General criteria of therapeutic strategy

Nicola Fazio, M.D., Ph. D.
Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors
European Institute of Oncology, Milan
DISCLOSURES

- **Personal financial interests:** Novartis, Ipsen, Pfizer, Merck Serono, Advanced Accelerator Applications, MSD (Advisory board, public speaking)

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- **Non-financial interests:**
  - ESMO: Coordinator of the Neuroendocrine, Endocrine neoplasms and CUP Faculty
  - ENETS: advisory board chairman
  - AIOM: coordinator for ITALIAN NEN guidelines
  - ITANET: Scientific committee member
Neuroendocrine neoplasms (NENs)
Terminology

Well (moderately) differentiated
or
Low / intermediate grade

Poorly differentiated
or
High grade

Tumours
NET
Carcinomas
NEC
Neuroendocrine tumors (NETs) 
Epidemiology

- Lung
- GEP
- Other
Neuroendocrine carcinomas (NECs)
Epidemiology

Lung

GEP

H&N, GU

MCC
High grade GEP NENs

Dasari et al., Cancer 2017
NEN DIAGNOSIS
NEN diagnosis:
suspected / probable

- Symptoms (e.g. chronic diarrhea)
- Biochemical markers (e.g. elevated CgA)
- Functional imaging (e.g. SSTR-related imaging)
- Morphological imaging (e.g. pancreatic nodule at CT-scan)

It is not enough
US-guided liver biopsy: “liver mets from neuroendocrine neoplasm”

Sure NEN diagnosis: pathology
The right diagnosis of a “pure NEN”

GEP NENs: right diagnosis

- **“Pure” NEN**
- **“Non pure” NEN**

**Adenocarcinoma** with a **neuroendocrine differentiation**

**Mixed** (at least 30% each component)
Combined, composited, anphicrin

**Non NEN**
GEP NETS: Main criteria for therapeutic choice

- Tumor grade (differentiation, Ki-67)
- Tumor stage (TNM; CT/MRI + PET/CT)
- SSTR-2 expression (intensity, homogeneity)
- Tumour primary site
GEP NENs: primary site

- **Midgut**

- **GI extra-midgut**

- **Pancreas**
Survival of NET patients has been reported to be related to stage, grade and primary site.

Dasari, JAMA Oncol 2017
GEP NETs: Goal of treatment

- **Radically resectable** (locally advanced or oligometastatic) → **Surgery**
- **Advanced unresectable** → **Potentially resectable**
  → **Never resectable**
Advanced GEP NETs: goals of treatment

- Syndrome
- Cytoreduction
- Tumour growth control (long-term stabilization)
Disease features to consider for therapy -1

Low/intermediate grade vs. high grade
Metastatic panNEN: clinical case - 3

US-guided liver biopsy:
“well-diff. NET”
Ki-67 = 10%

Primary tumor: pancreatic body/tail
Abdominal CT-scan
### WHO 2017 Pancreatic NEN classification

<table>
<thead>
<tr>
<th>NET (Tumours)</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Ki-67} \leq 2% \text{ and/or MI} &lt; 2 )</td>
<td>( \text{Ki-67} 3-20% \text{ and/or MI} 2-20 )</td>
<td>( \text{Ki-67} &gt; 20% \text{ and/or MI} &gt; 20 )</td>
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<th>NEC (Carcinomas)</th>
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Metastatic panNEN: clinical case - 3

Primary tumor: pancreatic body/tail

Abdominal CT-scan

US-guided liver biopsy: “well-diff. NET”
Ki-67 = 30%
| NET (Tumours) | G1  
|              | (Ki-67 \leq 2\% and/or MI < 2) |
|              | G2  
|              | (Ki-67 3-20\% and/or MI 2-20) |
|              | G3  
|              | (Ki-67 > 20\% and/or MI > 20) |

| NEC (Carcinomas) | G3  
|                 | (Ki-67 > 20\% and/or MI > 20) |
High grade GEP NENs

Fazio & Milione., Cancer Treat Rev 2016
Disease features to consider for therapy

- Functioning vs. non-functioning
- Inherited vs. sporadic
## GEP NETs: clinical syndromes

<table>
<thead>
<tr>
<th>GEP-NET</th>
<th>Syndrome</th>
<th>Incidence (new/100,000 year)</th>
<th>Secretory component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid tumours</td>
<td>Carcinoid syndrome</td>
<td>2–3</td>
<td>Serotonin, tachykinins</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Zollinger–Ellison syndrome (ZES)</td>
<td>0.5–1.0</td>
<td>Gastrin</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Endogenous hyperinsulinism</td>
<td>0.5–1.0</td>
<td>Insulin</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Verner–Morrison syndrome, WDHA</td>
<td>0.05–0.1</td>
<td>VIP</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Glucagonoma</td>
<td>0.01–0.05</td>
<td>Glucagon</td>
</tr>
<tr>
<td>Somatostinoma</td>
<td>Somatostatinoma</td>
<td>&lt;0.01</td>
<td>Somatostatin</td>
</tr>
<tr>
<td>ACTHoma</td>
<td>ACTH</td>
<td>&lt;0.05</td>
<td>ACTH</td>
</tr>
<tr>
<td>GHRHoma</td>
<td>GHRH</td>
<td>Unknown</td>
<td>GHRH</td>
</tr>
<tr>
<td>pNET causing carcinoid syndrome</td>
<td>Carcinoid syndrome</td>
<td>Unknown</td>
<td>Serotonin, tachykinins</td>
</tr>
<tr>
<td>pNET causing hypercalcaemia</td>
<td>PTHrPoma</td>
<td>&lt;0.1</td>
<td>PTHrP</td>
</tr>
<tr>
<td>Rare pNETs</td>
<td>LH, rennin, GLP-1, IGF-2, erythropoietin, CCK, enteroglucagon</td>
<td>1–5 cases</td>
<td>Various hormones</td>
</tr>
</tbody>
</table>

*Dimitriadis et al., End Rel Cancer 2016*
Disease features to consider for therapy - 3

**SSTR-2 + vs. SSTR-2**
*(functional expression)*
Somatostatin receptors (SSTRs)
Subtype-2 somatostatin receptor (SSTR-2)
### SUBCELLULAR PATTERN

<table>
<thead>
<tr>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
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</table>

- **(Negative)**
  - Pure cytoplasmic
  - Membranous usually incomplete
  - Membranous circumferential

### EXTENSION OF POSITIVE TUMOR CELL POPULATION

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<td><img src="image7.png" alt="Image" /></td>
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</table>

- **(Absent)**
  - 1-100%
  - <50%
  - >50%

### CONCORDANCE WITH OCTREOSCAN DATA

<table>
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<th>Score 2</th>
<th>Score 3</th>
</tr>
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<tbody>
<tr>
<td>50%</td>
<td>54%</td>
<td>87%</td>
<td>94%</td>
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Volante, Modern Pathology 2007

SSTR-2 IHC score
SSTR-2 functional expression: applications

• Prognosis
• Staging
• Prediction of response to PRRT
Metastatic panNEN: clinical case - 5

Abdominal CT-scan

$^{68}$Ga-PET-CT-DOTATOC
GEP NET: clinical presentation

At diagnosis mainly:

- Advanced (mostly liver)
- Non functioning (no clinical syndrome)
- Sporadic
- SSTR-2 positive (at $^{68}$Ga-DOTA-peptide-PET/CT)

*Cives et al., CA Cancer J Clin 2018*
Controversial criteria for choosing the first-line therapy

- Tumor burden
- Symptomaticity (mass-effect)
- Tumor status (stable or progressive disease)
Controversial criteria for choosing therapy in intermediate grade GEP NETs

$^{18}$FDG-PET/CT
1° step: multidisciplinary discussion to share a therapeutic strategy
NEN-dedicated multidisciplinary team (MDT)
Involvement of a NET referral Center

Multidisciplinary discussion (1° step of diagnostic-therapeutic management)

The MDT should be composed by NEN-dedicated specialists

The MDT should share a therapeutic strategy rather than the single therapy
European Institute of Oncology, IEO, Milan, Italy

ENETS Center of Excellence for GEP NETs

IEO NET multidisciplinary team