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Metastasis-associated Gene Products and Liver Metastases in Pancreatic Endocrine Tumors

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Background: Patient outcome in well-differentiated pancreatic endocrine tumors can be difficult to predict based exclusively on pathologic criteria. We recently identified a novel set of 3 metastasis-associated genes by microarray analysis of fresh-frozen pancreatic endocrine neoplasms: Palladin, p21, RUNX1T1. The aim of this analysis was to evaluate the potential for these markers, individually or in combination, to predict liver metastases as an indicator of adverse outcome.

Methods: Palladin, p21, and RUNX1T1 immunostains were carried out on a tissue microarray of 39 resected primary pancreatic endocrine neoplasms, 14 of which had hepatic metastases. The Allred score was independently determined by 2 pathologists as the sum of stain intensity (scored 0-3) and % cells stained (scored 0-5). Receiver operating characteristic (ROC) analysis was used to choose the cutpoint in Allred score (high vs low protein expression) to optimize sensitivity and specificity for predicting liver metastases.

Results: Nearly all tumors with liver metastases showed high Palladin and p21 expression (Allred score > 3 and > 4, respectively), while expression was lower in the majority of non-metastatic tumors. In contrast, RUNX1T1 expression was low (Allred score < 4) in most tumors with liver metastases, but was higher in all except one of the non-metastatic tumors. Individual test sensitivities for predicting liver metastases were 100% for high Palladin, 93% for high p21 and 85% for low RUNX1T1, while corresponding specificities were 63%, 75%, and 96%. Tumors were correctly classified as being metastatic or not (predictive accuracy) by Palladin, p21, or RUNX1T1 expression in 76%, 76%, and 92% of cases, respectively. If abnormal expression of even one of 3 proteins is considered a positive test (parallel testing), then sensitivity of all 3 together for predicting liver metastases was 100%, specificity 48%, and predictive accuracy 68%.

Conclusions: 1) High Palladin, high p21, or low RUNX1T1 expression have good sensitivity and specificity for predicting liver metastases in pancreatic endocrine tumors. 2) Parallel testing with all 3 markers achieved 100% sensitivity but at a cost of reduced specificity. 3) Differential expression of these biomarkers may predict aggressive tumor behavior that warrants more aggressive management.