Germline VHL genotype and VHL-related PNETs

Background – pancreatic manifestations in VHL

- Any pancreatic manifestation: 35-70%
- Pancreatic neuroendocrine tumor (PNET): 8-17%
- Multiple PNETs in 30-50%
- Metastatic disease in 8.3-12.8%

Which of the PNETs are at high risk to progress or metastasize?

Risk stratification parameters

High risk:
- Diameter >3 cm
- Tumor diameter doubling time <500 days
- Pathogenic variants in exon 3
- Type O blood type
- Protein expression by immunohistochemistry
- Gene expression

Low risk:
- Tumor diameter <15 mm

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Patients and methods

- A prospective study, with follow-up anatomic and functional imaging.
- 175 patients (489 PNETs), 156 had germline VHL genotyping.
- 29 patients (16.6%) underwent surgical interventions, nine patients (5.1%) had metastatic disease.

Pathogenic variant | Missense (n=76, 48.7%) | Other (n=80, 51.3%) | p-value
--- | --- | --- | ---
Age at inclusion (years) | 46.7±12.8 | 43.0±13.5 | 0.4
Female gender (%) | 39 (51.3%) | 46 (57.5%) | 0.4
Follow-up duration (months) | 50.3±21.3 | 53.7±19.8 | 0.8
Lesions characteristics | | | |
Number of lesions (n) | 2.9±2.0 | 2.6±1.9 | 0.3
Initial largest lesion diameter (cm) | 1.6±1.1 | 1.4±1.0 | 0.05 (MW)
Disease free interval (months) | 7.4±22.1 | 16.8±31.6 | 0.03
Progression free interval (months) | 45.4±23.6 | 46.2±27.7 | 0.9

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Germline VHL genotype analysis as a clinical tool in the management of patients with VHL-associated pancreatic neuroendocrine tumors

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Germline VHL genotype and VHL-related PNETs

Background – Genotype-phenotype association in VHL

- Genotype-phenotype association in von Hippel-Lindau disease

Mutation type | Pheochromocytoma | Renal-cell carcinoma | CNS hemangioblastoma
--- | --- | --- | ---
Deletions | 1% | 41% | 60%
Missense (Type I) | 0% | 31% | 60%
Missense (Type IIa) | 45% | 3% | 10%
Tyr98His | 39% | 3% | 54%
Missense (Type IIb) | 39% | 3% | 54%

Is there an association between VHL genotype and PNETs prognosis in VHL disease?

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Tumor size and risk for metastatic disease

- No patient with lesion diameter <1.2 cm required surgical intervention, or developed metastatic disease.
- Lesion diameter >3 cm was associated with higher risk for metastatic disease in multivariate analysis (HR 8.6, 95% CI 1.7-43.2, p=0.009).

Multivariate analysis (n=63)

HR 8.8, 95% CI 1.2-66.3, p=0.04

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in silico analysis-based model for PNET prognostication

- Five computational prediction models:
  - PolyPhen-2 (HumVar and HumDiv)
  - SNPs&GO
  - PANTHER
  - PhDSNP

High-risk consensus - All models had prediction >0.8 with a high analysis reliability score.

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Germline VHL genotype and VHL-related PNETs

The European-American-Asian VHL PanNET-Registry

- 2330 patients, of whom 273 patients (12%) had PNETs
- Metastatic PanNETs were diagnosed in 55 patients (20%) with a minimum diameter of ≥2.8 cm
- Higher 10y overall survival in patients operated vs. not, mainly explained by PNETs ≥2.8 cm (80% in operated vs. 50% in not-operated, \( P = 0.030 \)).
- Identified the 167 hotspot variants as high risk in terms of developing metastases.

Krauss, Ferrara, Links et al [Equal contribution] Endo Rel Can 2018

Germline VHL genotype and VHL-related PNETs

Potential reduction in cumulative lifetime radiation

In collaboration with
Dr Ami Berrington de González
Radiation Epidemiology Branch, NIH
Dr W. Marston Linehan
Urologic Oncology Branch, NIH

Radiation exposure in various imaging techniques/modalities used in VHL

Real-life vs. new-algorithm-based radiation exposure.

Tirosh, Journyet et al [equal contribution], Radiology, in press
Germline VHL genotype and VHL-related PNETs
Future perspectives

Are we over-simplifying the genotype-phenotype association in VHL?

We should consider studying a possible association between germline VHL genotype and epigenetic alterations, and their association with clinical phenotype.

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