All-Cause Mortality Among Patients with von Hippel-Lindau (VHL) Disease and Pancreatic Neuroendocrine Tumors

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Introduction: VHL diagnosis is based on a family history of VHL and one VHL-related manifestation. Additional criteria include detection of two HBs or one HB and visceral neoplasm ("International Criteria"), or detection of any two VHL-related manifestations ("Danish Criteria"). VHL-related morbidity and mortality are related mainly to central nervous system HB and RCC. Nevertheless, a poor prognosis may also be associated with subset of the patients harboring PNET, which may metastasize.

Aim: To assess the impact of diagnosis with PNET in patients with VHL on their risk for all-cause mortality (ACM).

Methods: Retrospective analysis based on the Surveillance, Epidemiology and End Results (SEER) database, including patients diagnosed with HB, RCC, PNET or pheochromocytoma. VHL diagnosis was determined according to the international/Danish criteria. Risk for ACM was compared among patients with VHL, with/without detection of PNET.

Results: Among 16,344 patients (age at diagnosis 63.7±11.5 years, 5,428 [33.2%] women), 159 (1.0%) were diagnosed with VHL, defined by co-diagnosis with RCC and PNET (n=80), RCC and HB (n=74) or RCC and PPGL (n=5). Of them 91 had VHL- related PNET, and 419 had sporadic PNET. Patients with VHL-related PNET (54.0±14.0 years) were younger at PNET diagnosis compared to those with sporadic PNET (60.2±13.0 years, $p<0.001$).

Stratification according to VHL diagnosis status demonstrated a comparable risk for ACM among patients with sporadic PNET vs. patients with sporadic HB, RCC or pheochromocytoma ($p=0.4$), whereas among patients with VHL, risk for ACM was higher among patients with PNET diagnosis vs. without ($p=0.011$)

The risk for ACM was higher in sporadic PNET patients with metastatic disease ($p=0.0057$) while among patients with VHL-related metastatic PNET there was similar trend ($p=0.1$).

Among patients with any type of PNET and with VHL-related PNET a higher risk for ACM was found in PNET diameter size ≥30mm vs. 11-29mm ($p=0.06$ and $p=0.1$, respectively).

In patients with sporadic PNET, a higher risk for ACM was found in grade 4 vs. grade 1 ($p=0.0001$), grade 4 vs. grade 2 ($p=0.005$) and grade 4 vs. grade 3 ($p=0.08$).

In multivariable analysis including patients with VHL, diagnosis with PNET by itself did not confer increased for ACM (HR 0.82, 95% CI 0.22-3.2, $p=0.8$). However, we found a trend for an increased risk for ACM among patients with metastatic PNET (HR 2.5, 95% CI 0.98-6.5, $p=0.055$). The small number of events (n=18) may explain the lack of statistical significance.

Conclusion: Diagnosis with PNET is a risk factor for ACM in patients with VHL. However, when considering the multiple potential co-manifestations of VHL, PNET by itself does not constitute independent risk factor for all-cause mortality. However, the presence of metastatic PNET may be associated with increased mortality risk, hence necessitating active surveillance to detect PNET at early stage, to allow timely prophylactic intervention.