Molecular Assessment of Isthmus Thyroid Carcinomas

Sina Jasim, MD,[1] Allan Golding, MD,[2] David Bimston, MD,[2] Yang Chen, PhD,[3] Rouchen Jiang, PhD,[3] Mohammed Alshalalfa, PhD,[3] Yangyang Hao, PhD,[3] Jing Huang, PhD,[3] Joshua P. Klopper, MD,[3] Richard T. Kloos, MD,[3] Taylor C. Brown, MD[1]

1. Washington University in St Louis, Saint Louis, MO, USA. **2.** Memorial Healthcare System, Hollywood, FL, USA. **3.** Veracyte, Inc, South San Francisco, CA, USA.

INTRODUCTION

- Thyroid nodules arising in the isthmus are more likely to be malignant than lobar nodules.[1]
- Isthmic differentiated thyroid cancer (DTC) demonstrates more aggressive behavior compared to those arising from either lobe.[2]
- The objective of this study was to assess molecular differences of DTC arising from the isthmus as compared to DTC from lobar locations.

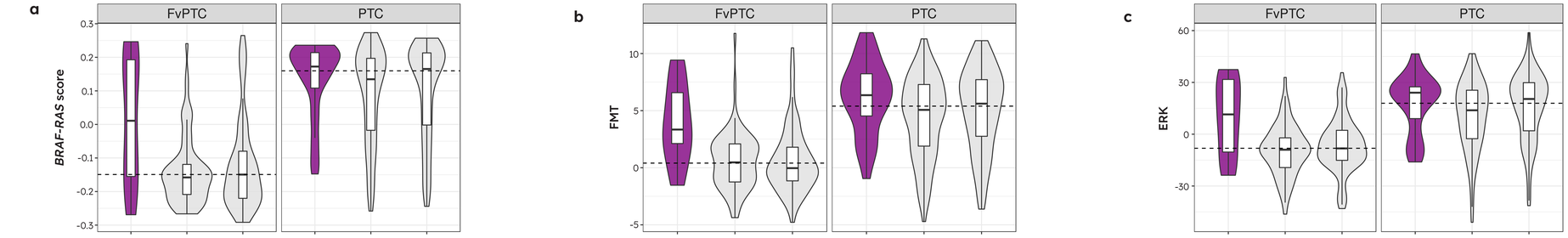
METHODS

- Histopathology reports (n = 541) from differentiated thyroid carcinoma (PTC [n=364] and FVPTC [n=177]) from Afirma Genomic Sequencing Classifier (GSC) algorithm training and from thyroid cancer patients managed at an integrative endocrine surgery community care practice were assessed for cytologic differences and gene expression signatures based on cancer location.

RESULTS

- 77% of the cohort were female with median age 48 yr. (IQR 37-58). 8.7% of samples were isthmus cancers and 87% of those were in women.
- FVPTC from the isthmus (n=13, 92% female, median age 56 yr. [50-59]) were more *BRAF*-like (like classic PTC) and had increased *ERK* and follicular mesenchymal transition scores (FMT) compared to those from either lobe (Wilcoxon rank-sum test p<0.05) (Figure 1a-c).
- PTC at the isthmus also showed higher FMT scores compared to those from the left lobe (but not the right lobe) and this difference was not noted for *BRAF*-like nor ERK scores (Figure 1a-c).
- FVPTC of the isthmus were more enriched with Bethesda V/VI cytology (cySFM/M) (7/13, 54%) compared to lobar FVPTC (30/163, 18%) (Fisher's exact test p<0.05). These Bethesda V/VI Isthmic FVPTC samples had significantly higher FMT and ERK scores than non-isthmic sites (p<0.05) though not compared to either lobe alone.
- There was no significant difference in the studied molecular characteristics from isthmic FVPTC arising from indeterminate cytology (Bethesda III/IV – CyI). This difference based on cytologic category was only seen in FMT and ERK with PTC when comparing the isthmus to the left lobe (Figure 2).
- *BRAF*V600E was the most common driver mutation seen in all samples.

FIGURE 1

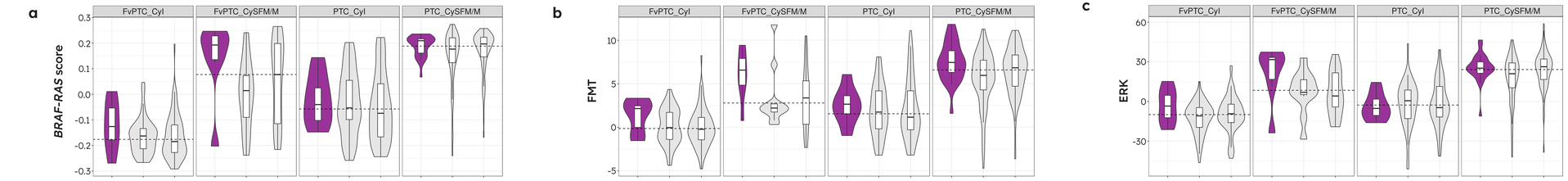


Nodule Location	Isthmus (n=13)	Left Side (n=71)	Right Side (n=93)	Isthmus (n=34)	Left Side (n=135)	Right Side (n=195)
Score Median	0.011	-0.158	-0.149	0.172	0.135	0.165
Adj P-value	ref	**0.017**	**0.017**	ref	0.277	0.415

Nodule Location	Isthmus	Left Side	Right Side	Isthmus	Left Side	Right Side
Score Median	3.343	0.469	-0.036	6.353	5.069	5.611
Adj P-value	ref	**0.002**	**0.002**	ref	**0.034**	0.143

Nodule Location	Isthmus	Left Side	Right Side	Isthmus	Left Side	Right Side
Score Median	11.46	-8.98	-8.23	24.04	13.85	20.40
Adj P-value	ref	**0.018**	**0.021**	ref	0.075	0.691

FIGURE 2



Nodule Location	Isthmus (n=6)	Left Side (n=59)	Right Side (n=74)	Isthmus (n=7)	Left Side (n=11)	Right Side (n=19)	Isthmus (n=9)	Left Side (n=45)	Right Side (n=61)	Isthmus (n=25)	Left Side (n=88)	Right Side (n=134)
Score Median	-0.126	-0.163	-0.185	0.193	0.014	0.077	-0.040	-0.053	-0.074	0.209	0.177	0.197
Adj P-value	ref	0.45	0.45	ref	0.13	0.31	ref	0.87	0.68	ref	0.25	0.65

Nodule Location	Isthmus	Left Side	Right Side	Isthmus	Left Side	Right Side	Isthmus	Left Side	Right Side	Isthmus	Left Side	Right Side
Score Median	2.155	-0.032	-0.221	6.573	2.214	3.376	2.656	1.750	1.166	7.450	5.963	6.838
Adj P-value	ref	0.22	0.22	ref	0.16	0.16	ref	0.80	0.80	ref	**0.025**	0.099

Nodule Location	Isthmus	Left Side	Right Side	Isthmus	Left Side	Right Side	Isthmus	Left Side	Right Side	Isthmus	Left Side	Right Side
Score Median	-3.46	-10.90	-9.25	31.71	6.95	4.19	-5.24	0.57	-4.63	25.23	21.04	26.31
Adj P-value	ref	0.35	0.35	ref	0.10	0.10	ref	0.73	0.73	ref	**0.049**	0.73

CONCLUSION

- Isthmic FVPTC have higher scores of *BRAF*-like molecular signatures, ERK, and FMT signaling relative to lobar cancers. Interestingly, classic PTC only showed higher levels of FMT and ERK in the isthmus relative to the left lobe (not the right). Whether this is due to biological differences in the left lobe of the thyroid versus the right needs to be investigated.
- Future studies should assess if a change in surgical therapy is warranted in isthmic thyroid cancers relative to lobar cancers and if this molecular data should influence isthmic thyroid cancer management and monitoring.

References

1. Pastorello R, Valerio E, Lobo A, Maia A, Saieg M. Do thyroid nodules that arise in the isthmus have a higher risk of malignancy? *Cancer Cytopathol.* 2020;128:520-2.
2. 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.

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