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Title: Characterizing the mutational landscape of pediatric thyroid nodules and assessing the utility of molecular testing in their surgical management
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Background: Molecular genetic testing used in conjunction with cytopathology may improve prediction of malignancy in thyroid nodules. While genetic profiling is common in adult patients, pediatric data are limited. We sought to investigate the correlation of molecular genetics of pediatric nodules to cytologic and histologic classification at time of definitive treatment and the distribution of mutations in pediatric thyroid nodules.

Methods: Retrospective single-institution chart review of 164 patients <22 years with available FNA or final histopathology molecular testing who underwent surgical resection of a thyroid nodule between February 2002 and July 2020. Molecular data was compared to reported cytology as well as final histopathology.

Results: 85 (52%) patients with a mean age of 16.7 years had molecular genetic testing performed pre-operatively by FNA (70), post-operatively on surgical pathology specimens (12), or both (3). BRAF V600E testing was performed on 84 patients, 31 (37%) of which were positive. Of the remaining 54, 21 had testing for additional mutations and fusions. In 12 (57%) of these, an alternate mutation/fusion (3 NRAS, 3 DICER1, 1 NTRK-TPR, 2 PAX8-PPARG, 2 ETV6-NTRK3, 1 STRN-ALK) was identified. Additionally, 1 RET-PTC mutation was identified in the patient who did not undergo BRAF testing. All 3 NRAS mutations were associated with benign adenomas while BRAF, DICER1 mutations, and gene fusions predicted malignancy in 100% of cases. BRAF mutations were found almost exclusively in Bethesda V and VI and were associated with classic papillary thyroid carcinoma. Of the 10 remaining non-BRAF malignant mutations, 7 (70%) were found in nodules classified as Bethesda IV on cytopathology, and of those, 5/7 were associated with thyroid cancer variants other than classic PTC. For Bethesda III and IV lesions, the presence of BRAF or DICER mutations or gene fusion had a 62% sensitivity, 100% specificity, 100% PPV, and 69% NPV. In Bethesda IV nodules, identification of gene fusion or DICER mutations altered or would have altered surgical decision making (upfront thyroidectomy rather than lobectomy) in 70% of the nodules submitted for genetic testing.

Conclusion: Expanded molecular genetic testing on FNA specimens of pediatric patients with thyroid nodules, particularly those with indeterminate cytology, can improve surgical decision-making and prediction of malignancy and should be used in pre-operative assessment of thyroid nodules.