Madrid-Symposium 2012
The TNM classification of neuroendocrine neoplasms of the gastroenteropancreatic system

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WHO - classification 2010
of neuroendocrine neoplasm of the digestive system

Premises

- All neuroendocrine neoplasms have a malignant potential

- The malignant potential has to be stratified
  low  ........  high

- The malignant potential depends on tumor localization
differentiation extension
**Neuroendocrine Neoplasms – NENs of the gastroenteropancreatic system**

<table>
<thead>
<tr>
<th>WHO 1980</th>
<th>WHO 2000</th>
<th>WHO 2010</th>
</tr>
</thead>
</table>
| I. Carcinoid | 1. Well-differentiated endocrine tumour (WDET)*  
2. Well-differentiated endocrine carcinoma (WDEC)*  
3. Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC) | 1. **NET G1** (carcinoid)  
2. **NET G2**  
3. **NEC G3** (large cell or small cell type) |
| II. Mucocarcinoid  
| IV. Pseudotumour lesions | 5. Tumour-like lesions (TLL) | 5. Hyperplastic and preneoplastic lesions |

**NET, neuroendocrine tumor – well diff.**; **NEC, neuroendocrine carcinoma – poorly diff.**; **G, Grade**

*In case that the Ki67 index exceeds 20 %, this NET may be labelled G3*
Standardized approach towards the diagnosis of NEN
European Neuroendocrine Tumor Society (ENETS)

- H&E histopathology: well or poorly differentiated

- IH neuroendocrine markers
  synaptophysin and chromogranin A

- IH proliferation
  Ki67/Mib1
well differentiated - NET

poorly differentiated - NEC

NEC small cell type

NEC large cell type
Standardized approach towards the diagnosis of NEN
European Neuroendocrine Tumor Society (ENETS)

- Must
- H&E histopathology: well or poorly differentiated
- IH neuroendocrine markers: synaptophysin and chromogranin A
- IH proliferation: Ki67/Mib1
Large gastric tumor

NEC (poorly differentiated neuroendocrine carcinoma)?
The many faces of NETs
Features of well diff. neuroendocrine neoplasms

91 - 97 % of GEP-NENs are NETs

- organoid architecture and well diff. cytology
- absence of nonneuroendocrine components
- components of G1 or G2 (exceptional: G3)
- usually strong immunoexpression of NE markers
- usually hormonal immunoexpression
- may show a hormonal syndrome
- may be associated with other diseases (CAG, MEN1)
NEC: poorly differentiated NEN - small cell type
Small cell type

SYN positive
CG negative (+)
CD 56 positive
CK dot-like pos.
Large cell type

- SYN positive
- CG positive
- CD 56 negative / (+)
- CK non-dot-like pos.
Features of poorly diff. neuroendocrine neoplasms

3 - 9 % of GEP-NENs are NECs

- less organoid architecture and distinctly atypical cytology
- absence of components of G1 or G2
- may have nonneuroendocrine components
- less intense immunoexpression of NE markers
- usually no hormonal immunoexpression
- usually no hormonal syndrome
- no association with other diseases
Standardized approach towards the diagnosis of NEN
European Neuroendocrine Tumor Society (ENETS)

- H&E histopathology: well or poorly differentiated

- IH neuroendocrine markers
  synaptophysin and chromogranin A

- IH proliferation
  Ki67/Mib1
Grading of GEP-NETs

<table>
<thead>
<tr>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67 index</td>
<td>&lt;2%</td>
<td>2-20%</td>
</tr>
<tr>
<td>Mitotic index</td>
<td></td>
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</tr>
</tbody>
</table>

Ki67/MIB1

6%

3%
European Neuroendocrine Tumor Society (ENETS): Standardized approach towards the diagnosis of NET 2009

- **mandatory**
  - expression of the neuroendocrine markers synaptophysin and chromogranin A (both or only syn)
  - histopathology (H&E): well or poorly differentiated
  - proliferative activity (Ki67/MIB1): G1 – G3

- **optional**
  - immunostaining for hormones and transcription factors (CDX2, Isl-1) because of CUP (liver meta) or hormonal symptoms
  - somatostatin receptor SSTR2 because of diagnosis and therapy
European Neuroendocrine Tumor Society (ENETS): Standardized approach towards the diagnosis of NET 2009

-mandatory

-expression of the neuroendocrine markers synaptophysin and chromogranin A

-histopathology (H&E): well or poorly differentiated

-proliferative activity (Ki67/MIB1): G1 – G3

-stage: pTNM ENETS 2007 and UICC 2009

-angioinvasion
TNM classification of GEP-NENs

Site-specific TNM staging of NETs of the gastroenteropancreatic system (stomach, duodenum, ileum, appendix, colo-rectum, pancreas)

ENETS: 2006 / 2007
Rindi, Klöppel, Ahlman, ..... Wiedenmann:

UICC: 2009
Pancreatic NETs, size and mets

Mets

GLU

No Mets
Size matters... in the pancreas

Schmitt et al AJSP 2007
ENETS pTNM classification and disease staging for endocrine tumors of the pancreas

**T – 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

**N – regional lymph nodes**

- **NX** regional lymph node status not assessed
- **N0** absence of lymph node metastasis
- **N1** regional lymph node metastasis

**M – distant metastasis**

- **MX** distant metastasis not assessed
- **M0** absence of distant metastases
- **M1** presence of distant metastasis
Survival in foregut (mainly pancreatic) NETs: ENETS- TNM-Classification 2006

Staging

Pape et al Cancer 2008
### Comparison of the criteria for the T category in the ENETS and UICC TNM classifications of pancreatic neuroendocrine tumors

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<tr>
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<th>ENETS TNM</th>
<th>AJCC/UICC TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Confined to pancreas, &lt;2 cm</td>
<td>Confined to pancreas, &lt;2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Confined to pancreas, 2-4 cm</td>
<td>Confined to pancreas, &gt;2 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Confined to pancreas, &gt;4 cm, or invasion of duodenum or bile duct</td>
<td>Peripancreatic spread, but without major vascular invasion (Truncus coeliacus, A. mesent. sup.)</td>
</tr>
<tr>
<td>T4</td>
<td>Invasion of adjacent organs or major vessels</td>
<td>Major vascular invasion</td>
</tr>
</tbody>
</table>
D2-40 for angioinvasion
GI NETs, size (<1cm), infiltration and mets

Infiltration of musc. wall matters …...except
ENETS TNM staging for

gastric neuroendocrine tumors

**T** – 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

any T add (m) for multiple tumors.

**N** - regional lymph nodes

N1     regional lymph node metastasis

**M** - distant metastasis

M1     presence of distant metastasis

Rindi, Klöppel, Ahlman, ..... Wiedenmann:
TNM staging of foregut neuroendocrine tumors: a consensus proposal including a grading system Virchows Archiv: 2006, 449, 395
Tiny well differentiated duodenal neuroendocrine tumor with lymph node meta

Pat. with Zollinger-Ellison syndrome

LN Met
Gangliocytic paraganglioma

Neuroendocrine neoplasms of the duodenum

benign course despite > 2 cm
Appendiceal NET

Regional lymph node metastases are rarely found (<1%) below a size of 2 cm

Appendiceal NET without infiltration of mesoappendix

Appendiceal NET with infiltration of mesoappendix
### ENETS TNM staging for NETs of the appendix\(^1\)

<table>
<thead>
<tr>
<th>T</th>
<th>Primary tumor</th>
<th>N</th>
<th>Regional lymph nodes</th>
<th>M</th>
<th>Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤1 cm invading submucosa and muscularis propria</td>
<td>N1</td>
<td>Regional lymph node metastasis</td>
<td>M1</td>
<td>Distant metastases</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor ≤2 cm invading submucosa, muscularis propria and/or minimally (≤3 mm) invading subserosa/mesoappendix</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;2 cm and/or extensive (&gt;3 mm) invasion of subserosa/mesoappendix</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades peritoneum/other organs</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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Comparison of the criteria for the T category in the ENETS and 7th edition- AJCC/UICC TNM classifications of appendiceal neuroendocrine neoplasms

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<th>AJCC/UICC TNM.</th>
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</table>
| T1| \( \leq 1 \text{ cm}; \) invasion of muscularis propria | T1a: \( \leq 1 \text{ cm} \)  
T1b: > 1 - 2 cm                              |
| T2| \( < 2 \text{ cm}; \) and \( < 3 \text{ mm} \) invasion of subserosa/mesoappendix | \( > 2 – 4 \text{ cm}; \) or invasion of cecum |
| T3| \( > 2 \text{ cm}; \) or \( > 3 \text{ mm} \) invasion of subserosa/mesoappendix | \( > 4 \text{ cm}; \) or invasion of ileum |
| T4| invasion of peritoneum/other organs            | invasion of peritoneum/other organs    |
Comparability of ENETS 2006/2007 with UICC/AJCC 2009 TNM classifications

for NETs (wd NETs/NECs):
- stomach yes
- duodenum yes
- jejunum / ileum yes
- colon / rectum yes
- appendix no
- pancreas no

for NECs (pd NECs):

no
70-year old female patient with endoscopically detected multiple polypous tumors in the gastric fundus.

The patient had previous removals of gastric polyps.

Removal of the largest polyp by mucosectomy because of....
Neuroendocrine tumor?

**Tumor positive for the neuroendocrine markers**

- Synaptophysin
- Chromogranin A
Criteria of neuroendocrine tumor assessment

- neuroendocrine nature
- histological type
- site (esophagus, stomach, duodenum, etc.)
- tumor size, extension and angioinvasion
- proliferative activity
Well differentiated
Criteria of neuroendocrine tumor assessment

- neuroendocrine nature
- histological type
- site (esophagus, stomach, duodenum, etc.)
- tumor size, extension and angioinvasion
- proliferative activity
Criteria of neuroendocrine tumor assessment

- neuroendocrine nature
- histological type
- site (esophagus, stomach, duodenum, etc.)
- tumor size, extension and angioinvasion
- proliferative activity
Mucosa

Submucosa

0.9 cm
Type 1(2) Gastric NET with CAG (MEN1)
Type 3 Gastric NET without CAG/MEN1

< 1cm / mucosa, submucosa
   – no metas

> 1 cm / and or muscular wall infiltration
   – In-metas: 5 % - 20% :
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

Any T add (m) for multiple tumors.

N – regional lymph nodes
NX regional lymph node status not assessed
N0 absence of lymph node metastasis
N1 regional lymph node metastasis

M – distant metastasis
MX distant metastasis not assessed
M0 absence of distant metastases
M1 presence of distant metastasis
Diagnosis:
Type 1 gastric NET G1
and CAG
T1NxMx
Ileal serotonin producing NET ("ileal carcinoid")
invasion of the muscle layer and subserosal tissue

NET G1 serotonin producing

serotonin
TNM classification for neuroendocrine tumors of the lower jejunum and ileum

**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** distant metastasis
Rectal NET G1
< 1 cm
Ln met risk almost zero
GEP-NEN: Histol Diff., Grade, TNM and Therapy

Well Differentiated NET
- T1-2 N0/N1 localized
  - G1: OP
  - G2: OP

- T3N1M1 metastasized
  - G1: SSA (CTx; MTT) OP
  - G2: Chemo: STZ; PRRT

Poorly Differentiated NEC
- localized
  - G3: OP ?
- metastasized
  - G3: Chemo: platin based
Summary:

The new WHO and TNM classifications of GEP-NENs determine prognosis - metastatic potential of the tumors based on
- histologic differentiation - well or poor
- proliferative activity - G1, G2, G3
- tumor extension – size
- angio invasion