# RAS Mutations and Associated Risk of Malignancy in the Thyroid

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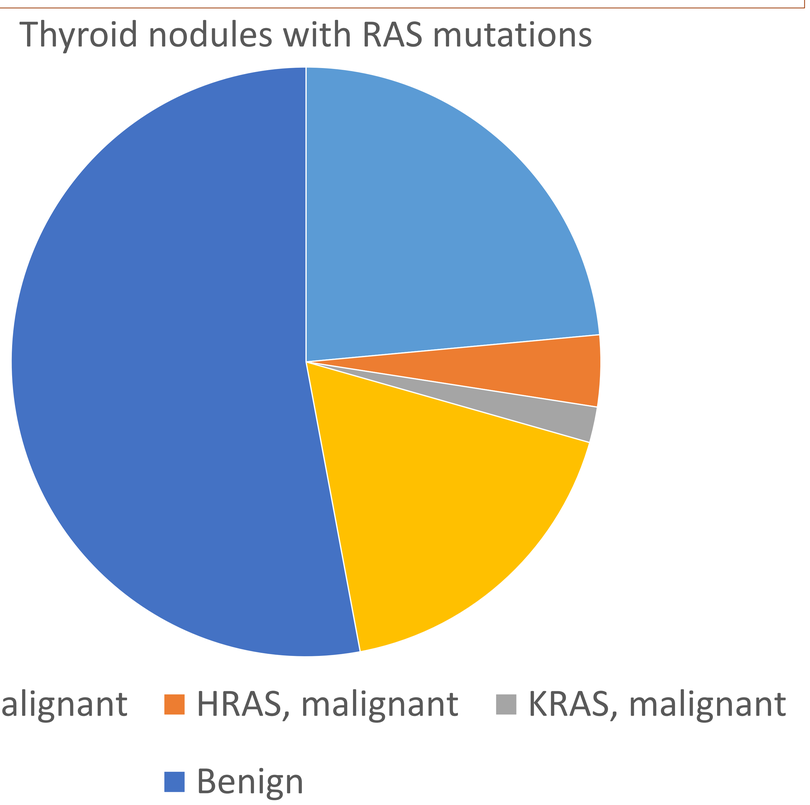
## Introduction

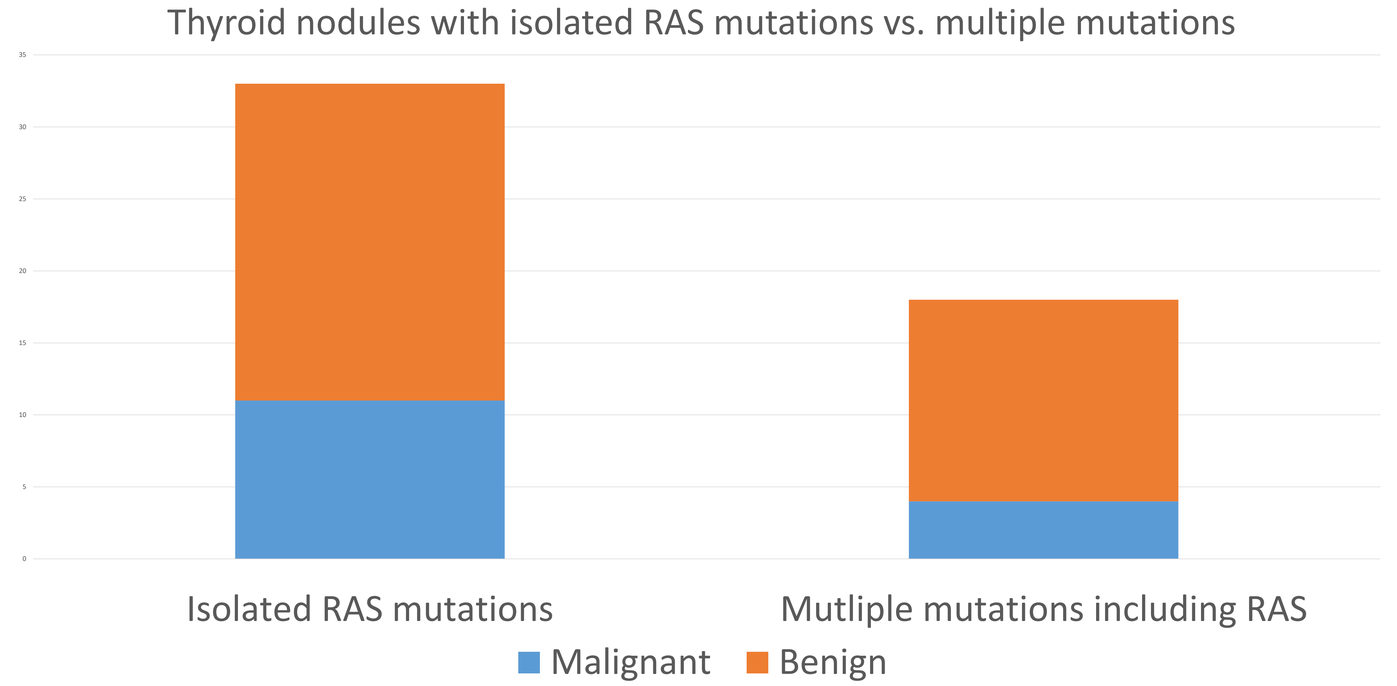
As the incidence of thyroid cancer increases, next generation sequencing panels, like Thyroseq, are advancing surgical planning capabilities in indeterminate thyroid nodules[1]. RAS mutations are found in both benign and malignant thyroid nodules[2]. This study aimed to describe rates of malignancy in a retrospective cohort of patients with thyroid nodules characterized as Bethesda III/IV on fine needle aspiration (FNA) cytology and with RAS mutation on Thyroseq molecular testing.

## Methods and Materials

We identified all thyroid FNA cases between March 2016 to January 2021 with any type of RAS mutation on Thyroseq molecular testing and determined which nodules were removed surgically. The Thyroseq results and the final histological diagnosis were recorded. Final tissue histology of individuals who had surgical excision performed was described and compared by RAS mutation on Thyroseq to characterize frequencies of cases diagnosed as malignant (risk of malignancy (ROM)).




**Graph 1.** Pathologic category of thyroid nodules with RAS mutations




**Graph 2.** Pathologic category of thyroid nodules with isolated RAS mutations vs multiple mutations including RAS

## Results

- A total of 64 cases were identified to have RAS mutations (with or without any molecular alterations).
- Of these cases, 51 were surgically excised with final histology. The overall ROM among this cohort was 29% (15/51).
- The ROM was higher among cases with RAS mutations only (11/33; 33%) versus cases with additional mutations (4/18; 22%), however the difference was not statistically significant (p=0.53).
- ROMs among isolated NRAS, HRAS, and KRAS mutations were 35% (12/34), 15% (2/13), and 25% (1/4), respectively.
- Cases with a Bethesda IV cytologic diagnosis had a similar ROM (4/12; 33%) to the cases with a category III diagnosis (11/39; 28%).
- Nine of the 51 cases (17%) were Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) with 47% (24/51) of the cases being either malignant or NIFTP. Of the 15 malignant cases, 13/15 (87%) were PTC, and 2 (13%) were FTC.

## Conclusions

The overall ROM among Bethesda III/IV thyroid nodules with RAS mutations at our institution was 29%. Isolated NRAS mutations appeared to have a higher ROM (35%) than HRAS and KRAS mutations (18%), however more work is needed to characterize potential variation in ROM in larger cohorts. 47% of RAS mutation nodules were malignant or NIFTP.

## References

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