MON-649

Prostate-Specific Membrane Antigen (PSMA) Expression in Cytologically Indeterminate and Malignant Thyroid Nodules

Rabail Sadiq, M.B.B.S.,[1] Jonathon O. Russell, MD,[1] Paul W. Ladenson, MD,[1] Mohammed Alshalalfa, PhD,[2] Yangyang Hao, PhD,[2] Jing Huang, PhD,[2] Joshua P. Klopper, MD,[2] Richard T. Kloos, MD,[2] Prasanna Santhanam, MBBS, MD[1]

1. Johns Hopkins University School of Medicine, Baltimore, MD, USA. 2. Veracyte, Inc, South San Francisco, CA, USA.

INTRODUCTION

- Prostate-specific membrane antigen (PSMA), a transmembrane protein encoded by the gene FOLH1 is a relatively novel target for molecular imaging and therapy in prostate cancer imaging.
- PSMA-based positron-emission tomography (PET) imaging is approved in the United States for biochemical recurrence after prostate cancer treatment and supported by international guidelines.
- Recent literature reported that this receptor is often expressed on the cell membrane of neovascular endothelial cells of other solid tumors in addition to prostate cancer.
- Immunohistochemical studies reported that the intensity of neovasculature PSMA staining in papillary and follicular thyroid cancers correlated with more aggressive behavior.
- Several recent studies evaluated the performance of PET imaging with PSMA-targeting radiopharmaceuticals in thyroid diseases, especially for radioiodine-refractory thyroid cancer.
- Here we characterize the PSMA expression in a large set of thyroid nodules.

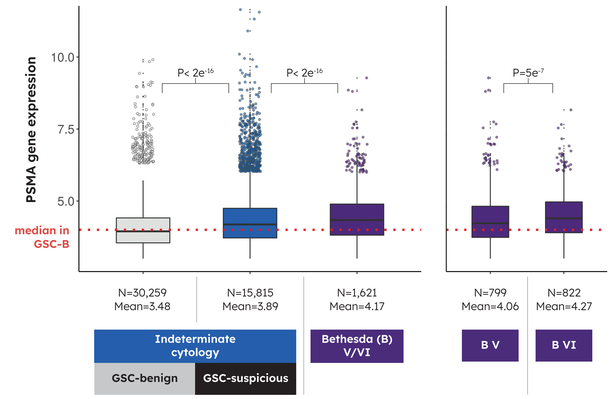
METHODS

- FOLH1 mRNA (PSMA) expression was analyzed in 47,695 thyroid nodule specimens sent for Afirma Genomic Sequencing Classifier (GSC) molecular testing.
- Differential PSMA expression was explored across Afirma benign and suspicious categories, cytology categories, and relative to different molecular alterations identified by the Afirma GSC and Xpression Atlas.
- Correlation analysis was conducted to assess correlation between PSMA and radioiodine transporters.

RESULTS

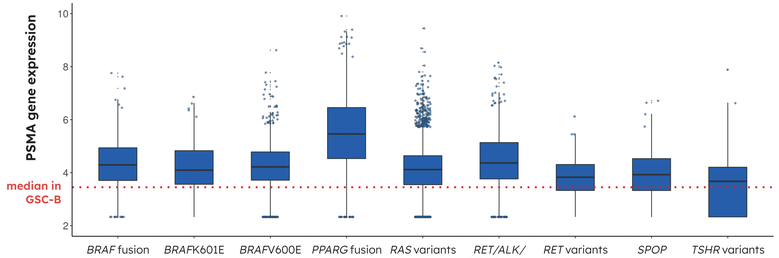
- There were 30,259 cytologically indeterminant (Bethesda III/IV) nodules classified as GSC-Benign (GSC-B) and 15,815 as GSC-Suspicious (GSC-S); 1,621 were cytologically Bethesda V or VI.
- Mean expression of PSMA gene was higher in GSC-S and Bethesda V/VI nodules compared to GSC-B. Relative to GSC-B, GSC-S and Bethesda V/VI had fold changes (FC) of 1.12 and 1.2, respectively (figure 1).
  - PSMA expression was higher in Bethesda VI compared to Bethesda V ($p=5e^{-7}$).
- Compared to GSC-B, GSC-S samples with *PAX8-PPARG, ALK/RET* fusions had higher PSMA expression (FC 1.57, 1.28, respectively, $p<2e^{-16}$ for both) (figure 2).
- Among Bethesda V/VI nodules, PSMA was higher in samples with *PPARG* fusions (*CREB3L2-PPARG, PAX8-PPARG*), *ALK*, or *RET* fusions compared to other alterations (p= 0.002) (figure 3).
- Samples with *TSHR* variants had the lowest PSMA expression in both GSC-S and Bethesda V/VI samples (FC 1.06 and 1.03 respectively with respect to GSC-B) (figures 2 and 3).
- A negative trend was observed between PSMA and sodium iodide symporter (NIS) expression with samples with highest PSMA having the lowest NIS expression (figure 4).

FIGURE 1.
FOLH1 (PSMA) Expression Across Cytogenomic Groups



- Mean expression of the PSMA gene was higher in cytologically indeterminate nodules that were classified as suspicious by Afirma GSC (GSC-S) and Bethesda V/VI (Cyto M/SFM) nodules as compared to GSC-Benign (GSC-B) (Wilcoxon rank-sum p-value < $2e^{-16}$ for both).
- PSMA expression was higher in Bethesda VI compared to Bethesda V ($p=5e^{-7}$)

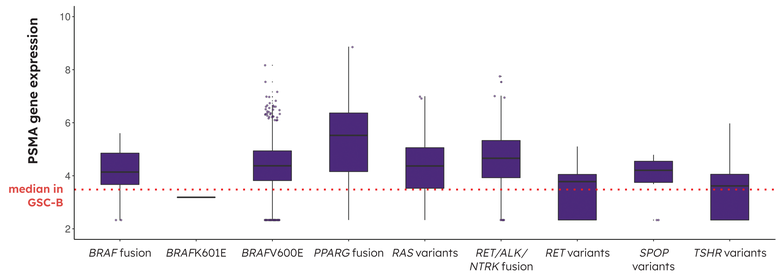
FIGURE 2.
PSMA Expression Across Most Common Genomic Alterations in GSC-Suspicious



	BRAF fusion	BRAFK601E	BRAFV600E	PPARG fusion	RAS variants	RET/ALK/ NTRK fusion	RET variants	SPOP variants	TSHR variants
FC (GSC-B)	1.24	1.17	1.22	1.57	1.17	1.28	1.1	1.11	1.06
Mean	4.33	4.09	4.24	5.48	4.08	4.45	3.79	3.87	3.54
N	116	176	791	384	3,964	362	55	144	179

- FC (GSC-B) — the fold change relative to the median level of GSC-Benign samples.
- Within GSC-S group, PSMA was highest in samples with *PPARG* fusions (p<0.0001 compared to all other alterations).
- Compared to GSC-B, nodules with *PPARG, BRAF, RET/ALK/NTRK* fusions have significantly higher expression (p<0.0001 for all).
- PSMA expression in thyroid is lower than PSMA in prostate cancers.
- PSMA expression is higher in samples with alterations compared to samples with no alterations (p<0.0001).

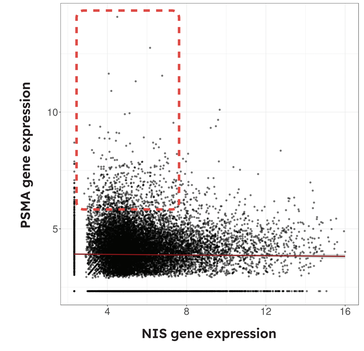
FIGURE 3.
PSMA Expression Across Most Common Genomic Alterations in Bethesda V/VI



	BRAF fusion	BRAFK601E	BRAFV600E	PPARG fusion	RAS variants	RET/ALK/ NTRK fusion	RET variants	SPOP variants	TSHR variants
FC (GSC-B)	1.21	0.91	1.26	1.56	1.23	1.35	1.02	1.14	1.03
Mean	4.2	3.18	4.39	5.44	4.29	4.68	3.54	3.95	3.56
N	26	1	786	5	64	101	17	13	12

- Within Bethesda V/VI samples, PSMA was highest in samples with *PPARG* fusions .
- Compared to GSC-B, nodules with *PPARG, BRAF, RET/ALK/NTRK* fusions have significantly higher expression (p<0.0001 for all).

FIGURE 4.
Correlation Between PSMA and NIS Expression



Within GSC-S group, there was no strong correlation between NIS and PSMA (r= -0.11), but high PSMA samples have low NIS (red box). This may indicate that samples with high PSMA may not be good candidates for RAI treatment.

CONCLUSIONS

- PSMA expression in indeterminate and malignant thyroid nodules varies across cytology groups and in the presence of different molecular alterations.
- PSMA expression may provide further thyroid tumor prognostic information in the context of cytology and associated molecular variants.
- The basis for increased PSMA expression in the setting of *PPARG* and other fusions is an opportunity for future investigation, as are the roles of preoperative assessment of PSMA expression and PSMA-based imaging and therapy in the setting of advanced thyroid cancer.