Edinburgh Pathology 2013:
NeuroEndocrine Tumors of the Pancreas

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Incidental 1.5 cm tumor in a 45-year old man:

Most probable diagnosis - Pan NEN. What should be done?
Incidental 1.5 cm tumor in a 45-year old man:

Most probable diagnosis - Pan NEN.

What should be done?

- Remove “at once”
- “Watch and wait” (how long?) and then remove
Survival in surgically treated patients with Pan NENs

- Overall 5-year: 45 %
- 10-year survival: 20 %
Survival in surgically treated patients with PanNENs < 2 cm (T1 accord. To UICC/ENETS)

Resected T1 PanNENs

43% 32%

Incidental tumor – 1.5 cm – in a 45-year old man: Pan NEN

The tumor should be removed, but there is no hurry
- NEN positive for SYN and CG
- WHO classification 2010:
  NET G2 (6%)
- UICC/ENETS TNM classification:
  pT1 N0 M0
Standardized approach towards the diagnosis of GEP-NEN

- 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

- stage: pTNM  ENETS 2007 and UICC 2009

Klöppel et al Neuroendocrinology 2009
Risk of malignant behavior in neuroendocrine neoplasms of the pancreas

- Very low risk of malignant behavior:
  Well differentiated, functioning (e.g. insulinoma) and non-functioning, non-angioinvasive, G1 (Ki-67 < 2%) neoplasm, <2 cm in size.

- Low risk of malignant behavior:
  Well differentiated, functioning and non-functioning, non-angioinvasive or angioinvasive, G2 (Ki-67 2 - 5%) neoplasm, 2 - 4 cm in size.

- Low-grade malignant behavior:
  Well-differentiated, functioning and non-functioning neoplasm with gross local invasion and/or metastases, angioinvasive, G2 (Ki-67 >5 – 20 %)

- High-grade malignant behavior:
  Poorly differentiated neoplasm of small or large cell type, usually non-functioning, G3 (Ki-67 >20%)
The Neuroendocrine Neoplasms
of the gastroenteropancreatic system:
The WHO classification: the problems

- **NET G1**  
  < 2% or < 5%?

- **NET G2**  
  > 5% to 20%  
  or >5 – 10%?  
  >10 – 20%?

- Is there a **NET G3** or are all **NENs >20%** –  
  neuroendocrine carcinomas – **NEC G3 >20%**?
NET: well differentiated NEN
G1 <2% or G2 -2% - 20%
NEC: poorly differentiated NEN
  - small cell type  G3 > 20%
NEC: poorly differentiated NEN
-large cell type G3 > 20 %
well differentiated NEN - NET
- slow growth
- favorable prognosis
- hormonal syndro. possible
- hereditary syndromes
- genetics differ from NEC
- unrelated to smoking

poorly differentiated NEN - NEC
- fast growth
- bad prognosis
- no hormonal syndromes
- genetics: mutations of basic genes such as p53
- related to smoking
Stem cell origin of GEP-NENs

Intestinal stem cell

- NGN3
- Is1?

Endocrine-precursor cell

- duodenum

Somatostatin cell

- NGN3

Gastrin cell

CDX2

MATH1

Stem cell

- P53
- Isl-

Endocrine-precursor cell

- Pancreas

Poorly differentiated - NEC

Well differentiated - NET

PP cell

Glucagon cell

Insulin cell

Gastrin cell

Somatostatin cell

Isl1, PDX1

Isl1

Isl1

Isl1

Isl1
Well diff NEN

- NET

Agaimy Modern Pathol 2013
Natural history of Pan NENs

Time course - years

Tumor Size - cm

3 cm

2 cm

1 cm

10 20 30 40 50 60

metastases

NET G3

NET G1-2

NEC G3

NET G1-2

NEC G3

1 cm

2 cm

3 cm
Natural history of Pan NENs

Tumor size vs. time course in years

- 1 cm
- 2 cm
- 3 cm

Time course - years

Metastases
Microadenoma in the MEN1 and "normal" pancreas
Frequency / Incidence of Pan NENs

- **Frequency of microadenomas (0.5 cm) in p.m. pancreata**
  
  10% 
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  10,000 / 100,000

- **Incidence of PanNENs in the population**
  
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  2 / 100,000
Gastrin  Glucagon  Insulin  PP  Somatostatin  Unclassified

Endokrine Hyperplasie  sstr2 +

Lk Metastasen

Endokrine Tumore

≥ 5 mm

< 5 mm - 1 mm

< 1 mm - 0.5mm

< 0.5 mm

Anlauf et al. AJSP 2008
Development of MEN1 tumors in the pancreas

Perren et al. JCEM 2007
Glucagon cell adenomatosis


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