Impact of diagnosis with Pancreatic Neuroendocrine Tumors on Mortality in Patients with Von Hippel-Lindau Disease

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What are Neuroendocrine Tumors (NET)?

- Originate from neuroendocrine cells

- The incidence of NET has increased

- Most PNET are sporadic

- They can also develop as part of inherited syndromes, such as von Hippel-Lindau (VHL).
## Sporadic PNET vs. VHL-related PNET

<table>
<thead>
<tr>
<th></th>
<th>VHL-related PNET</th>
<th>Sporadic PNET</th>
</tr>
</thead>
<tbody>
<tr>
<td>High grade(^1)</td>
<td>Rare</td>
<td>7%</td>
</tr>
<tr>
<td>Functional(^2)</td>
<td>&lt;1%</td>
<td>~10%</td>
</tr>
<tr>
<td>Metastases(^3,4)</td>
<td>7.5-20%</td>
<td>40.3%</td>
</tr>
</tbody>
</table>

\(^1\)Garcia-Carbonero et al., 2016, \(^2\)Blansfield et al., 2007, \(^3\)Krauss et al., 2018, \(^4\)Igarashi et al., 2014
Pancreatic Neuroendocrine Tumor (PNET) in VHL

- **Prevalence:** 8-17%

- **Median age at onset:** 34y (14-55)

- **Surveillance - Size (genotype)**

- **Management is mainly surgical**

Blansfield et al., 2007, Igarashi et al., 2014, Lonser et al., 2003, Tirosh et al., 2017, Krauss et al., 2018

*68*Ga-DOTATATE PET/CT
(somatostatin receptor-based imaging)
Leading contributors for VHL morbidity and mortality:

- Central nervous system hemangioblastoma (HB)
- Clear cell renal cell carcinoma (RCC)

What is the impact of diagnosis with PNET on the overall mortality in patients with VHL?

Lonser et al., 2003
Diagnosis with PNET and VHL outcome
Methodology

• **Retrospective study**, based on the Surveillance, Epidemiology and End Results (SEER) database.

• **Patients**: Diagnosed with RCC, PNET, HB and/or PPGL

• **VHL diagnosis**: ✓ “International Criteria”
  ✓ “Danish Criteria”

• **Analysis**: Univariate analysis with survival analysis by Kaplan-Meier curves, Multivariable analysis using the Cox proportional regression.

### Results

#### Patients Characteristics - Entire Cohort

<table>
<thead>
<tr>
<th></th>
<th>VHL</th>
<th>Sporadic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>170</td>
<td>16,174</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>46.6 (17.0)</td>
<td>63.9 (11.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RCC</td>
<td>164</td>
<td>15,620</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PNET</td>
<td>91</td>
<td>419</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HB</td>
<td>83</td>
<td>75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPGL</td>
<td>7</td>
<td>60</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD, standard deviation; RCC, renal cell carcinoma; PNET, pancreatic neuroendocrine tumor; HB, hemangioblastoma; PPGL, pheochromocytoma/paraganglioma
## Results

### Patients Characteristics-Sporadic vs. VHL-related PNET

<table>
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<th>VHL</th>
<th>Sporadic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=91</td>
<td>n=419</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis mean (SD)</td>
<td>54.0±14.0</td>
<td>60.2±13.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex n(%)</td>
<td>48 (52.7)</td>
<td>229 (54.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Metastatic PNET n(%)</td>
<td>32 (45.7)</td>
<td>217 (57.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diameter n(%)</td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>≤10 mm</td>
<td>10 (16.9)</td>
<td>27 (9.2)</td>
<td></td>
</tr>
<tr>
<td>11-29 mm</td>
<td>31 (52.5)</td>
<td>114 (38.6)</td>
<td></td>
</tr>
<tr>
<td>≥30 mm</td>
<td>18 (30.5)</td>
<td>154 (52.2)</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation; PNET, pancreatic neuroendocrine tumor;
Patients with VHL-related PNET had lower ACM risk compared to patients with sporadic PNET.

Higher ACM risk in patients with VHL and PNET vs. those without PNET.

Patients with VHL-related PNET had lower ACM risk compared to patients with sporadic PNET.
A trend for higher risk for ACM was found in patients harboring PNET with diameter $\geq 30$ vs. $<30$ mm ($p=0.06$ and $p=0.1$ in patients with sporadic and VHL-related PNET, respectively).

**Results**

Kaplan-Meier Analysis – Comparison by PNET diameter

**All PNET**

**Sporadic PNET**

**VHL-related PNET**
• Higher ACM risk in patients with sporadic advanced PNET, with a similar trend among patients with advanced VHL-related PNET.

• Similar trend of higher ACM risk with higher grades in VHL-related and sporadic PNET.

However, is PNET diagnosis an independent risk factor for ACM in VHL?
• Diagnosis with PNET was not associated with increased risk for ACM (HR 0.42, 95% CI 0.12-1.5, p=0.18).

• An increased risk for ACM was detected among patients with metastatic PNET (HR 3.71, 95% CI 1.4-9.8, p=0.008).
Discussion

Does PNET diagnosis affect ACM in patients with VHL?

Localized PNET
- Has no independent impact on ACM in patients with VHL.
- Complex effect of multiple VHL-related tumors on ACM.

Advanced PNET
- Higher ACM risk in patients with advanced PNET.
- Importance of surveillance for early detection of high-risk PNET.

Do patients with sporadic and VHL related PNET differ in ACM risk?

- Diameter
- Grade
- Stage

VHL-related PNET

ACM

sporadic PNET.
Limitations

- Underestimation of VHL population (SEER database)
- Some of the variables have missing values
- No data on VHL genotype
- No longitudinal data on tumor size dynamics
Conclusions

• **PNET surveillance** in VHL may affect ACM by reducing the rate of metastatic disease.

• The impact **of early detection of high-risk PNET** on ACM should be investigated in future studies.

• **Caregiver-patient relations** may assist in timely execution of the VHLA guidelines for optimal screening.
Thank You For Your Attention!