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Introduction

- 24-57% of thyroid ultrasound guided fine needle aspirations (USFNA) have an indeterminate result (Bethesda III or IV).
- Molecular testing as an adjunct to USFNA can help characterize the underlying nature of thyroid nodules.
- Mutations of the BRAF V600E gene have been associated with aggressive tumor characteristics, tumor recurrence and poor prognosis.
- Mutations in the three RAS genes are associated with less prominent nuclear features of PTC, more frequent encapsulation and a lower rate of lymph node metastases than those with BRAF mutations.

Objectives

We ascertain the association between Bethesda category and molecular mutations assessed with ThyroSeq V3 or ThyGeNEXT in patients with thyroid nodules undergoing thyroidectomy.

Methods

- Retrospective multicenter cohort study of patients undergoing thyroidectomy at one of two academic centers.
- The extent of thyroidectomy performed (hemi, total or completion thyroidectomy) and the postoperative histopathology (benign disease, malignant or non-invasive follicular thyroid neoplasm with papillary-like nuclear features [NIFTP]) were noted.
- The association between Bethesda category and type of molecular mutation of dominant thyroid nodule on USFNA was compared using Chi-square testing and logistic regression.

Results

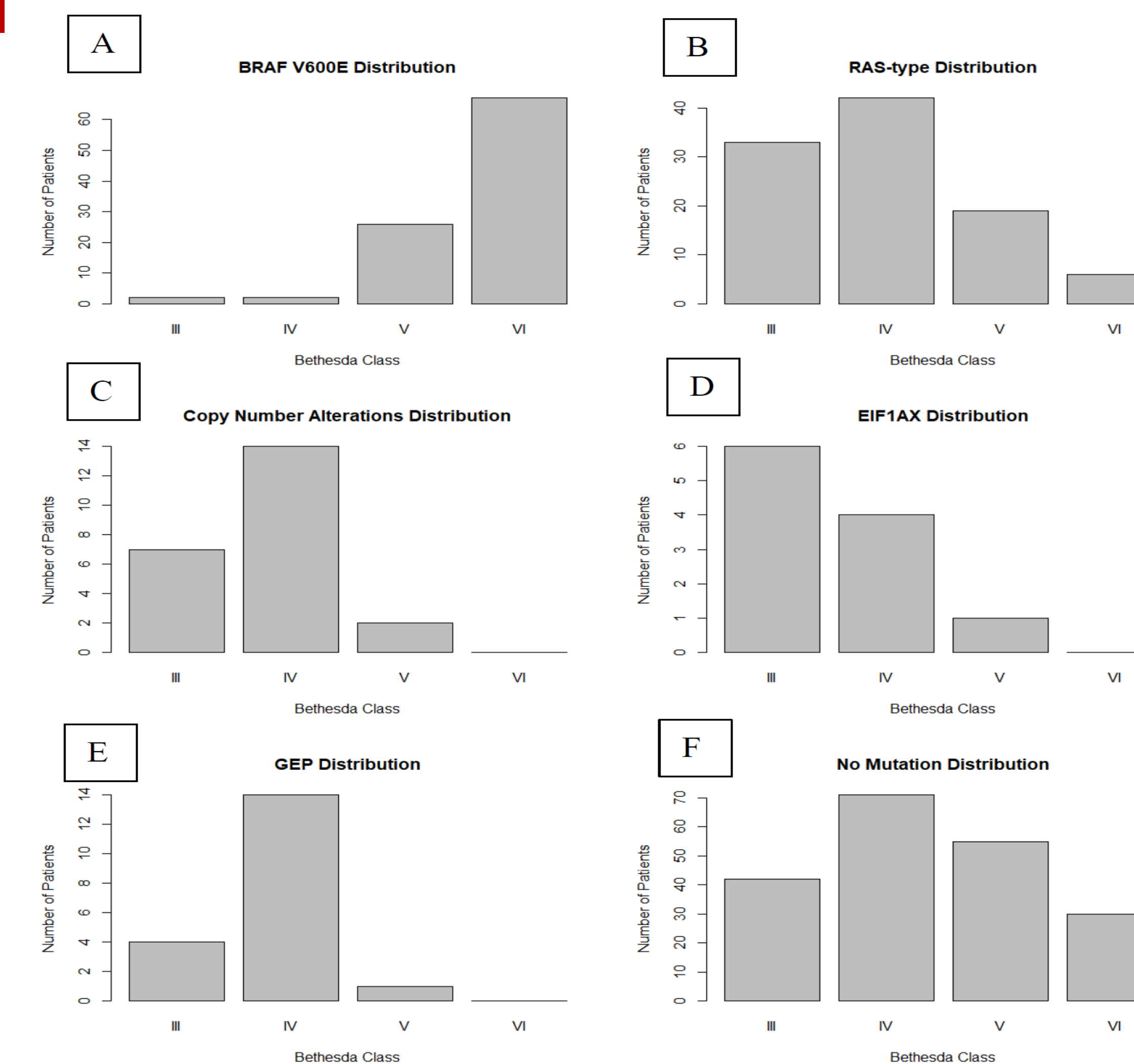
- 451 patients undergoing thyroidectomy (72% hemithyroidectomy) were included in the analysis.
- 95.9% (93/97) of patients with a BRAFV600E mutation had a Bethesda category V or VI (P<0.001), and all had confirmed thyroid cancer on postoperative pathology.

Association between molecular mutation and postoperative pathology

Mutation	Malignancy	NIFTP	Aggressive Thyroid Cancer	Central Neck Lymph Node Metastasis
BRAF V600E	100% (97/97)	0	69.1% (67/97)	55.7% (54/97)
TERT	85.7% (6/7)	0	57.1% (4/7)	14.3% (1/7)
RAS-type	83% (83/100)	35.7% (5/14)	22% (22/100)	7% (7/100)
Copy Number Alterations	82.6% (19/23)	7.1% (1/14)	34.8% (8/23)	4.3% (1/23)
Mutation/Fusion	100% (2/2)	0	100% (2/2)	100% (2/2)
EIF1AX	81% (9/11)	0	18.2% (2/11)	0% (0/11)
GEP	100% (19/19)	0	36.8% (7/19)	5.2% (1/19)
No Mutation	64.6% (128/198)	50% (7/14)	15.7% (31/198)	6.6% (13/198)

- Those with H, K or N RAS or EIF1AX mutations, gene expression profiling (GEP) or copy number alterations showed an association with Bethesda categories III and IV (P≤0.01).
- Those with no identified molecular mutation had a lower incidence of aggressive thyroid cancer compared to those with an identified mutation (12.6% vs 44.3%, P<0.01).

Frequency distribution of Bethesda category by molecular mutation



Frequency distributions illustrate the number of identified mutations on molecular profile testing of thyroid nodules by Bethesda category.

Conclusion

BRAF V600E mutations were mostly associated with Bethesda categories V and VI, whereas RAS and EIF1AX mutations, copy number alterations, and GEP were related to Bethesda categories III and IV.

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