Long-term prognosis of resected pancreatic NETs in VHL disease is favorable and not influenced by small tumors left in place.

**Service d’Hépato-Gastroentérologie et de Cancérologie Digestive**
Hôpital Robert Debré, Reims

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**Surgical treatment of VHL-PNETs**

**Criteria for surgical resection:**
- Size > 30 mm (20 mm in the head)
- During abdominal surgery for other VHL-related tumors
- Or symptoms whatever the size
- (exon 3? Doubling time?)

**Objectives when surgical resection is indicated:**
- Minimize the metastatic risk
- Spear pancreatic parenchyma
- Avoid surgical morbidity (fistulas 24%, ++ if enucleation)

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**VHL-PNETs: challenging management**

- 10-20% of VHL patients
- Associated with cysts and/or serous cystadenomas in 70%
- Multiple tumors
- Malignant in 20-30% with possible metastases
- Potentially life-threatening

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**Objectives**

- Natural history not well known
- No specific comparisons with sporadic PNETs
- Undefined role in VHL-related mortality
- Extent of surgical resection
- Should all tumors be resected?

**Objective of our study:**
Compare the long-term outcome of patients with VHL-PNET and patients with sporadic non-functioning PNET who undergo pancreatic resection

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Libutti et al., Surgery 1997; Hammel et al., Gastroenterology 2000; Corcos et al., Pancreas 2007; Blansfield et al., Surgery 2007
Retrospective case-control study

VHL-PNETs (n=23)  
Pairing Size (± 2 mm)  
ENETS/WHO stage Ki67 (± 2 %)

Sporadic PNETs (n=23)

PNETs surgical resection between 1997 and 2013 at Beaujon Hospital

Annual follow-up (TDM and/or MRI)

Follow-up 107 months (IQ range: 57 – 124)

Follow-up 71 months (IQ range: 58 – 131)

Primary endpoint = recurrence-free survival = from the date of surgery to the date of recurrence (local or distant) or PNET-related death

Patients

<table>
<thead>
<tr>
<th></th>
<th>VHL (n=23)</th>
<th>Sporadic (n=23)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>7 (30%)</td>
<td>12 (52%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36 (29-44)</td>
<td>56 (51-58)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diameter of largest tumor (mm)</td>
<td>30 (26-40)</td>
<td>30 (25-40)</td>
<td>NS</td>
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<tr>
<td>Positive SRS</td>
<td>13 (57%)</td>
<td>17 (74%)</td>
<td>NS</td>
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</tbody>
</table>

In the VHL group:  
Asymptomatic PNETs in all but 2 patients  
Multiple PNETs in 70% (2 to 8 tumors)  
61% also operated on for renal cell carcinomas  
65% also operated on for pheochromocytomas  
Hemangioblastomas in 78%

Surgical procedures

<table>
<thead>
<tr>
<th></th>
<th>VHL (n=23)</th>
<th>Sporadic (n=23)</th>
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<tbody>
<tr>
<td>Type of surgery (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Duodeno-pancreatectomy</td>
<td>14 (61)</td>
<td>11 (48)</td>
<td>NS</td>
</tr>
<tr>
<td>Left pancreatectomy</td>
<td>8 (35)</td>
<td>6 (26)</td>
<td></td>
</tr>
<tr>
<td>Median pancreatectomy</td>
<td>0</td>
<td>3 (13)</td>
<td></td>
</tr>
<tr>
<td>Enucleation</td>
<td>1 (4)</td>
<td>3 (13)</td>
<td></td>
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<tr>
<td>Postoperative morbidity</td>
<td>35 %</td>
<td>57 %</td>
<td>NS</td>
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Surgery in the VHL group:  
8.5 years after VHL diagnosis  
6 months after PNET diagnosis  
1-5 « small » PNETs (< 15 mm) left in place in 11 patients (50%)

Pathological findings

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<thead>
<tr>
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<th>VHL (n=23)</th>
<th>Sporadic (n=23)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Ki-67 Index (%)</td>
<td>3 (1.5-7)</td>
<td>4 (2-8)</td>
<td>NS</td>
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<tr>
<td>Grade</td>
<td></td>
<td></td>
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<tr>
<td>G1</td>
<td>9 (39%)</td>
<td>8 (35%)</td>
<td>NS</td>
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<tr>
<td>G2</td>
<td>13 (57%)</td>
<td>15 (65%)</td>
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<tr>
<td>G3</td>
<td>1 (4%)</td>
<td>0</td>
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<tr>
<td>WHO/ENETS stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (4%)</td>
<td>2 (9%)</td>
<td>NS</td>
</tr>
<tr>
<td>II</td>
<td>12 (52%)</td>
<td>14 (61%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>10 (43%)</td>
<td>7 (30%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>12 (52%)</td>
<td>14 (61%)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive margins</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>NS</td>
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VHL-PNETs  
Micro-adenomatosis in 30%  
Calcifications in 48%
Quality of pairing

Outcomes

Recurrences in the VHL group (n=2)
1) Unique PNET, 55 mm, stage IIIb, Ki67 1% → bone metastases after 33 months
2) Multiple (3) PNETs, 50 mm, stage Ila, Ki67 25% → relapse in the resection site after 69 months

5 deaths, only 1 related to PNETs

Recurrences in the sporadic group (n=7)
Liver metastases (n=5)
Lymph-node metastases (n=2)

1 death, not related to PNETs

Discussion – Conclusions

• Low recurrence rate following VHL-PNETs resection
• Close follow-up if predictive factors of unfavorable course
• Better prognosis than sporadic PNETs
• Small VHL-PNETs left in place are not at high risk of progression
• VHL prognosis more related to other, more life-threatening tumors? (0.3% mortality related to VHL-PNETs metastases, Blansfield et al, Surgery 2007)

→ Less aggressive surgical management
→ Pancreas-spearing resections
## Special thanks

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<tr>
<th>Location</th>
<th>People</th>
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</table>
| **Beaujon Hospital, Clichy, France** | • Pr Pascal Hammel  
  • Dr Sebastien Gaujoux  
  • Pr Philippe Ruszniewski  
  • Dr Jérôme Cros  
  • Pr Alain Sauvanet  
  • Dr Olivia Hentic  
  • Dr Marie-Pierre Vullierme |
| **Robert-Debré Hospital, Reims, France** | • Pr Guillaume Cadiot  
  • Dr Hedia Brixi |
| **Bichat Hospital, Paris, France** | • Pr Anne Couvelard |
| **PREDIR Centre, Le Kremlin-Bicêtre, France** | • Pr Stéphane Richard  
  • Mme Marie-Laurence Richard |
| **Association VHL France**         | • Mme Claire Blesbois |