14th International VHL Medical Research Symposium

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

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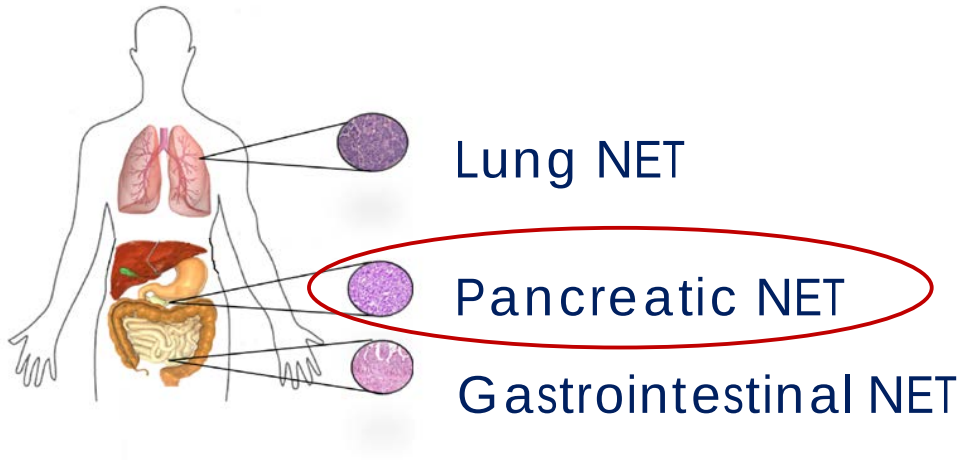
What are Neuroendocrine Tumors (NET)?

- **Originate from neuroendocrine cells**
- **Anatomic Location:**



- **Most NET are sporadic**
- **They can also arise as part of inherited syndromes, such as von Hippel-Lindau (VHL).**

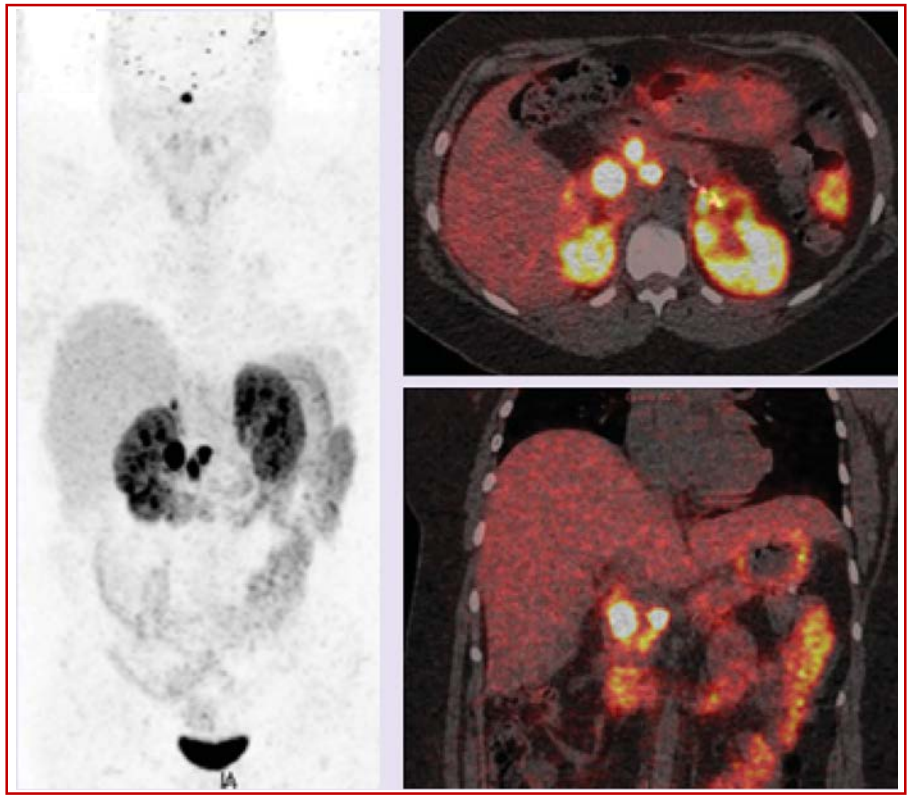
Sporadic PNET vs. VHL-related PNET

	VHL-related PNET	Sporadic PNET
High grade[1]	Rare	7%
Functional[2]	<1%	~10%
Metastases[3,4]	7.5-20%	40.3%

[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)
- **Almost never functional**
- **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*

Von Hippel-Lindau (VHL)

- Leading contributors for VHL morbidity and mortality:

❑ Central nervous system hemangioblastoma (HB)

❑ Clear cell renal cell carcinoma (RCC)

- **The impact of diagnosis with PNET on the overall mortality in patients with VHL is yet to be defined.**

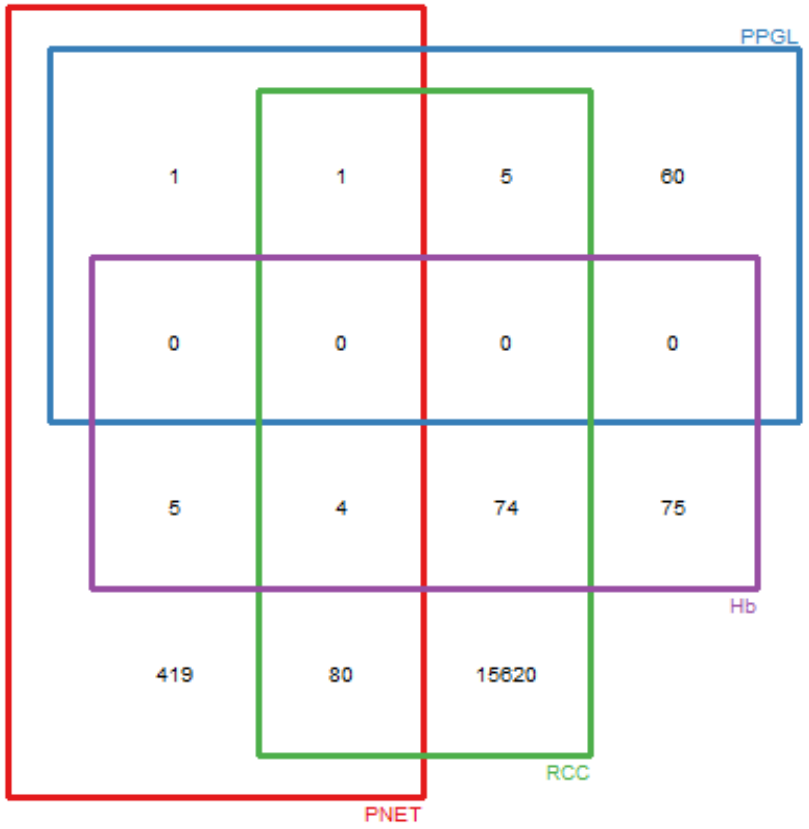
Lonser et al., 2003

Methodology

- **Retrospective study**
- **Database:** Surveillance, Epidemiology and End Results (SEER, Nov 18th edition)
- **Inclusion**: Diagnosis by RCC, PNET, HB and/or PPGL (ICD-O-3 + anatomic site)
- **VHL diagnosis:**
  - ✓ Detection of two HBs, or one HB and a visceral neoplasm ("International Criteria")
  - ✓ Detection of any two VHL-related manifestations ("Danish Criteria")
- **Analysis:** Univariate analysis with survival analysis by Kaplan-Meier curves. Multivariable analysis using the Cox proportional analysis.

Binderup, M. L. M. *et al.* (2017)

Results
Patients Characteristics - Entire Cohort



	VHL	Sporadic	p value
n	170	16,174	
Mean age (SD)	46.6 (17.0)	63.9 (11.3)	<0.001
RCC	164	15,620	<0.001
PNET	91	419	<0.001
HB	83	75	<0.001
PPGL	7	60	<0.001

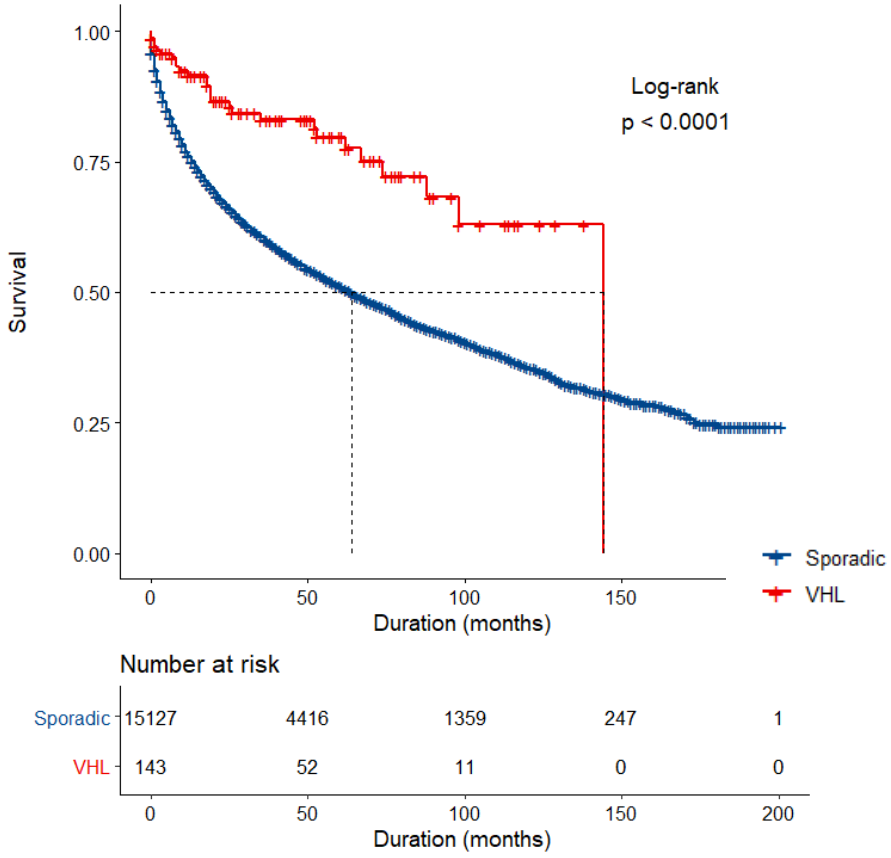
SD, standard deviation; RCC, renal cell carcinoma; PNET, pancreatic neuroendocrine tumor; HB, hemangioblastoma; PPGL, pheochromocytoma/paraganglioma

Results
Patients Characteristics-Sporadic vs. VHL-related PNET

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

SD, standard deviation; PNET, pancreatic neuroendocrine tumor;

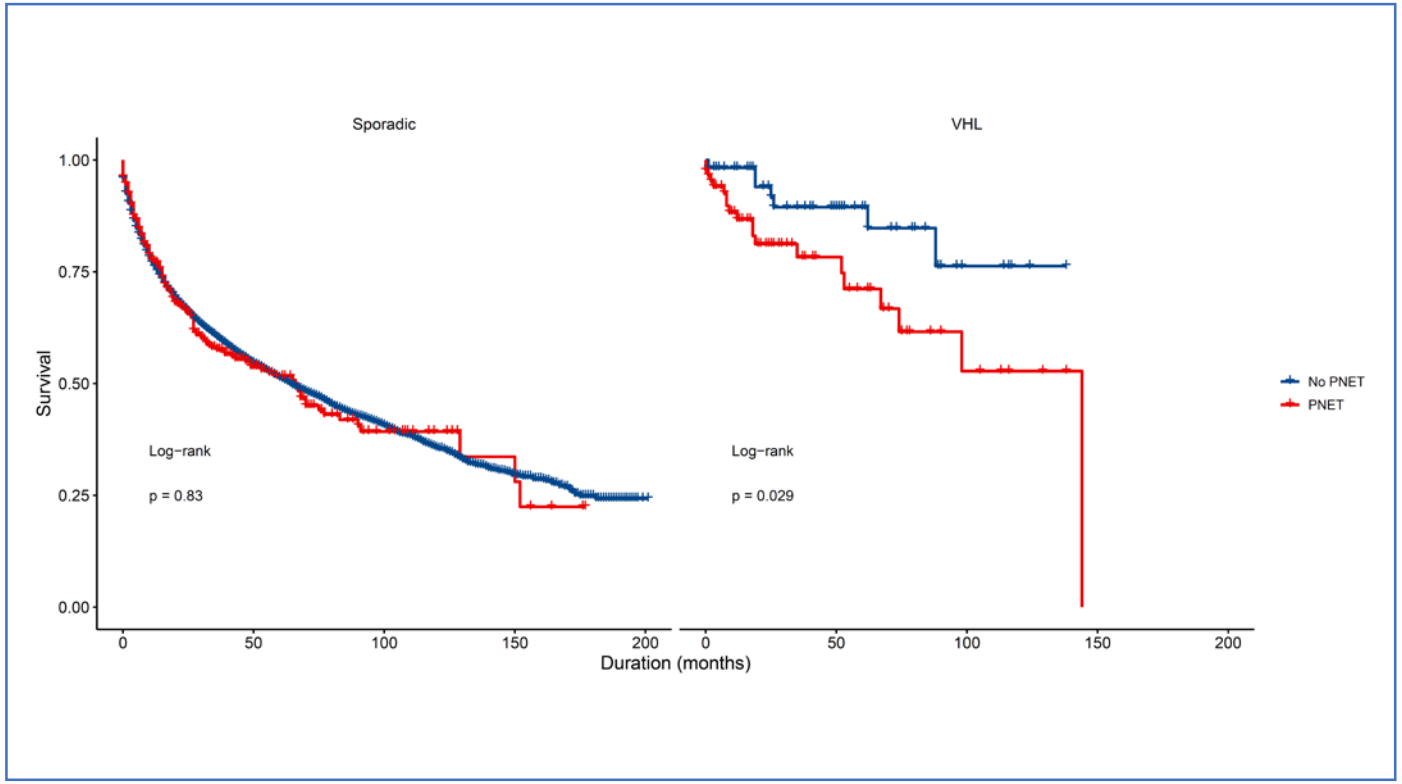
Survival analysis



- Patients with VHL-related PNET had lower ACM compared with sporadic PNET

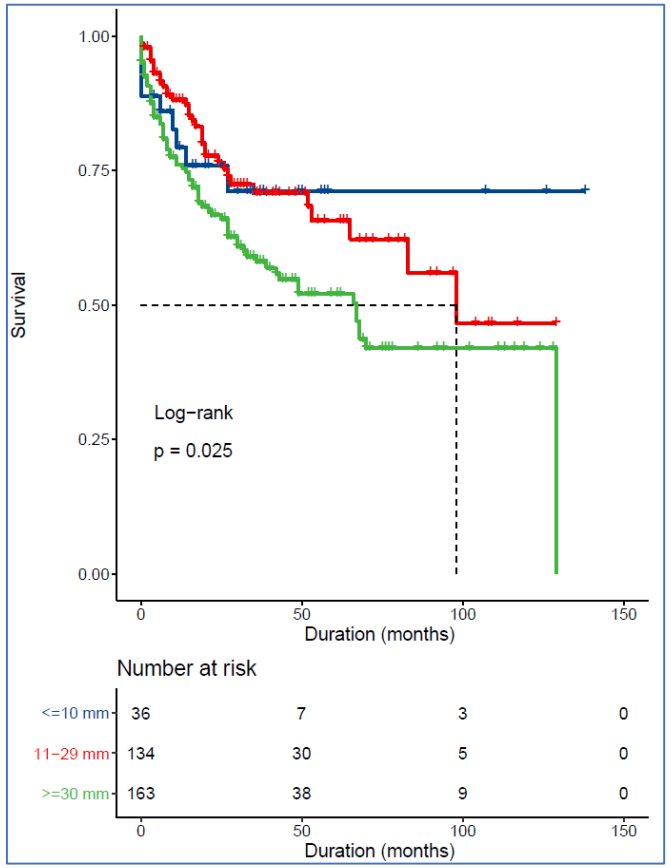
- A comparable risk for ACM among patients with sporadic PNET vs. other sporadic neoplasms.

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

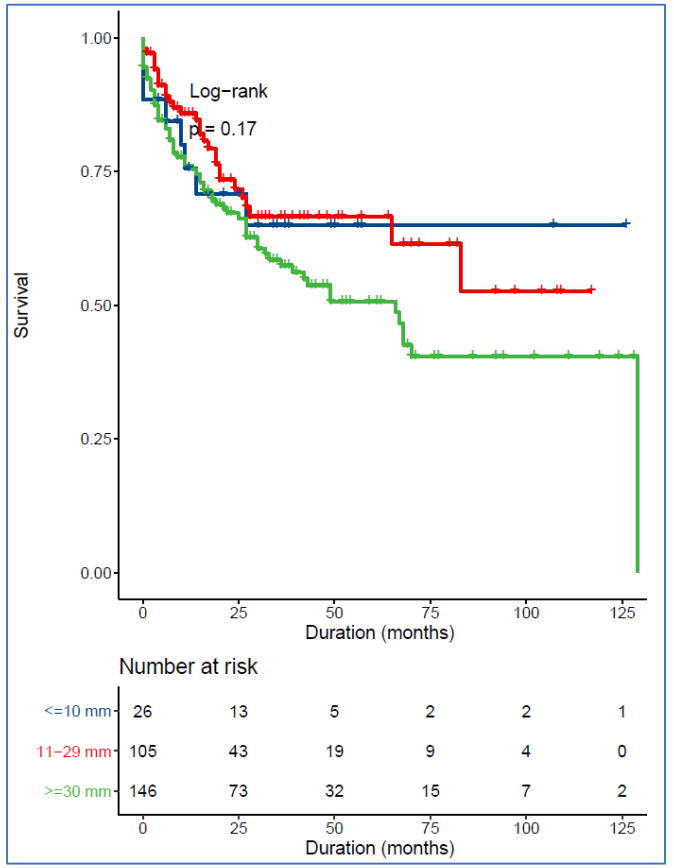


Impact of primary tumor diameter

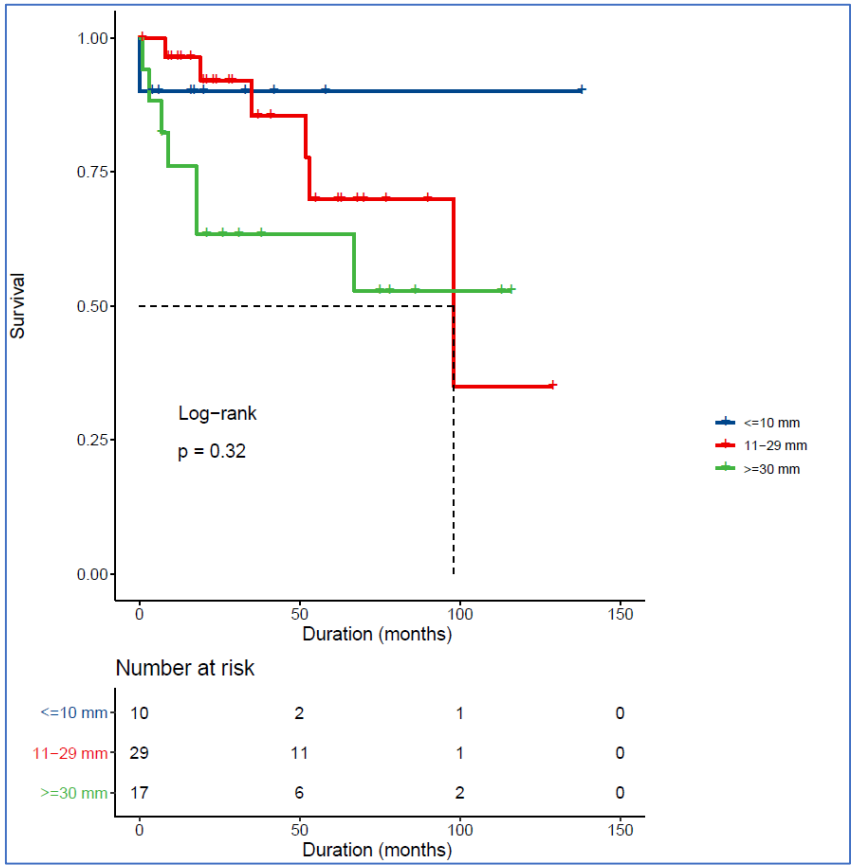
All patients



Sporadic PNET



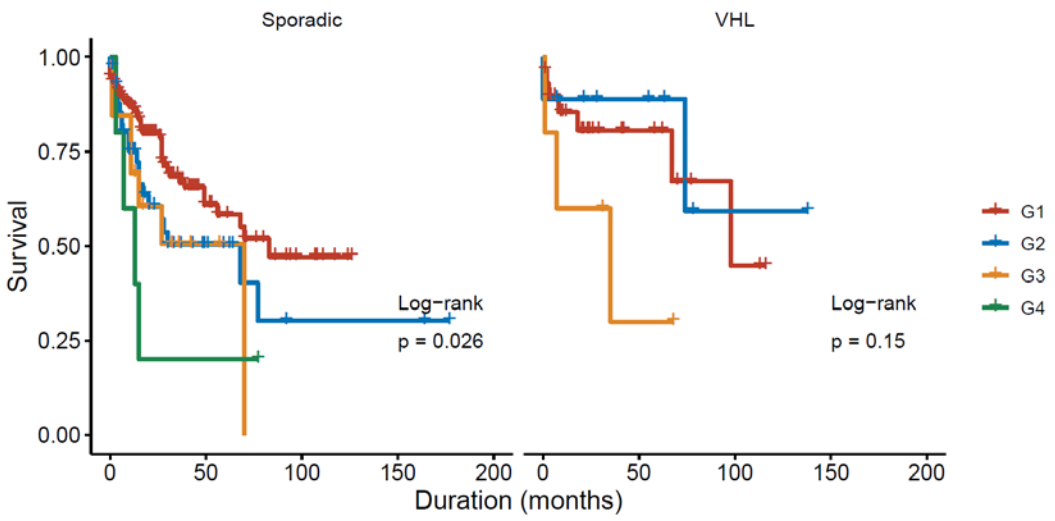
VHL-related PNET



A higher risk for ACM was found in patients harboring PNET with diameter ≥30 vs. <30 mm (p=0.06 and p=0.1 in patients with sporadic and VHL-related PNET, respectively).

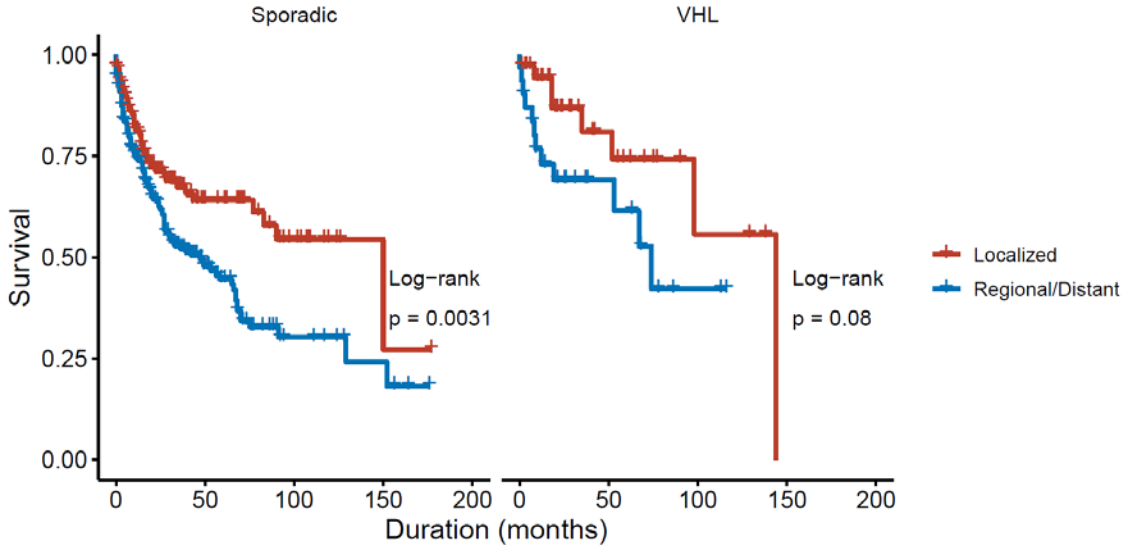
Results
Kaplan-Meier Analysis – Comparison by PNET Grade

Grade



- Similar trend of higher ACM risk in VHL-related and sporadic PNET

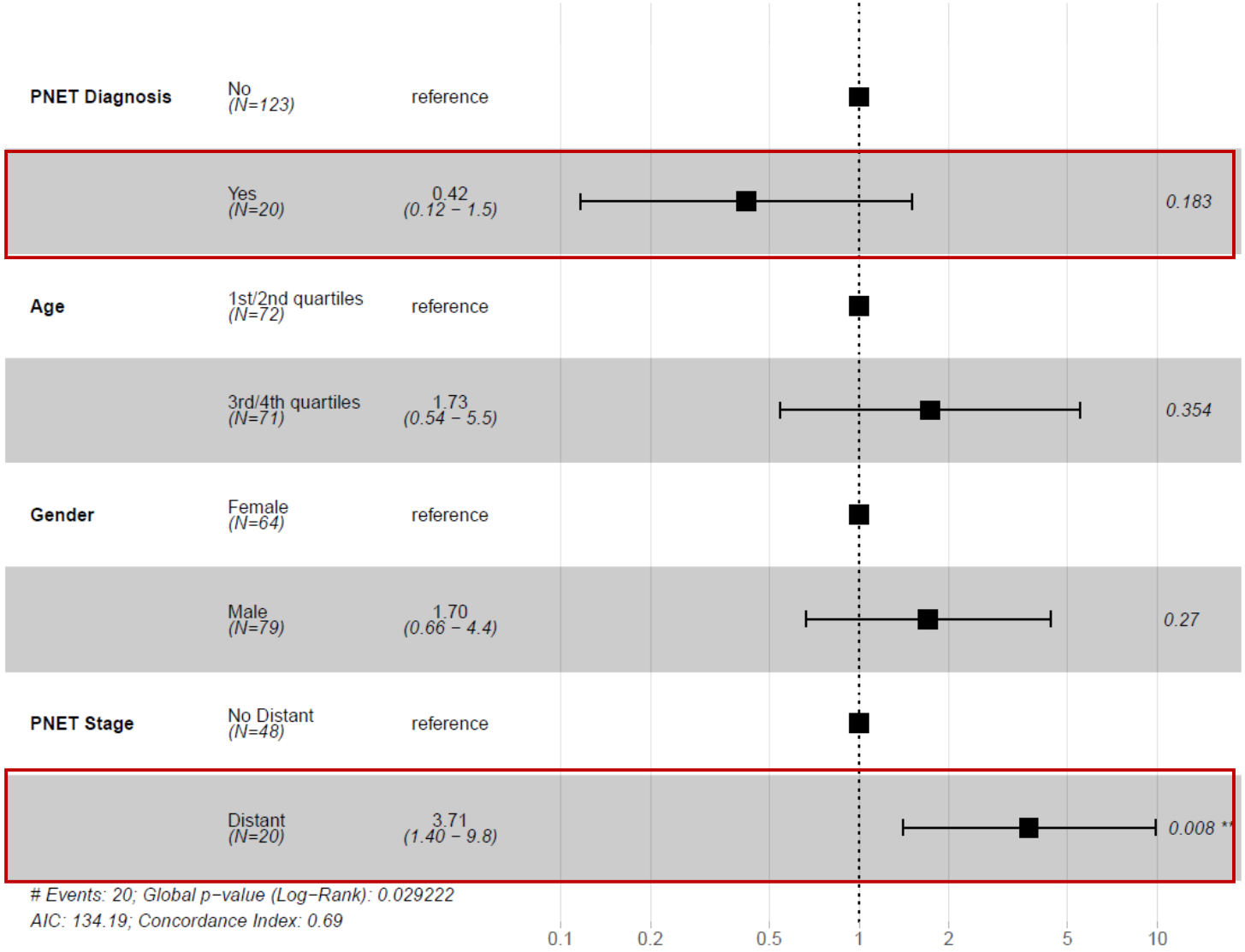
Stage



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

Multivariable analysis

- Diagnosis with PNET by itself did not confer increased 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).



Conclusions

- Diagnosis with PNET is not an independent risk factor for ACM in patients with VHL
- The presence of metastatic PNET may be associated with increased mortality risk, necessitating active surveillance to detect PNET at early stage, to allow timely prophylactic intervention.

Thank You For Your Attention!

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