THU-680

Cytologic and Molecular Assessment of Isthmus Thyroid Nodules

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INTRODUCTION

- Thyroid nodules arising in the isthmus are more likely to be malignant and demonstrate more aggressive behavior relative to thyroid nodules from either thyroid lobe.[1,2]
- Preliminary studies of papillary thyroid cancers (PTC) studied in The Cancer Genome Atlas (TCGA) indicate molecular profiles that may explain the more aggressive phenotype of isthmic PTC, including an increased ERK signaling molecular profile.[3]

STUDY GOAL

The goal of this study was to interrogate the Veracyte thyroid nodule database and assess cytologic and molecular differences of thyroid aspirates sent for Afirma Genomic Sequencing (GSC) testing from isthmus nodules relative to lobar nodules.

RESULTS

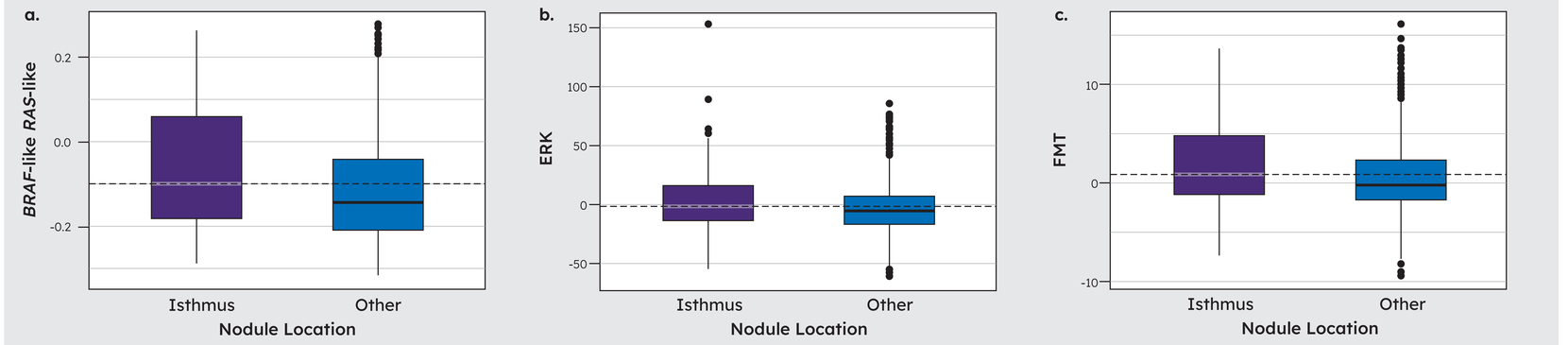
- Samples from isthmus nodules represented 4.8% of all samples.
- Relative to lobar nodules, isthmus nodules **(Table 1)**:
  - Had a lower proportion of Bethesda III/IV cytology
    - 91.8% isthmus vs 95.7% lobes
  - Had a higher proportion of Bethesda V/VI cytology
    - 8.2% isthmus vs 4.3% lobes
      - All results significant (p<0.001)
- There was no significant difference in the Afirma-benign vs Afirma-suspicious result in isthmus nodules as compared to lobar nodules
- Molecular alterations in Afirma-suspicious isthmus nodules vs lobar nodules **(Table 2)**
  - *BRAF*V600E: Isthmus – 20.8%, Lobe – 10%
  - *ALK/NTRK/RET* fusions: Isthmus – 4.6%, Lobe – 2.6%
  - *NRAS*: Isthmus – 7.7%, Lobe – 12.8%
  - *HRAS*: Isthmus – 4.5%, Lobe – 8.1%
    - All results significant (p<0.001)
- Isthmus nodules had significantly higher *BRAF*-like signature, ERK signaling, and follicular-mesenchymal transition scores compared to lobar nodules **(Figure 1)**
  - (p < 0.01)

TABLE 1. BETHESDA CYTOLOGY OF ISTHMUS NODULES COMPARED TO LOBAR NODULES:

	Bethesda III/IV	Bethesda V/VI	Sum
Isthmus	7828 (91.8%)*	699 (8.2%)*	8527
Non-Isthmus	161,529 (95.7%)*	7171 (4.3%)	168,700
Sum	169,357 (95.6%)	7870 (4.4%)	177,227
% Isthmus	4.6%	8.9%	4.8%

* = p<0.01

FIGURE 1. ISTHMUS NODULES HAD SIGNIFICANTLY HIGHER BRAF-LIKE SIGNATURE, ERK SIGNALING, AND FOLLICULAR-MESENCHYMAL TRANSITION (FMT) SCORES COMPARED TO LOBAR NODULES



Wilcoxon test was applied with Isthmus set as the reference group (p <0.01)

TABLE 2.

XA Positive Findings	NODULE LOCATION			Isthmus in Comparison to Lobe
	Isthmus	Lobe	Average	
BRAF:p. V600E	20.8%***	10.4%***	10.9%	High in Isthmus
*ALK/NTRK/RET*_Fus	4.6%***	2.5%***	2.6%	
*SPOP*_Var	1.5%***	0.8%***	0.8%	
*NRAS*_Var	7.7%***	13%***	12.7%	Low in Isthmus
*HRAS*_Var	4.5%***	8.2%***	8%	
*PAX8*_PPARG	1.1%***	2.3%***	2.2%	
*RET*_Var	0.1%**	0.5%**	0.5%	
*KRAS*_Var	1.7%	1.9%	1.9%	No Significant Difference
*DICER1*_Var	1.5%	1.4%	1.4%	
*TSHR*_Var	1.1%	1.1%	1.1%	
BRAF:p.K601E	0.8%	1%	1%	
*BRAF*_Fus	0.7%	0.6%	0.6%	
*EIF1AX*_Var	0.5%	0.5%	0.5%	

Percent XA_group: 0 5 10 15 20

SUMMARY

- Thyroid nodules sent for Afirma molecular testing arising from the isthmus are more likely to have Bethesda V and VI cytology and, amongst Afirma suspicious ITN and Bethesda V and VI lesions, have higher levels of molecular markers of aggressiveness relative to lobar nodules.
- This study expands upon the data seen in histologic PTC samples from the TCGA as the fresh fine needle aspiration samples of most thyroid tumors referred for molecular testing have Bethesda III and IV cytology and thus are enriched for follicular lesions including follicular variants of PTC and follicular carcinomas.

FUTURE DIRECTIONS

Future studies should investigate the final histopathology of these molecularly tested isthmus nodules as well as oncologic outcomes.

REFERENCES

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3. Eileen R. Smith, MD, C. Corbin Frye, MD, Sina Jasim, MD, MPH, T.K. Pandian, MD, MPH, William E Gillanders, MD, John A. Olson, MD, PhD, and Taylor C. Brown, MD, MHS. Molecular Characteristics of Isthmus Papillary Thyroid Cancers: Supporting Evidence for Aggressive Clinical Behavior. *AAES* 2023.