NET und NEC

Endoscopic and oncologic therapy
Classification

- well-differentiated NET - G1 and G2 - „carcinoid“
- poorly-differentiated NEC - G3 - like SCLC
- well differentiated NET G3 -> elevated proliferation rate - WHO 2017
## Grading

<table>
<thead>
<tr>
<th>Differenzierung</th>
<th>Grading</th>
<th>Mitotic rate: Mitosen/10 HPF</th>
<th>Ki-67 Index %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated NET</td>
<td>G1</td>
<td>&lt; 2</td>
<td>&lt; 3</td>
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<tr>
<td>Well-differentiated NET</td>
<td>G2</td>
<td>2-20</td>
<td>3-20</td>
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<tr>
<td>Poorly-differentiated = NEC (small or large cell type, MANEC)</td>
<td>G3</td>
<td>&gt; 20</td>
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5 year survival - 96%, 73% and 28%
Anatomy

- **Foregut** - esophagus, stomach, duodenum, upper jejunum, biliary tract, pancreas

- **Midgut** - lower jejunum, ileum, appendix, cecum, proximal colon

- **Hindgut** - distal colon and rectum

- old classification of limited value
Clinical Course

• rare tumors, high spectrum of aggressiveness
• most grow slowly - indolent course
• 40% already metastasized - still several years
• functioning and non-functioning tumors
• not „carcinoid“ as they do metastasize
Carcinoid Syndrome

- functioning NET G1+2 - midgut, liver metastasis
- serotonin and other vasoactive substances
- abdominal pain, flushing, diarrhea
- right-sided valvular heart disease
- 24h-urine - 5-hydroxyindoleacetic acid - 5-HIAA
- Chromogranin A not as screening -> monitoring
Gastric NET

- Type 1 - 70-80%, chronic atrophic gastritis and pernicious anemia, small tumor, maybe multiple, usually non-functioning, indolent, rarely mets

- Type 2 - 5%, gastrinomas, ZES and MEN1 syndrome, frequently multifocal and indolent

- Type 3 - 20%, sporadic carcinoids, most aggressive, two thirds metastasized
Midgut NET

- increased frequency secondary to endoscopy
- most commonly within 60 cm of IC valve
- 25% have several lesions
- asymptomatic, but regularly metastasized - even small tumors, majority carcinoid syndrome
Rectal NET

- usually non secretory, even when metastatic
- asymptomatic, incidental finding
- 75-85% localized at diagnosis
- 6% mets if 1-2 cm in size, 24% if larger
- deep invasion, high mitotic rate -> poor prognosis factors
Diagnosis

- OGD and colonoscopy
- CT or MRI - highly vascular tumors
- Octreoscan - somatostatin receptors positive
- 68-Ga DOTATATE PET/CT more sensitive
- > 90% of NET are positive
- poorly differentiated NEC low somatostatin levels
Endoscopic treatment

- **<1cm** - type 1+2 gastric NET and superficial rectal NET -> very low risk of mets - EMR/ESD/FTRD

- **1-2cm** - EUS to exclude muscular invasion and lymph nodes before local resection

- small intestine NET - increased risk of metastasis irrespective of size -> surgery
Surveillance

- gastric type I+II < 2cm - EGD every 6 months for 3 years, annually thereafter
- rectal NET < 1cm - no follow-up
- rectal NET 1-2cm - proctoscopy 6+12 months
Prognosis

- 5-year survival - localized, regional, distant
- gastric - mostly type I G1 - > 90% survival
- small bowel - 95 - 72 - 42 % - 40-85% totally
- rectal - 90 - 49 - 26 % - 88% in total
- colonic - 83 - 65 - 27 % more aggressive - 62% in total, often right sided with late symptoms
Metastatic NET

- metastatic well-differentiated NET - G1 and G2
- clinical course highly variable, may survive for many years
- liver metastasis -> carcinoid syndrome
- MRI for metastasis best and always SSRS
Biochemical Monitoring

- Elevated 5-HIAA urinary levels highly specific for serotonin-producing tumors - midgut NET - 75%

- Chromogranin A - pancreatic NET, foregut and rectal carcinoid tumors

- CgA correlates with treatment response, elevated levels with shorter overall survival

- Elevated with PPI, renal and liver insufficiency

- NT-proBNP - severity of tricuspid regurgitation
Treatment G1+2

- surgery with curative intent - even with liver mets
- resection of primary if symptomatic
- combination of RFA and surgery with bil. mets
- hepatic arterial embolization or TACE
- OLT no standard option
- 94% disease recurrence in 5 years
Medical Treatment G1+2

- pancreatic NET worse prognosis than carcinoids, but better response to systemic therapy

- hormone related symptoms - somatostatin analogs
  -> octreotide or long-acting lanreotide

- asymptomatic patients just observation - if rapidly progressive start SSA - new data PROMID trial

- SSA in symptomatic, unresectable patients - control of tumor growth
Medical Treatment G1+2

- progressive disease - increase SSA, switch to everolimus, targeted radiotherapy

- debulking liver surgery or TACE in hepatic-predominant unresectable disease

- very individualized decisions -> tumor board

- side effects SSA - normally mild, nausea, bloating, loose stools -> tend to subside
Molecularly Targeted Therapy

• NET highly vascular and express VEGF and its receptor

• progression free survival with everolimus - mTOR inhibitor - and sunitinib - tyrosine kinase inhibitor in pancreatic NET

• carcinoids less established, but given - same for chemotherapy, but streptozocin-based regimens can be considered
Algorithmic approach to management of metastatic gastrointestinal neuroendocrine tumors (GINET)

1. Metastatic gastrointestinal neuroendocrine tumor
   - Potentially resectable?
     - No
       - Symptomatic from tumor bulk or hormone production?
         - No
           - High tumor burden?
             - No
               - Observe
             - Yes
               - Progression
               - Long-acting somatostatin analog therapy
               - Symptoms controlled?
                 - Yes
                   - Continue long-acting somatostatin analog
                 - No
                   - Escalate dose of long-acting somatostatin analog
                     - Progression
                     - Hepatic predominant disease?
                       - Yes
                         - Debulking surgery or nonsurgical liver-directed therapy
                       - No
                         - Systemic therapy
                           - Tumor expresses somatostatin receptors?
                             - No
                               - Everolimus
                             - Yes
                               - Everolimus or radiolabeled somatostatin analog, where available
Pancreatic NET

- more aggressive course than other NET
- around 75% non-functioning tumors
- functioning pancreatic NET - insulinoma, gastrinoma, glucagonoma, VIPoma - 10-30%
- resection may provide prolonged control, but majority will recur
- unresectable disease -> somatostatin analogs, non-surgical liver therapy, systemic therapy
Medical Treatment

• generally somatostatin analogs - functioning and non-functioning tumors -> controls tumor bulk
• insulinoma - diazoxide, inhibits insulin release
• gastrinoma - high dose PPI
• everolimus and sunitinib improve PFS
• rapidly progressive -> chemotherapy
Chemotherapy

- pancreatic NET clearly respond to CTX
- highly symptomatic from tumor bulk or rapidly enlarging metastasis
- streptozocin-based combination therapy - plus FU or doxorubicin
- toxic - myelosuppression, nausea, renal failure
- dacarbazine and temozolomide less toxic
Radiolabeled SSA

- targeted radiotherapy - limited availability
- $^{90}$Yttrium or $^{177}$Lutetium commonly used
- randomized studies needed
Case

- 58 y.o. lady
- dermatomyositis with dominant dermatitis
- CT screening for paraneoplastic explanation, highly vascular lesion in the pancreas
- EUS with FNA
HYPOLDENSITAET NEBEN V. LIENALIS
Histology

- neoplastic cells consistent with a neuroendocrine tumor, no high-grade dysplasia

- laparoscopic distal pancreatectomy - pT1, N0 (0/3), L0, V0, Pn0, G1, R0 -> Glucagonoma

- unfortunately persisting symptoms despite OP
Neuroendocrine Carcinoma G3

- very rare tumor - but aggressive course - do not rise from well-differentiated NET

- poorly differentiated tumor with early and widespread metastases - 57% of patients

- overall prognosis poor - similar to SCLC

- WHO 2017 NET G3 - better differentiated but still high Ki-67 rates -> overall improved survival
Symptoms + Diagnosis

- most commonly in the rectum, then cecum
- systemic and site-specific symptoms
- nearly all carcinomas are nonsecretory - Octreo-scan not useful
- staging by CT and FDG-PET
- tumor markers not well established
MANEC

- 40% of NEC contain a non-neuroendocrine component - adeno- or signet ring cell carcinoma and rarely squamous cell cancer

- mixed adenoneuroendocrine carcinoma -> both components > 30%

- treated as pure NEC - no definite prognostic difference
Treatment

• general lack of prospective trials - data of SCLC
• rapid disease progression with poor prognosis
• surgery alone rarely curative - adjuvant or even neoadjuvant treatment
• platinum based chemotherapy plus etoposide, alternatively irinotecan plus cisplatin
• no standard second line therapy
Prognosis

- median survival localized, regional and distant - 38 - 16 - 5 months

- poor prognostic signs - advanced stage, high proliferation rate, elevated LDH, thrombocytosis, esophageal and colonic primary
NET G3 - new!!

- histologically well or moderately differentiated
- Ki-67 proliferation index typically 20-55%
- most appropriate therapy not established
- low response to standard platinum/etoposide
- treat as NET - even surgical approach