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RUNX1T1 and Palladin Outperform Pathologic Criteria of Malignancy in Predicting Liver Metastases in Primary Pancreatic Endocrine Carcinomas

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Background: The clinical course of pancreatic endocrine tumors/carcinomas (PETs/PECAs) is currently unpredictable with substantial variability in rate of disease progression and patient outcomes. Using Affymetrix platform, we discovered and validated a set of molecular markers of metastases including RUNX1T1 and palladin. Here we present a comparative analysis of RUNX1T1 and palladin versus conventional pathologic criteria of malignancy as predictors of liver metastasis in primary pancreatic endocrine neoplasms.

Patients and Methods: Thirty-five primary well-differentiated (WD) PETs/PECAs (13 metastatic, 22 clinically localized) were immunostained for RUNX1T1 (Sigma) and palladin (ProteinTech) proteins on a custom-designed tissue microarray (TMA). Expression of these markers was quantified by the Allred-score, based on intensity (1-3) and % stained cells (0-5). Allred-score thresholds for optimal sensitivity and specificity of each marker were determined by receiver operating characteristic (ROC) analysis. Using those thresholds, the predictive accuracy of each marker was compared with conventional pathologic criteria of malignancy: Tumor size, mitotic count, Ki-67 index, and tumor necrosis (Fisher's exact test).

Results: *Metastatic primaries (MP-PECAs) (N=13):* Presence of liver metastases was more accurately predicted by the molecular markers [RUNX1T1-11/13 (85%), palladin-13/13 (100%)] than the pathologic criteria. *Non-metastatic PETs (N=22):* Absence of liver metastases was more frequently predicted by the molecular markers and mitotic-count [RUNX1T1-21/22 (95%), palladin-15/22 (68%), mitotic-count 17/22 (77%)] than other pathologic criteria. Overall, *RUNX1T1* had higher predictive accuracy to identify patients *with and without* liver metastases than mitotic-count ($p=0.02$), Ki-67 index ($p=0.01$), tumor size ($p=0.004$) and necrosis ($p=0.03$). However, predictive accuracy of *palladin* was higher than mitotic-count ($p=0.01$), tumor size ($p=0.02$) and necrosis ($p=0.001$).

Conclusion: In pancreatic endocrine neoplasms, molecular markers (RUNX1T1 and palladin) emerge as more accurate predictors of liver metastases than conventional pathologic criteria. These proteins may serve as surrogate markers to identify patients with resected, clinically localized primaries who may benefit from close surveillance and adjuvant therapy trials.