Managing Pancreatic Lesions in VHL Syndrome

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Disclosures

I have no professional conflicts of interest with regards to the content of this lecture.

It’s easy to hurt a patient with VHL syndrome with bad decision making.
Overview

I. Natural history of PNETs and pancreatic cysts
   I. Patients live a long time in the absence of treatment-related morbidity

II. PNETs in patients with syndromes
   I. MEN1, VHL, NF

III. Differential diagnosis
   I. Appearance and clinical findings

IV. Non-functional PNETs have heterogeneous behavior
VHL Syndrome

- Autosomal dominant inherited syndrome caused by mutations of VHL
- Incidence 1:36,000
- Penetrance 90% by age 65 yrs
- Clinical manifestations:
  - CNS hemangioblastomas
  - RCC
  - Retinal angiomas
  - Pheochromocytoma
  - PNETs
  - Others: panc cysts, renal cysts, epididymis cysts

Pancreatic cysts in VHL

Frequent finding

Cysts are present in 70+% of patients

Two types of cysts

Simple cyst (common) and

Serous cystadenoma (uncommon)

Complications of pancreatic cysts (rare)

Bile duct obstruction
Pancreatic cysts in VHL

VHL-associated pancreatic cysts:
- Usually small
- Can be found throughout the pancreas
- May enlarge to cause symptoms (pain, duct obstruction)
- Do not cause dysfunction of the pancreas (e.g. diabetes, EPI)
Islets of Langerhans
• 2% of the total pancreatic mass
• Receive 20% of the pancreatic blood supply

Alpha cells
Glucagon, 20% of islet cells, body and tail

Beta cells
Insulin, 75% of islet cells, evenly distributed

Delta cells
Somatostatin, 5% of islet cells, head

PP cells
Pancreatic polypeptide, 5% of islet cells, head
VHL Syndrome:
Clinical Presentation of Pancreatic Neuroendocrine Tumors (PNETs)

- **Non-functional PNETs (>75%)**
  - Asymptomatic

- **Functional PNETs (20%)**
  - **Gastrinoma (50%)**
    - Zollinger-Ellison Syndrome
  - **Insulinoma (20%)**
    - Hypoglycemic or Neuroglycopenic Syndrome
  - **VIPoma (5%)**
    - WDHA Syndrome
  - **Glucagonoma (2%)**

Non-functional PNETs

Large size if clinical symptoms present
Obstruction (stomach, duodenum, CBD, colon), pain, or bleeding, jaundice
*Incidental finding

Hypervascular

CT findings: cystic changes, calcification
Approx ½ of tumors LN+ and/or liver mets
Histology: neuroendocrine phenotype, synaptophysin and chromogranin IHC+

Treatments:
Resection (or ablation) primary
*Observation
Non-functional PNETs Location

PNETs Detection: Cross-sectional Imaging

**Advantages:**
- Convenient
- Sensitive
- Operative planning
- Reasonable cost

**Disadvantages:**
- Misses smaller tumors (i.e. < 1 cm)
- No duodenal evaluation
- Misses small volume metastases
PNETs: Detection by EUS

Advantages:
• Very sensitive
• Non-invasive
• Evaluate duodenum

Disadvantages:
• Operator dependent
• Costly
• Incidental findings >> Increased chance for patient harm

Gastrinoma Triangle
DOTA-NOC or TATE Imaging

DOTANOC - PET

$^{68}$Ga-DOTA, 1-Nal-Octreotate

High affinity for SST receptors 2, 3, 5

*Insulinoma low SST expression for types 2 and 5, high SST 3 expression

NF-PNETs, gastrinoma, VIPoma, carcinoids high SST 2 and 5 expression
# Imaging for Localization and Staging


<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Primary Tumor</th>
<th>Liver Metastasis</th>
<th>Extrahepatic and Liver Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUS</td>
<td>95%</td>
<td>46%</td>
<td>29%</td>
</tr>
<tr>
<td>CT</td>
<td>31%</td>
<td>42%</td>
<td>38%</td>
</tr>
<tr>
<td>MRI</td>
<td>30%</td>
<td>71%</td>
<td>45%</td>
</tr>
<tr>
<td>Angio</td>
<td>28%</td>
<td>62%</td>
<td>40%</td>
</tr>
<tr>
<td>SRS</td>
<td>58%</td>
<td>92%</td>
<td>70%</td>
</tr>
<tr>
<td>DOTA-NOC</td>
<td>85%</td>
<td>93%</td>
<td>95%</td>
</tr>
</tbody>
</table>
Incidental PNET

- 42 yo woman with hereditary VHL syndrome
- CT reveals a 15 mm solid and cystic lesion in the tail
- EUS + FNA: PNETs w cystic features, 14 mm, Ki67 <2%
- Now what?

- Further staging?
- Observe? How frequently w imaging?
- Resect?
Nonfunctioning pancreatic tumors

Recommended:
- Multiphasic CT or MRI
- As appropriate: Somatostatin scintigraphy
- EUS
- Pancreatic polypeptide (category 3)
- Chromogranin A (category 3)

Locoregional disease

Small (<2 cm)

Large (>2 cm), or invasive tumors

Head

Distal

Enucleation ± regional nodes
- or Distal pancreatectomy ± regional nodes/splenectomy
- or Pancreatoduodenectomy ± regional nodes
- or Consider observation in selected cases

Distal pancreatectomy + splenectomy + regional nodes

Metastatic disease

See Metastases (PanNET-7)

See Surveillance (PanNET-6)
Factors Influencing Malignancy: Does Size Matter?

Non-functional PNETs are Heterogeneous

## Pancreatic Neuroendocrine Tumors: WHO Classification (2017)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Differentiation</th>
<th>KI-67 Index (%)</th>
<th>Mitotic count/10 HPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (low)</td>
<td>well</td>
<td>&lt; 2</td>
<td>&lt;2</td>
</tr>
<tr>
<td>G2 (intermediate)</td>
<td>Well</td>
<td>3-20</td>
<td>2-20</td>
</tr>
<tr>
<td>G3 (high)</td>
<td>Poor</td>
<td>&gt; 20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>
Prognostic factors for PNETs

Factors associated with poor prognosis
- Liver metastasis
- Extent of liver metastasis
- Lymph node metastasis
- Extrahepatic metastasis
- Development of paraneoplastic syndrome
- Excessive hormone hypersecretion

Histologic grade
- ? Intact MGMT expression

Jensen RT. Ann Oncol. 1999;10(Suppl 4)

Overall Survival for Resected PNETs by Stage

Evans DB. Cancer, Principles and Practice of Oncology. 2015; 1205-17.
VHL: Non-functional PNETs

- Usually asymptomatic (surveillance)
- Usually multifocal
- Even distribution thru pancreas
- Concomitant with functional PNETs
- Variable biology
  - Size, mitotic rate, proliferative index
  - Specific VHL mutations, type 1/2

When should these tumors be removed?
With what operation?

Interventions for PNETs

**SURGICAL**
- High-risk/grade tumors
  - Pancreatoduodenectomy
  - Left pancreatectomy + splenectomy
- Low-risk/grade tumors
  - Enucleation
  - Central pancreatectomy
  - Spleen-preserving left pancreatectomy

**NON-SURGICAL**
- EUS-guided ablation
- Radiotherapy
- PRRT
Pancreatic Neuroendocrine Tumors

What should be done with small nonfunctional pancreatic neuroendocrine tumors?

Observe or Resect?
Nonfunctional PNETs < 2 cm: Resect v Observe

Overall Survival of Nonsurgical Management vs. Surgical Resection of Pancreatic Neuroendocrine tumors (< 2 cm)

**Meta-analysis**

11 studies (2 prospective)

Surgical (N=1491), Nonsurgical (N=1607)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>(D+L)</th>
</tr>
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<tbody>
<tr>
<td>Gratian</td>
<td>2014</td>
<td>1.48 (1.18, 1.85)</td>
<td>52.62</td>
</tr>
<tr>
<td>Sharpe SM</td>
<td>2015</td>
<td>1.97 (1.52, 2.56)</td>
<td>47.36</td>
</tr>
<tr>
<td>D+L Overall (I-squared = 65.1%, p = 0.091)</td>
<td></td>
<td>1.69 (1.27, 2.26)</td>
<td>100.00</td>
</tr>
<tr>
<td>M-H Overall</td>
<td></td>
<td>1.72 (1.45, 2.04)</td>
<td></td>
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</tbody>
</table>

NOTE: Weights are from random effects analysis

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<tr>
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<td>2014</td>
<td>2.01 (1.45, 2.81)</td>
<td>49.78</td>
</tr>
<tr>
<td>Sharpe SM</td>
<td>2015</td>
<td>2.42 (1.74, 3.37)</td>
<td>50.22</td>
</tr>
<tr>
<td>D+L Overall (I-squared = 0.0%, p = 0.438)</td>
<td></td>
<td>2.21 (1.75, 2.79)</td>
<td>100.00</td>
</tr>
<tr>
<td>M-H Overall</td>
<td></td>
<td>2.22 (1.76, 2.81)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Treatment Toxicity for Non-Functional PNETs


Graph showing mortality rates over different hospital case volumes for 30-day and 90-day outcomes.
Metastatic PNETs
Resection and Directed Therapies
Metastatic PNETs
Resection and Directed Therapies

Survival after liver resection*

\[
p = 0.06
\]

TIME AFTER INITIAL RESECTION (MONTHS)

OUTCOMES AFTER LIVER RESECTION*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>26</td>
</tr>
<tr>
<td>Number of tumor recurrences</td>
<td>16</td>
</tr>
<tr>
<td>Liver-only recurrences</td>
<td>12</td>
</tr>
<tr>
<td>Liver and local recurrences</td>
<td>1</td>
</tr>
<tr>
<td>Widely systemic recurrences</td>
<td>3</td>
</tr>
<tr>
<td>Median time to tumor recurrence (range)</td>
<td>20 mo (7-36)</td>
</tr>
<tr>
<td>Treatment for tumor recurrences</td>
<td>8</td>
</tr>
<tr>
<td>Repeat wedge resection(s) of liver</td>
<td>5</td>
</tr>
<tr>
<td>RFA</td>
<td>3</td>
</tr>
<tr>
<td>Hepatic artery chemoembolization</td>
<td>3</td>
</tr>
<tr>
<td>Combinational cytoreductive therapy</td>
<td>5</td>
</tr>
<tr>
<td>Systemic chemo/hormonal therapy</td>
<td>4</td>
</tr>
<tr>
<td>Median time from recurrence to death (range)</td>
<td>33 mo (3-102)</td>
</tr>
</tbody>
</table>

Chemotherapy for PNETs

Multi-center randomized trial of 105 patients with unresectable metastatic neuroendocrine carcinoma

- Streptozocin plus doxorubicin superior to streptozocin plus fluorouracil

<table>
<thead>
<tr>
<th></th>
<th>STZ/5-FU</th>
<th>STZ/doxorubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor regression*</td>
<td>45%</td>
<td>69%</td>
</tr>
<tr>
<td>Time to tumor progression*</td>
<td>6.9 months</td>
<td>20 months</td>
</tr>
<tr>
<td>Median survival*</td>
<td>1.4 years</td>
<td>2.2 years</td>
</tr>
</tbody>
</table>

*p < 0.05

PNET: Targeted Therapy

**Monoclonal antibodies**
- Cetuximab (EGFR)
- Erbitux (EGFR)
- Panitumab (EGFR)
- Matuzumab (VEGFR)
- Bevacizumab (VEGFR)

**Tyrosine kinase inhibitors**
- Sunitinib (VEGFR, PDGFR, c-Kit, FLT-3)
- Sorafenib (VEGFR, PDGFR, Raf-1 protein)
- Vatalanib (VEGFR, PDGFR, c-Kit)
- Imatinib (Abl, PDGFR, c-Kit)
- Gefitinib (EGFR, Her2)
- Erlotinib (EGFR, Her2)

**mTOR inhibitors**
- Sirolimus (Rapamycin)
- Everolimus (RAD 001)
- Temsirolimus (CCI-779)
- AP 23573
Radiation Therapy

Somatostatin receptor radionuclide therapy (SRRT)

Tumor response to [(177)Lu] DOTA-Octreotate in patients with neuroendocrine tumors

| Tumor response to [(177)Lu] DOTA-Octreotate in patients with neuroendocrine tumors |
|-------------------------------------|---|
| 50-100% reduction                   | 39% |
| 25-50% reduction                    | 6%  |
| No change                           | 44% |
| Tumor progression                   | 11% |

LuTate Therapy

- Somatostatin receptor (+) tumors
- The toxicity was generally mild bone marrow toxicity

RJ Hicks. *Ca Imaging* 2010.
VHL Pancreatic Neuroendocrine Tumors
Recommendations for Follow-up Surveillance

Q 1 year

Physical exam

Biochemical markers
  (Chromo A)

Plus one of the following:

EUS
MRI
CT abdomen

DOTA-TATE – SPECT*

*only for malignant PENs
TAKE HOME MESSAGE

- Pancreatic endocrine tumors (PNETs) occur in 10% of patients with VHL Syndrome
- Clinical and biochemical diagnosis
- Imaging for localization and staging
- Resection when technically possible (even for stage IV)
  - Treatment sequencing recommendations are unclear
- Palliation: debulking, ablation, liver embolization, Octreotide, chemotherapy, PRRT (Lutathera)