

GLIS-Rearranged Hyalinizing Trabecular Tumors Detected in FNA Samples: Can surgery be avoided?



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CONTACT INFORMATION

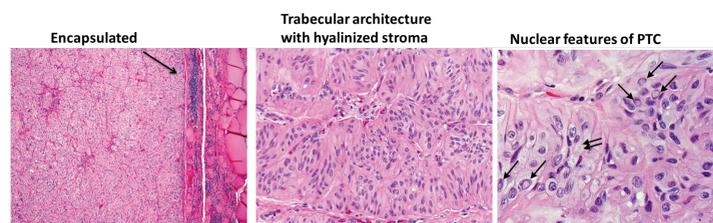
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INTRODUCTION

- Hyalinizing trabecular tumors (HTT) are rare thyroid neoplasms with distinct histopathological appearance.

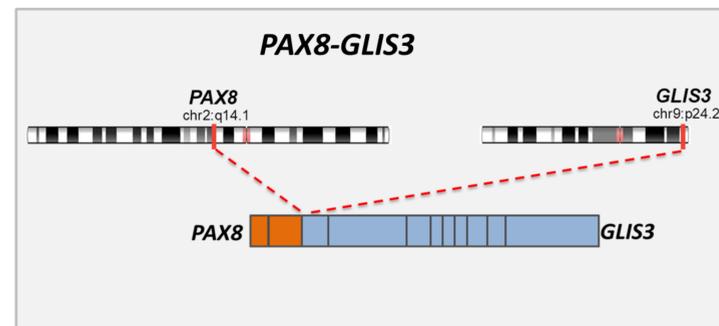


- Due to prominent nuclear features of papillary thyroid carcinoma (PTC), HTT frequently yield suspicious (Bethesda V) or positive for malignancy (Bethesda VI) FNA cytology diagnosis.
- Non-invasive HTT have no documented tumor recurrence or metastasis (1).
- Genetic mechanisms of HTT and relationship to PTC have been a subject of long-standing controversy.
- Recently, *PAX8-GLIS* fusions, most frequently *PAX8-GLIS3*, were reported in the majority of HTT but not in PTC, providing strong evidence for distinct etiology of these two tumor types (2).

RESULTS

PAX8/GLIS3 Fusion Detected in HTT, but not in PTC

- Interchromosomal rearrangement: *PAX8* (2q14.1) and *GLIS3* (9p24.2)
- Most common type of *GLIS* fusions detected in HTT



- Not detected in 704 cases of papillary carcinomas

	<i>PAX8-GLIS3</i>
PTC unselected (n=220) ¹	0/220
PTC TCGA (n=484) ²	0/484
Total PTC (n=704)^{1,2}	0/704 (0%)

¹Nikiforova et al. *Thyroid* (2019); ²TCGA *Cell* (2014)

Follow-Up Findings for *PAX8/GLIS3* Positive Nodules and HTT

- Prospectively established surgical pathology diagnosis was available for 6 patients. All nodules were diagnosed as HTT on surgical pathology. No lymph node metastasis was found at presentation.
- Clinical follow-up was available on 9 patients with resected HTT positive for *PAX8/GLIS3* fusions. No tumor recurrence was noted on follow-up.

Clinical Parameter	Results (n=9 <i>GLIS</i> -positive HTT)
Patient Age	57 (31-75)
FNA Cytology	1 Bethesda III (AUS/FLUS) 2 Bethesda IV (FN/SFN) 3 Bethesda V (SMC) 3 Bethesda VI (PMC)
Clinical follow-up	No tumor recurrence on 65 month (range, 4-181 mo) follow-up

- In the largest study to date by Carney et al. (1), 118 resected tumors with histopathologic features of HTT and no invasion showed no recurrence or regional or distant metastases at presentation or on 10-year mean follow-up.

AIMS

To evaluate the feasibility and frequency of detection of *GLIS* fusions in thyroid fine needle aspiration (FNA) samples and correlate the pre-operative findings of these fusions with surgical pathology and clinical outcomes.

METHODS

- Prevalence of *PAX8-GLIS3* fusions was studied in 13,703 consecutive FNA samples from thyroid nodules with indeterminate (Bethesda III-V) cytology.
- ThyroSeq v3 Genomic Classifier was used to detect *PAX8/GLIS3* fusions.
- Prospective surgical pathology follow-up was collected. Clinical follow up was collected on 9 additional preselected *PAX8/GLIS3* positive nodules with diagnosis of HTT.

Frequency of *PAX8/GLIS3* Fusion Detection in Thyroid FNA Samples with Indeterminate Cytology Diagnosis

13,703 consecutive FNA samples (BIII-V)
 Prospective analysis

10,565 Bethesda III 2,016 Bethesda IV 561 Bethesda V

ThyroSeq

PAX8-GLIS3 Fusions Detected

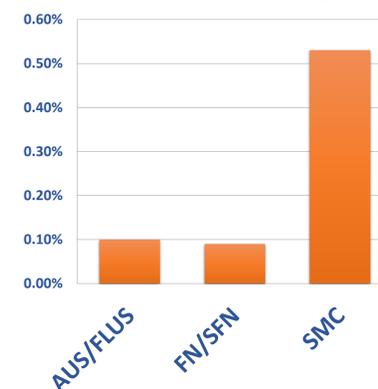
14 (0.1%) nodules

Prospective Surgical Follow-up

6/6 (100%) HTT

- Among 13,703 consecutive FNA samples with indeterminate cytology (10,565 AUS/FLUS, 2,016 FN/SFN, 561 SMC), *PAX8-GLIS3* was identified in 14 (0.1%) samples, including 9 (0.09%) nodules with AUS/FLUS cytology, 2 (0.1%) with FN/SFN cytology and 3 (0.53%) nodules with SMC cytology.

PAX8/GLIS3 Frequency in Bethesda III-V Categories



- PAX8-GLIS3* fusions were more frequently found in samples with SMC (Bethesda V) cytology.

CONCLUSIONS

- In a large series of consecutive FNA samples with indeterminate cytology, *PAX8-GLIS3* fusion was detected in 0.1% of cases and was predictive of HTT.
- Based on the limited follow-up in this study and previous reports, HTT demonstrate benign clinical behavior.
- These findings raise a possibility that active surveillance may be considered for patients with thyroid nodules tested positive for *PAX8-GLIS3* fusions, including those with suspicious for malignancy or malignant FNA cytology.
- This information may contribute to the general trend for de-escalating surgical management of patients with thyroid tumors.

REFERENCES

- Carney, et al. Hyalinizing trabecular tumors of the thyroid gland are almost all benign. *Am J Surg Pathol.* 2008 Dec;32(12):1877-89.
- Nikiforova, et al. *GLIS* Rearrangement is a Genomic Hallmark of Hyalinizing Trabecular Tumor of the Thyroid Gland. *Thyroid.* 2019 Feb;29(2):161-173.