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Computerized Mutation Prediction Models May be Used to Determine VHL-Associated PNETs Aggressiveness

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BACKGROUND: About 20% of patients with von Hippel-Lindau disease (vHLd) harbor pancreatic neuroendocrine tumors (PNETs). vHLd patients with missense VHL mutations have more severe phenotype, reflected also by higher risk to develop PNETs metastases. In the current analysis we aimed to further define PNETs prognosis according to VHL genotype.

METHODS: A prospective study of patients with vHLd and pancreatic lesions with imaging follow-up. Prediction of VHL mutation impact was analyzed using five computational prediction models (PolyPhen-2: HumVar and HumDiv, SNPs&Go, PANTHER and PhD-SNP). Patients were divided into those with prediction >80% for disease causing mutations in all models (High predicted risk, HPR), and others (Low predicted risk, LPR). The risk for metastases, requiring an intervention and disease progression (>20% growth of the largest lesion) during follow-up were compared between the groups. Patients with >1 prediction with low reliability index (<5) were excluded.

RESULTS: 69 patients with missense VHL mutations, 13 patients were excluded for low prediction reliability. In the remaining 56 patients (45 with PNETs, 11 with pancreatic cysts), 43 and 13 were included in the HPR and LPR groups, respectively. Two patients developed metastatic disease, 12 required surgical

intervention and 31 had disease progression during a median follow-up of 60 months (range 13-84).

In the survival analysis, HPR group had higher rate of disease progression both in univariate (log-rank test, p=0.006), and multivariable analysis, controlling for number of PNETs, evaluation rate, hotspot mutation, gender, age and tumor diameter (hazard ratio 3.6, 95% CI 1.1-11.9, p=0.037), and for developing metastases (p=0.015). Among the patients with codon 167 hotspot mutations (n=26), those in HPR vs. LPR groups had higher risk for disease progression (p=0.03).

CONCLUSION: Computational models for predictions of the VHL protein function may be used as a prognostic factor in patients with PNETs in the context of vHLd.