Short Term Outcome of Radioactive Iodine Ablation Therapy in Patients of Papillary Thyroid Carcinoma with B-RAF Mutation: Experience in NINMAS

Papia Akhter, Jasmin Ferdous and Fatima Begum

National Institute of Nuclear Medicine & Allied Sciences, Block-D, BSMMU campus, BAEC, Dhaka-1000

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Introduction

The most prevalent malignancy among all forms of thyroid cancers is papillary thyroid carcinoma (PTC). The prognosis is excellent with overall 10 years survival rate of 90%. Recently some study shows that genetic mutations have contributins for clinical and behavioral metastatic risk factors. The most common genetic mutation involved in PTC is BRAF(V600E) mutation. So, this study was done to see the short-term outcome of PTC patients with BRAF(V600E) mutation after radioactive iodine ablation (RAIA).

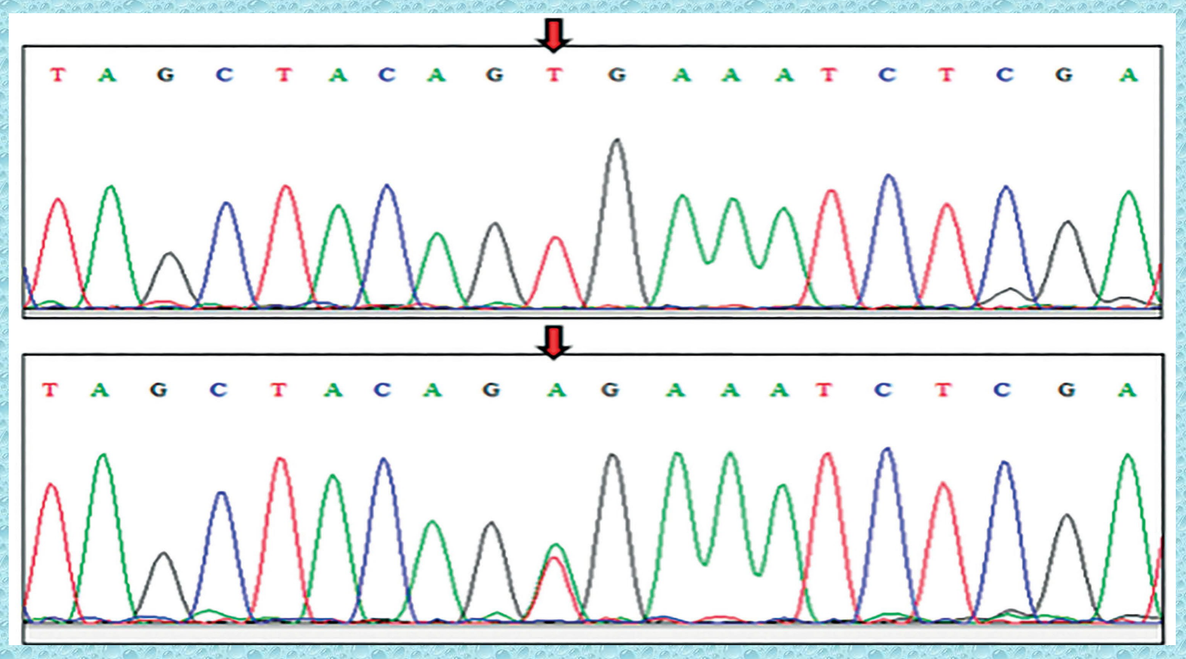

Figure: Representative DNA sequencing of BRAF exon 15. A) Wild-type *BRAF*.
B)Heterozygous *BRAF* (V600E) mutation.

Materials & Methods

A total of 63 patients with thyroidectomy who were referred to NINMAS for RAIA were included in this prospective cohort study. All of them were tested for BRAF(V600E) mutation. Patients were followed up three monthly for one year. Tg level <1 ng/ml was considered disease-free and Tg > 1 ng/ml was considered persistence of disease based on Tg. Progression of disease was considered in case of rising Tg, local recurrence, positive diagnostic whole-body scan (DxWBS). The outcome based on Tg level, metastasis, recurrence, or local aggressiveness was observed.

Test Requested	BRAF V600E	
Test Name	**Test Method**	**Result**
BRAF V600E	Real Time PCR	Positive

Test Description :
BRAF mutation by Real Time PCR. BRAF inhibition with oral small-molecule TKIs (eg. vemurafenib, dabrafenib) appear to be an effective strategy in the treatment of progressive BRAF V600-mutant thyroid cancer patients. Real-time polymerase chain reaction amplification is carried out in the presence of 2 fluorescent probes that detect BRAF V600E mutation and wild-type BRAF. Mutation-positive samples will be validated by Sanger sequencing of PCR product.

Interpretive Information :
This test allows detection of 1% mutant DNA in a background of 99% normal DNA to evaluate for the presence of BRAF V600E and V600K mutations to determine whether a patient might be a candidate for BRAF kinase inhibitors. A positive result indicates the presence of an activating BRAF mutation.

Specificity:
A non-clinical panel of cell lines as well as clinical specimens known for specific BRAF mutation. A T1799 point mutation in exon 15 of BRAF gene, resulting in a valine to glutamate substitution at codon 600 (V600E) affecting the kinase domain of the BRAF protein, is the common oncogenic driver mutation.

Sensitivity:
Analytical sensitivity: 5% mutant allele in background of wild-type allele. Cross-reactivity for nonV600E mutations is 18% for V600D, 68% for V600E2, and 31% for V600K.

Limitations:
Sensitivity may be affected by specimen collection, storage condition and the presence of interfering substances, presence/absence of other mutations and/or DNA sequence polymorphisms. A negative BRAF mutation result does not exclude the possibility of mutations at other locations and associated resistance to therapies.

Figure: Laboratory report showing positive *BRAF*- (V600E) mutation

Results

A total of 63 patients, male 25 (39.7%) and female 38(60.3%), were included in this study. Among them, 23 (36.51%) were BRAF (V600E) positive, and 40 (63.49%) were negative. Extrathyroidal extension, lymphovascular invasion, capsular margin involvement, larger tumor size was significantly associated with BRAF mutation. No significant association was found with age, histological type, lymph node involvement, multifocality, tumor staging and grading. After one year follow up among 23 BRAF mutation positive patients 04 (17.4%) were disease free; 17 (73.9%) persistent disease and 2 (8.7%) showed progression of disease; among 40 BRAF negative patients 26 (65%) were disease free; 10 (25%) showed persistent disease and 04 (10%) progression of disease was seen in this group; p-value was 0.016 which was statistically significant.

Conclusions

In this study, patients with positive BRAF mutation showed aggressive presentation and poorer outcome compared to BRAF mutation negative patients. BRAF mutation analysis in PTC patients provides important prognostic value. These patients might be benefited by receiving more intensive management and frequent follow up.

Presenter: Papia Akhter /01712324996/papia1078@gmail.com