cell cancers of the lung or of any other sites.

Mitotic count and Ki-67 index We propose that mitoses should be counted on hematoxylin and eosin-stained slides in at least 40 HPFs, where possible. The mitoses should be assessed in areas where they are most frequent after a general slide survey. For Ki-67 assessment, the MIB1 antibody is recommended at the conditions that have been established at the laboratory in question. The Ki-67 index should be assessed in 2,000 tumor cells in areas where the highest nuclear labeling is observed (often but not exclusively at the tumor periphery).

Concluding remarks

Requests for standardization in the management of patients with gastroenteropancreatic NETs recently resulted in the development of several guidelines, including those proposed by ENETS [16, 17, 22, 23]. However, it was never attempted to reach consensus on specific practical issues. The TNM staging system we propose here was developed to meet a clinical need, is based on the current WHO classifications of endocrine and digestive tumors, and is the result of a consensus conference held by specialists involved in the management of digestive endocrine tumor patients. Along the same line, the grading system described here attempts to close the gap between the advances of the most recent WHO classifications and the need for a better prognostic assessment of NETs. It is obvious, of course, that all our proposals have to be validated by future clinicopathological work.

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