Abstract #1168

SYSTEMATIC REVIEW OF THE POSITIVE PREDICTIVE VALUE OF RAS MUTATIONS IN CYTOLOGICALLY INDETERMINATE THYROID NODULES

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Objective: The positive predictive value (PPV) of RAS mutations in cytology indeterminate (cyto-I) Bethesda Category III, IV or V nodules is uncertain, and factors accounting for differences between publications are unknown.

Methods: We conducted a systematic literature review in PubMed through 12/1/2015. Studies were included that reported RAS mutations in cyto-I nodules with confirmed histology. We abstracted the true positive (TP), false positive (FP), true negative (TN), and false negative (FN) rates of RAS mutations in cyto-I categories. Meta analyses were constructed calculating the sensitivity, specificity, and PPV of RAS mutations in cyto-I nodules.

Results: Seventeen studies reported clinical or surgical follow-up for all cyto-I nodules positive and negative for RAS mutations. Among these 2,035 cyto-I nodules, RAS mutations had a sensitivity for detecting malignancy of 30.4% and a specificity of 94.0%. In total, 264 (13.0%) RAS mutations were identified in histology benign and malignant nodules. A meta-analysis was performed of 19 studies reporting the TP and FP rates for RAS mutations with surgical follow-up in 2,099 nodules. The overall RAS PPV was 67.7% (range 13.3%-100%). In only 4 studies the histopathologist was blinded to the RAS mutation status. There was a discordance in the overall PPV between studies with unblinded histopathology compared to blinded studies (68.8% vs 60.0%, respectively). Furthermore, when comparing the 6 UPMC based studies (all unblinded) vs the 13 nonUPMC studies there was a significant difference in the overall PPVs (84.0% vs 51.5% respectively, $p<0.01$).

Discussion: Multiple studies report the PPV of RAS mutations among cyto-I nodules. With few exceptions, these studies are single-center retrospective clinical experience studies with unblinded histology leading to significant variation in the reported PPV. The significant probability of nodule benignity despite a RAS mutation limits its role in surgical decision making. In addition, RAS mutation analysis misses 70% of cancers in cyto-I nodules. Together, these findings raise questions about the validity of this biomarker to rule-in or rule-out thyroid carcinoma.

Conclusion: The reported PPV of a RAS mutation is highly variable. Unblinded pathologists diagnose RAS mutated thyroid nodules as malignant more frequently than those blinded to the molecular test result. These findings raise significant questions about the value and accuracy of RAS mutations to identify or predict malignancy in cyto-I thyroid nodules. Physicians should be cautious that pathologists are more likely to label a nodule as malignant when they know a RAS mutation is present. This bias may result in cancer over-diagnosis and over-treatment.