Neuroendocrine Neoplasias

2016-02-16
Incidence

all malignant neoplasms

NET

1973: 1.09:100’000 → 2004: 5.25:100’000

Prevalence

2004: 35:100’000
<table>
<thead>
<tr>
<th>Primary site</th>
<th>10 year survival distant disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymus</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Lung</td>
<td>15%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Stomach</td>
<td>15%</td>
</tr>
<tr>
<td>Duodenum</td>
<td>4%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>15%</td>
</tr>
<tr>
<td>Jejunum/Ileum</td>
<td>15%</td>
</tr>
<tr>
<td>Ileum</td>
<td>15%</td>
</tr>
<tr>
<td>Cecum</td>
<td>2%</td>
</tr>
<tr>
<td>Appendix</td>
<td>15%</td>
</tr>
<tr>
<td>Colon</td>
<td>1%</td>
</tr>
<tr>
<td>Rectum</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Gastroenterol up2date.*
2011; 7:313-339. Pape UF.

*JCO 2008; 26:3063-3072*
TUMOR CLASSIFICATION

Nomenclature
Grading
Staging ENETS vs. TNM
• G1, G2 neuroendocrine tumor (NET)
  – Are not called carcinoma, despite metastatic potential
• G3 neuroendocrine tumor (NET)
  – Very rare. Grade 3 but morphologically like G1/G2 NET
  – No information on biologic behaviour available

• G3 small cell or large cell neuroendocrine carcinoma (NEC)
# Williams and Sandler Classification

<table>
<thead>
<tr>
<th>Gut tube proper</th>
<th>Derivatives of gut tube</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Foregut:</strong></td>
<td></td>
</tr>
<tr>
<td>Tr. coeliacus</td>
<td></td>
</tr>
<tr>
<td>pharynx</td>
<td>thyroid</td>
</tr>
<tr>
<td>esophagus</td>
<td>parathyroid glands</td>
</tr>
<tr>
<td>stomach</td>
<td>tympanic cavity</td>
</tr>
<tr>
<td>proximal duodenum</td>
<td>trachea, bronchi, lungs</td>
</tr>
<tr>
<td></td>
<td>liver, gallbladder</td>
</tr>
<tr>
<td></td>
<td>pancreas</td>
</tr>
<tr>
<td><strong>Midgut:</strong></td>
<td></td>
</tr>
<tr>
<td>A. mes. sup.</td>
<td></td>
</tr>
<tr>
<td>proximal duodenum to right half of transverse colon</td>
<td>urinary bladder</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hindgut:</strong></td>
<td></td>
</tr>
<tr>
<td>A. mes. inf.</td>
<td></td>
</tr>
<tr>
<td>left half of transverse colon to anus</td>
<td></td>
</tr>
</tbody>
</table>

*(These three regions are defined by their blood supply)*
Architectural Patterns in NET

Type A nested: ileum, appendix
Type B trabecular: colon, rectum
Type C glandular: ampulla
Type D with atypia
Mixed type

Soga and Tazawa Classification
Cancer 1971; 28:990-998
Salt and Pepper Chromatin
**Grading**

<table>
<thead>
<tr>
<th>Ki-67</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=2%</td>
<td>3-20%</td>
<td>&gt;20%</td>
<td></td>
</tr>
</tbody>
</table>

| Mitoses/10 HPF | <=2 | 3-20 | >20 |

Mitoses: 50 hpf hotspot.
Report higher grade if result of mitotic count and Ki-67 is discordant.
G1 Neuroendocrine tumor

G2 Neuroendocrine tumor

G3 small cell carcinoma

G1: Ki-67 index <1%

G2: Ki-67 index 7%

G3: Ki-67 index 70%
**Tumor Grade and Survival**

Foregut tumors:
- Stomach
- Duodenum
- Pancreas

**Graphical Representation:**
- Cumulative Survival
- Survival Time (mo)
- G1 vs G2: $P=0.040$
- G1 vs G3: $P<0.001$
- G2 vs G3: $P<0.001$

References:
This is a neuroendocrine tumor
not a neuroendocrine carcinoma
Differences in pancreatic and appendiceal tumors: indicate both classifications!
GASTROINTESTINAL NEUROENDOCRINE NEOPLASIAS
Stomach: ECL-Zell NET
Duodenum: Gastrin +
Papilla: Somatostatin +
Appendix: Serotonin +

Pancreas: Insulin +
Glucagon +
Somatostatin +
PP +
Gastrin +
VIP +

Ileum: Serotonin +

Rectum: Glucagon + / PP +
(CDX2-, CGA-, PSAP+)
## Gastric NEN

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>70-80%</td>
<td>5-6%</td>
<td>14-25%</td>
<td>6-8%</td>
</tr>
<tr>
<td><strong>Macro</strong></td>
<td>&lt;1cm multiple corpus</td>
<td>1-2cm multiple corpus</td>
<td>&gt;2cm solitary corpus/antrum</td>
<td>3-5cm solitary ulcerated corpus/antrum</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>NET G1 ECL-cells</td>
<td>NET G1 ECL-cells</td>
<td>NET G1/G2 ECL-cells</td>
<td>NEC G3 NE-cells</td>
</tr>
<tr>
<td><strong>Background Precursor</strong></td>
<td>Autoimmune gastritis ECL-cell hyperplasia</td>
<td>MEN1, ZES ECL-cell hyperplasia</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td><strong>Serum Gastrin</strong></td>
<td>high</td>
<td>high</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td><strong>Metastatic disease</strong></td>
<td>5% LN 2-5% liver</td>
<td>10-30%</td>
<td>25-75%</td>
<td>80-100%</td>
</tr>
</tbody>
</table>

*Pathologe 2015; 36:237-245*
Conclusion:
endoscopic follow-up in diffusely atrophic mucosa of type A CAG if
• Severe hyperplasia (> 5 chains per linear mm)
• Dysplastic proliferation
Jejunal NET
A distinct tumor type?
< 50 cm from Treitz: better prognosis
> 50 cm from Treitz: ileal-like

Virchows Arch 2013, 462:489-499. Chopin-Laly et al
Mixed Tumors: MANEC

• Mixed adenoneuroendocrine tumors
  – Lung
  – Prostate
  – Breast (% no longer defined)
  – Gastroenteropankreatic
    mixed adenoneuroendocrine carcinoma (MANEC)
    WHO 2010: each component at least 30% (morphology and immunohistochemistry)

Virchows Arch 2011, 458:393-402. Volante et al. FAQ No. 9
METASTATIC NEN
Metastatic NET: Location of the primary

CUP: Jejunoileal primary most likely

Midgut: CDX2+++ TTF1- PAX8-
Lung: CDX2- TTF1+ PAX8-
Pancreas: PAX8+, Isl1+

Metastatic disease: Prognosis

Ki-67

Liver biopsy: G1 may be true G1 or missed G2
50% G2 are missed on FNA
Count the hotspot!

Ki67 <1%

Ki67 8%

Liver metastasis (autopsy)

Yang et al.
Metastatic disease: Prediction

UMB-1 antibody
% positive cells + to +++
>10% successful in vivo
Somatostatin receptor targeting
1-10% inconclusive

Am J Surg Pathol
2012, 36 (2):242-252
Körner et al.

SSTR2a
Confirmation of NE differentiation
Grading
SSTR 2alpha
Site of origin of metastatic NET

ROLE OF IMMUNOHISTOCHEMISTRY
SSTR 2A Immunohistochemistry


- 1+ = faint staining at 100 x
- 2+ = strong staining at 100 x
  - not the entire circumference of tumor cell membranes stained at 400 x
- 3+ = strong staining at 100 x
  - the entire circumference of tumor cell membranes stained at 400 x

Only membranous staining!!!
FIGURE 9. IHC workup of a metastatic WDNET of unknown origin. IHC indicates immunohistochemistry; NE, neuroendocrine; PI, proliferation index; pPAX8, polyclonal PAX8; PR, progesterone receptor; PrAP, prostatic acid phosphatase; WDNET, well-differentiated neuroendocrine tumor.
NET / small or large cell NEC / MANEC (%/%)  
WHO grade  
TNM classification UICC/ENETS  
CGA, SYN, Ki67, SSTR2a +/+++ %, (hormone)  
Clinical-pathologic correlation
Example Diagnostic Report

Somatostatin producing neuroendocrine tumor of the papilla Vateri, max. diameter 17mm, infiltration of the muscularis propria and the pancreatic parenchyma (sporadic, functionally inactive according to clinical information), lymphangitic carcinomatosis. Tumor free margins.

Metastases in 9/11 locoregional lymph nodes, max. diameter 12mm, no perinodal spread.

Liver metastasis, max. diameter 15mm. Tumor free margins.

TNM (UICC 7. ed. and ENETS): pT3, pN1 (9/11), pM1 (liver), L1, V0, G2 (15% Mib-1 proliferation index, 2 mitoses /10 HPF).
SSTR2a positive: 90% +++