TITLE: Evaluation of Cell Cycle Regulators in 205 Thyroid Lesions Reveals the Diagnostic Utility of p16, p21, cyclinD1 and cyclinE

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ABSTRACT BODY:
Introduction: Differentiated thyroid cancer (DTC) generally has a favorable outcome, but there remain some patients who develop local recurrence and/or distant metastases, and ultimately succumb to their disease. Currently, there is a lack of clinically utilized molecular markers that accurately predict tumor behavior. The aim of this study was to ascertain the role of 9 cell cycle regulators (p16, p21, p27, p53, p57, p63, cyclinD1, cyclinE and mdm2) in predicting malignant histology and tumor behavior in DTC.

Methods: Tissue microarrays consisting of 100 benign and 105 malignant thyroid lesions, as well as 24 lymph node samples from node-positive cancer patients, were stained for p16, p21, p27, p53, p57, p63, cyclinD1, cyclinE and mdm2. The chi-squared test was utilized to compare the expression of the markers in benign versus DTC lesions and correlate their expression with patient clinicopathologic characteristics. A p value of less than 0.05 was considered statistically significant.

Results: p16, p21, cyclinD1 and cyclinE showed significantly increased expression in DTCs when compared to benign thyroid lesions (54.2% vs. 5%, $p<0.001$; 68.8% vs. 38%, $p<0.001$; 77.1% vs. 43%, $p<0.001$; 70.1% vs. 37%, $p<0.001$ respectively). For the remaining 5 markers (p27, p53, p57, p63 and mdm2), there was no significant difference in their expression between benign and DTC lesions. The expression of p16 correlated significantly with extrathyroidal tumor extension ($p=.02$) and lymph node positivity ($p=.03$).

Conclusion: Expression of the cell cycle regulators p16, p21, cyclinD1 and cyclinE helps distinguish DTCs from benign thyroid lesions. Furthermore, p16 expression correlates with clinicopathologic variables that predict poor outcome in DTC. These results suggest that evaluation of the derrangement of the cell cycle in thyroid tumors may serve as a useful tool for DTC diagnosis.