Title:

Non-Functional Pancreatic Neuroendocrine Tumors: ATRX/DAXX and Alternative Lengthening of Telomeres (ALT) Assess Prognosis Independently from Islet-Cell Subtype and Tumor Size

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Abstract:

Background: Recent studies have found the classification of NF-PanNETs using ARX/PDX1 expression that define islet-cell subtype and the status of ATRX/DAXX and ALT to be promising prognostic biomarkers. However, they have not been comprehensively evaluated, especially among small NF-PanNETs (=2.0 cm). Moreover, their status in neuroendocrine tumors (NETs) from other sites remains unknown.

Materials and Methods: An international cohort of 1,241 NETs was evaluated by immunolabeling for ARX/PDX1 and ATRX/DAXX, and telomere-specific fluorescence in situ hybridization for ALT. This cohort included 561 primary NF-PanNETs, 82 metastatic NF-PanNETs, and 598 primary/metastatic non-pancreatic NETs. The results were correlated with numerous clinicopathologic features including relapse-free survival (RFS).

Results: ATRX/DAXX loss and ALT were associated with several adverse findings and distant metastasis/recurrence ($p<0.001$). The 5-year RFS rates for patients with ATRX/DAXX-negative and ALT-positive NF-PanNETs were 40% and 42% as compared to 85% and 86% for wild-type NF-PanNETs ($p<0.001$ and $p<0.001$). Shorter 5-year RFS rates for =2.0 cm NF-PanNETs patients were also seen with ATRX/DAXX loss (65% vs. 92%, $p=0.003$) and ALT (60% vs. 93%, $p<0.001$). By multivariate analysis, ATRX/DAXX and ALT status were independent prognostic factors for RFS. Conversely, classifying NF-PanNETs by ARX/PDX1 expression did not correlate with known prognostic factors, distant metastasis/recurrence or RFS. Except for 4% of pulmonary carcinoids, ATRX/DAXX loss and ALT were only identified in primary (25% and 29%) and metastatic NF-PanNETs (34% and 44%).

Conclusions: The status of ATRX/DAXX and ALT should be considered in the prognostic evaluation of NF-PanNETs including =2.0 cm tumors, and are highly specific for determining pancreatic origin for metastatic NETs of unknown primary.