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Expression of CDX 1 and 2 Distinguishes Periapillary Lesions by Site of Origin, Tumor Stage, Metastatic Potential, and Patient Outcome

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Periapillary lesions frequently pose a diagnostic dilemma regarding site of neoplastic origin; pancreatic ductal adenocarcinomas, ampullary carcinoma, and biliary tract carcinoma can present as periapillary masses demonstrating a similar invasive histology, but profoundly different long-term survival rates. To date, no reliable immunohistochemical marker is available to categorize these lesions either by site of origin or by biologic behavior. We have identified ectopic expression of the homeodomain transcription factors CDX 1 and CDX 2 in 40-50% of ampullary cancers and in 7% of extrahepatic biliary tract carcinomas, but not in pancreatic ductal adenocarcinomas. Furthermore, high frequency CDX 1 and CDX 2 expression correlated with favorable histologic and staging parameters in these lesions. Within ampullary cancers, high frequency CDX 1 expression occurred in 83% of T1 lesions, but only 21% of T3 lesions (Fisher's exact test, $p = 0.0177$). A significant relationship was also identified between CDX 1 expression and concurrent lymph node metastases in ampullary cancers;. Low frequency (<25% labeling) CDX 1 expression was associated with a 68% risk of nodal metastases as compared to a 31% risk for high frequency ($\geq 25\%$ labeling) CDX 1 labeling (Fisher's exact test, $p = 0.0316$). In all studies, CDX 2 expression tended to mirror CDX 1, although CDX 2 did not achieve significance with respect to predicting T stage or N stage. Examination of 53 specimens of ampullary cancer demonstrated that CDX 1 and 2 expression in ampullary cancer significantly influenced patient outcome. Patients expressing CDX 1 demonstrated a median survival of greater than 5 years versus 20 months for patients lacking expression of CDX 1 ($p = 0.0173$). Similarly, CDX 2 expression correlated with a median survival of greater than 45 weeks versus 20 weeks for non-expressors ($p = 0.0217$). We propose that CDX 1 and CDX 2 may serve as a useful diagnostic tool for periapillary lesions of unknown origin and may function as useful predictors of aggressive biology and patient outcomes.

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