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Real-Time Prospective DAXX/ATRX Testing of 186 Consecutive Surgically Resected Pancreatic Neuroendocrine Tumors Reveals Loss of Expression Correlates with Distant Metastasis

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BACKGROUND

Pancreatic neuroendocrine tumors (PanNETs) are a heterogeneous group of neoplasms with increasing incidence and unpredictable behavior. Whole-exome sequencing studies of metastatic PanNETs have found recurrent genomic alterations in DAXX and ATRX, which correlate with corresponding loss of protein expression. Loss of DAXX/ATRX in PanNETs is reported to be associated with several, adverse clinicopathologic features and poor patient disease-free survival (DFS). However, prior studies have been retrospective in nature and, therefore, the aim of this study was to prospectively evaluate the status of DAXX/ATRX among surgically resected PanNETs and assess its prognostic clinical significance.

METHODS

Within a timeframe of 5 years, 186 consecutive patients underwent surgical management for a primary PanNET. This patient cohort included 175 non-functional PanNETs, 10 insulinomas, and 1 somatostatinoma. Additionally, 7 patients had multiple endocrine neoplasia type 1 (MEN1) and 1 patient had von Hippel Lindau (VHL) syndrome. The status of DAXX/ATRX was immunohistochemically evaluated as part of routine pathologic assessment for each surgically resected PanNET. The results of DAXX/ATRX staining were correlated with standard clinicopathologic features and patient follow-up that ranged from 5 months to 5 years (median, 2.25 years).

RESULTS

Loss of DAXX, ATRX, both proteins, or either protein within the prospective cohort was identified in 26 (14%), 21 (11%), 1 (1%), and 46 (25%) cases. DAXX/ATRX loss was associated with tumor size of >2.0 cm (94% vs 56%, $p< 0.001$), higher WHO grade (41% vs 14%, $p< 0.001$), perineural invasion (72% vs 29%, $p< 0.001$), lymphovascular invasion (87% vs 42%, $p< 0.001$), synchronous distant metastasis (26% vs 9%, $p=0.004$), and the development of metachronous distant metastases (35% vs 6%, $p< 0.001$). No statistical significance was observed between DAXX/ATRX status and functional status or predisposing syndrome. Among patients without synchronous distant metastases (n=162, 87%), the 3-year DFS for patients with DAXX/ATRX-negative PanNETs was 65% as compared to 95% for DAXX/ATRX-positive PanNETs. By multivariate analysis to include WHO grade, T-stage, and N-stage, loss of DAXX/ATRX was a negative, independent prognostic factor for DFS ($p=0.023$).

CONCLUSIONS

Consistent with retrospective studies, the detection of DAXX/ATRX loss in surgically resected PanNETs was associated with multiple adverse clinicopathologic features and an increased risk of patients developing distant metastatic disease. While continued long-term follow-up is being accrued for this study cohort, the assessment of DAXX/ATRX should be clinically considered in the prognostic evaluation of surgically resected PanNETs.

ABSTRACT ID 23368