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TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system

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Abstract Criteria for the staging and grading of neuroendocrine tumors (NETs) of midgut and hindgut origin were established at the second Consensus Conference in Frascati (Rome) organized by the European Neuroendocrine Tumor Society (ENETS). The proposed tumor–node–metastasis (TNM) classifications are based on the recently published ENETS Guidelines for the Diagnosis and Treatment of gastroenteropancreatic NETs and follow our previous proposal for foregut tumors. The new TNM classifications for NETs of the ileum, appendix, colon, and rectum, and the grading system were designed, discussed, and consensually approved by all conference participants. These proposals need to be validated and are meant to help clinicians in the stratification, treatment and follow-up of patients.

Keywords Neuroendocrine tumors · Ileum · Appendix · Colon · Rectum · Staging · TNM · Grading · Mitotic index · Ki-67 index

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Background

Based on recognized differences in morphology, function and clinical behavior [1, 2, 21, 30], the current WHO classification provides a prognosis-oriented definition of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [3, 5, 8, 12, 13, 34].

All GEP-NETs probably have a malignant potential, but their biological behavior differs from tumor type to tumor type [9, 10, 14–17, 22, 25, 26, 36]. Given their rarity [10, 14–17], correct diagnosis and appropriate treatment are often difficult in nonexpert settings and even for appendiceal "carcinoids," probably the best known GEP-NETs with the most benign behavior [31]. Recent data on ileal, appendiceal, and rectal carcinoids, also indicated several variables influencing survival and prognosis [6, 15, 29, 35].

Guidelines for the management of patients with GEP-NETs were developed by the recently established European Neuroendocrine Tumor Society (ENETS) [23, 37]. In two separate meetings a consensus was sought on these guidelines. The papers deriving from the first conference dedicated to foregut tumors, including a detailed tumor–node–metastasis (TNM)/staging and grading proposals, have been published meanwhile [4, 27]. The "Consensus Conference on the ENETS Guidelines for the Diagnosis and Treatment of Neuroendocrine Gastrointestinal Tumors, Part 2: Midgut and Hindgut Tumors" was held in Frascati (Rome, Italy) from November 1 to 4, 2006. In this paper, we present the TNM staging and grading proposals for pure NETs of the lower jejunum/ileum, appendix, and colon/rectum.

Materials and methods

Fifty-seven experts in the field of GEP-NETs from 18 different countries attended the consensus conference. The attendees represented all medical branches involved in managing patients with GEP-NETs. They formed four working groups according to their specific clinical expertise: (1) pathology and genetics (11 participants, all listed as

Table 1 Proposal for a TNM classification for endocrine tumors of lower jejunum and ileum

	TNM
T-primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades mucosa or submucosa and size ≤1 cm
T2	Tumor invades muscularis propria or size >1 cm
T3	Tumor invades subserosa
T4	Tumor invades peritoneum/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 metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1[a]	Distant metastasis

[a] M1 specific sites defined according to Sobin LH, Wittekind C [32].

Table 2 Disease staging for endocrine tumors of lower jejunum and ileum

Stage Disease stages	T-primary tumor	N-regional nodes	M-distant metastasis
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

coauthors), (2) surgery (8 participants), (3) imaging and radiology (7 participants), (4) medicine and clinical pathology (31 participants, including the coauthor B.W.). Most of the participants also attended the first consensus conference held in Frascati in November 2005.

The conference was divided sequentially into five sessions devoted to specific topics on an anatomical basis (ileal well-differentiated NETs; appendiceal well differentiated NETs; colorectal well differentiated NETs; NETs metastatic to the liver; poorly differentiated neuroendocrine carcinomas of midgut and hindgut origin).

A working booklet with the ENETS guidelines text [23] and specific queries had been prepared in advance by the organizing committee. The work was organized as previously detailed [4, 27]. This procedure was followed for all five sessions. The TNM staging proposal was prepared by the pathology and genetics working group and amended and approved by the plenary session of the consensus conference. The grading system was mainly discussed and defined by the pathology and genetics working group.

Results and discussion

The consensus guidelines have been reported elsewhere. The TNM staging proposal for NETs of midgut and hindgut origin together with a grading system is intended to reflect, like its forerunner for the NETs of the stomach, duodenum and pancreas [27], the prognostic assessment by the pathologist. The intestinal NETs were separated into lower jejunum/ileum, appendix, and colon/rectum, but were not distinguished according to specific functional activity, main tumor cell type, or genetic background.

TNM staging proposal

The currently published TNM format was adopted as working template (see Tables 1, 2, 3, 4, 5, and 6) [32].

Tumor There is no proposed definition for in situ endocrine tumor of the jejunum, ileum, appendix, colon and rectum, because no specific precursor lesion has been described in the literature so far. For the lower jejunum and ileum, the size limits indicated for T1 and T2 are those defined for tumors of "benign behavior" and "uncertain behavior," respectively, according to the WHO site-specific clinico-pathological correlations [5, 8, 34]. For the appendix and colon and rectum tumors, lower size limits were defined for T1 and T2 based on current data [6, 15, 29]. For colon and rectum tumors, T1 was divided into T1A and T1B based on current information on the biology of tumors below 1 cm in size and between 1 and 2 cm [6].

Deeply invasive and large tumors are included in the T3 and T4 categories, taking into account site-specific features. For any T definition, the maximum tumor size should be reported and, in the case of multiple lesions, the largest one. The use of T3 category subdivision (pT3a, b, c, and d) according to distance below or higher than 5 mm from *muscularis propria* as proposed for the adenocarcinoma [33], could be of value. Its application could be implemented once data on endocrine carcinomas will be generated.

Lymph nodes N1 indicates the presence of any single or multiple metastases in the regional lymph node group, according to TNM rules. A minimum of 12 nodes should be identified in a surgical specimen, assessed and, when possible, named according to their location in relation to tumor. Although regional lymph node metastases are a negative prognostic factor in GEP-NETs [11], the signifi-

Table 3 Proposal for a TNM classification for endocrine tumors of the appendix

TNM	
T-primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤1 cm invading submucosa and muscularis propria
T2	Tumor ≤2 cm invading submucosa, muscularis propria and/or minimally (up to 3 mm) invading subserosa/mesoappendix
T3	Tumor >2 cm and/or extensive (more than 3 mm) invasion of subserosa/mesoappendix
T4	Tumor invades peritoneum/other organs
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

[a] M1 specific sites defined according to Sobin LH and Wittekind Ch [32].

Table 5 Proposal for a TNM classification for endocrine tumors of colon and rectum

TNM	
T-primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades mucosa or submucosa
	T1a size <1 cm
	T1b size 1–2 cm
T2	Tumor invades muscularis propria or size >2 cm
T3	Tumor invades subserosa/pericolic/perirectal fat
T4	Tumor directly invades other organs/structures and/or perforates visceral peritoneum
For any T add (m) for multiple tumors	
N-regional lymph nodes	
NX	Regional lymph node status cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M-distant metastases (subspecification as in small bowel)	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1[a]	Distant metastasis

[a] M1 specific sites defined according to Sobin LH and Wittekind Ch [32].

cance of the number of metastatic nodes is not yet known. Therefore, similar to the previous foregut TNM proposal, the N1 status in stage IIIB in Tables 1, 2, 3, 4, 5, and 6 has to be specified with regard to the number of lymph nodes involved to allow validation.

Distant metastasis M1 indicates the presence of any single or multiple metastases at any distant anatomical site (including nonregional nodes). As extrahepatic bone metastases are a negative prognostic factor [7, 21], it is recommended to specify the anatomical site of the metastasis according to the TNM classification rules (PUL, pulmonary; HEP, hepatic; OSS, osseous; etc.) [32].

Staging 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, although 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 metastases (Stage IIIB). Stage IV always implies the presence of distant metastases.

Table 4 Disease staging for endocrine tumors of the appendix

Stage Disease stages	T-primary tumor	N-regional nodes	M-distant metastasis
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

Grading proposal

Grading Studies on well-differentiated NETs of midgut and hindgut origin have shown the usefulness of a grading system (see Table 7) [6, 35, 36]. Well-differentiated endocrine tumors with proliferative activity greater than 2%, but below that usually found in poorly differentiated endocrine carcinomas, may have a prognosis intermediate between the "2% NETs" and poorly differentiated carcino-

Table 6 Disease staging for endocrine tumors of colon and rectum

Stage Disease stages	T-primary tumor	N-regional nodes	M-distant metastasis
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

Table 7 Grading proposal for (neuro)endocrine tumors of ileum, appendix, colon and rectum

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

* 10 HPF (High Power Field)=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density; ** MIB1 antibody; % of 2000 tumor cells in areas of highest nuclear labeling.

mas [18–20, 23, 24]. We decided to follow the same grading system proposal as that devised for foregut tumors, with the aim of distinguishing G2 from G1 and G3 GEP-NETs. The three tumor categories are defined as follows: G1, <2 mitoses per 2 mm^2 (10 high-power fields, HPF, 40× magnification) and/or Ki-67 index ≤2%; G2, 2–20 mitoses per 2 mm^2 and/or Ki-67 index between 3% (intended as >2%) and 20%; G3 with 21 or more mitoses per 2 mm^2 and Ki-67 index >20%.

The G1 and G2 well-differentiated NETs usually display diffuse and intense expression of the two general immunohistochemical neuroendocrine markers, chromogranin A and synaptophysin [28]. Punctate necrosis is per se indicative of a more aggressive tumor and points to a G2 or G3 status, which is then determined by the mitotic count and the proliferation fraction. G3 indicates a poorly differentiated neuroendocrine carcinoma with high mitotic counts/Ki-67 index, fields of necrosis, significantly reduced chromogranin A expression and intense staining for synaptophysin, meeting the current WHO histological criteria [5, 8, 34].

Mitotic count and Ki-67 index As for the foregut proposal, mitoses should be counted on hematoxylin and eosin stained slides in at least 40 HPF when 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

The TNM staging system proposed here for midgut and hindgut NETs closely follows its forerunner for foregut tumors [27]. It has the same basis, i.e., the current WHO classifications of GEP-NETs, and results from a consensus conference held by specialists and practicing physicians involved in the management of patients with GEP-NETs. The grading system described here is substantially identical to that proposed for foregut NETs and again attempts to close the gap between the advances of the most recent WHO classifications and the need for a better prognostic assessment of NETs. These proposals, as well as those already published, await confirmation by clinicopathologic work.

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