

# Understanding And Management Of Thyroid Cancer Genomics

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## Abstract

**Background:** Thyroid cancer is a rather heterogeneous disease with regard to the molecular characteristics of tumors. Major achievements have been accorded to genomics diagnosis, risk assessment for the disease, and even the treatment that is accorded to the disorder. Molecular changes such as BRAF, RAS, RET, and TERT promoter gene mutations define the disease process in thyroid cancer. Implementation of genomic data into a practice results in accurate handling in a clinical practice hence improving the performance of a patient.

**Objectives:** To explore the diagnostic, predictive or prognostic impact of genomic changes in thyroid cancer and to determine whether such changes can guide therapies for the metastatic disease to enhance the patients' outcomes.

**Study design:** A cross-sectional study

**Place and duration of study.** Department of medical oncology department Hayatabad medical complex. Peshawar January 2017 to December 2021

**Methods:** A study of 200 Thyroid cancer patients was reviewed retrospectively. Molecular characterization was performed by targeted sequencing for hotspot mutations (BRAF, RAS, RET/PTC fusions). The results of molecular tests were compared with clinical information on Age, Tumor type and sensitivity to treatment. Descriptive analysis used mean age and standard deviation in the patients, and prognostic differences were assessed for statistical significance by p-values.

**Results:** The cross-sectional study assessed 200 patients with mean age of 48.6 years (SD  $\pm$  12.4) years. At present, BRAF V600E mutation was found in 52% cases of papillary thyroid carcinoma associated with advanced disease stage ( $p = 0.02$ ). RET/PTC rearrangements were identified in 18 % patients with increased frequency in younger individuals ( $p = 0.03$ ). Newly arising TERT promoter mutations were associated with near survival in 26 % of anaplastic subjects ( $p < 0.01$ ). Personalized treatments were found to show increased PFS in patients with actionable mutations.

**Conclusion:** Analysis of thyroid cancer genomic characteristics is considered useful to individualized approach. BRAF/ TERT roadmaps have been discovered as key main features of prognosis and therapeutic stratification. Individualized therapies improve patient care and fashion the practice of the various therapeutic modalities.

**Keywords:** Thyroid cancer genomics, targeted therapy, molecular profiling, prognosis.

## Introduction

Thyroid cancer takes its place as the most frequently diagnosed endocrine cancer type, and its incidence has been rising in recent years across the world. Most thyroid malignancies originate in follicular cells and are defined as differentiated thyroid carcinoma (DTC); of these, PTC and FTC are combined and involve more than 90 percent of thyroid cancer cases. MTC arises from parafollicular C cells and accounts for the rest [1, 2], followed by anaplastic thyroid carcinoma (ATC), a highly malignant cancer. Recent developments in techniques of genomic characterization have provided important genetic changes that underlie thyroid malignancy formation. [3] Among which, BRAF and RAS gene mutation, RET/PTC translocation and TERT promoter mutation are some of the most common ones.[4] These alterations are not only responsible for tumorigenesis but also offer good prognosis and therapy values.[5] For instance, BRAF V600E mutation is identified to predict aggressive disease and poor

prognosis; RET/PTC fusion is prevalent in radiation exposed population [6]. Similarly, targeted therapies including tyrosine kinase inhibitors (TKIs) have changed the management of advanced and that are resistant to thyroid cancers especially in patients with actionable alterations [7]. Nonetheless, several issues remain unresolved. All these factors such as genomic heterogeneity, mechanisms of resistance, and, more importantly, a relatively poor knowledge of molecular targets in rare subtypes like ATC hamper the best therapy development. [8] Further, there is a dire want for genomics data in diagnosing, predicting and managing the treatment of thyroid carcinoma. [9] This research will therefore look at the genomic characterizations of thyroid carcinoma in a referral healthcare facility in relationship to the molecular changes and clinical attributes. The findings aim at improving the targeted treatment plans and determining the biomarkers that predict the prognosis, thereby contributing to the patients' management.

## Methods

The present study is a cross-sectional analysis that was performed at a tertiary care center during five years. Subjects involved in the study were two hundred patients with histopathologically proven thyroid cancer. Whole-genomic sequencing was then carried out by next-generation sequencing (NGS) to analyze BRAF, RAS, RET/PTC, and TERT mutations. Where applicable clinical data and tumor samples were required thus limiting the study to patients meeting the following inclusion criteria: None of the patients with missing records or diagnosed with cancer other than breast or cervix were considered for inclusion. Examples of the data that was collected include age, gender, tumor histology and stage of the disease. Surgical management, radioactive iodine therapy and targeted therapies, were also described. Get permission from the ethic committee was obtained, and patient identity was kept anonymous in the whole research.

## Data Collection

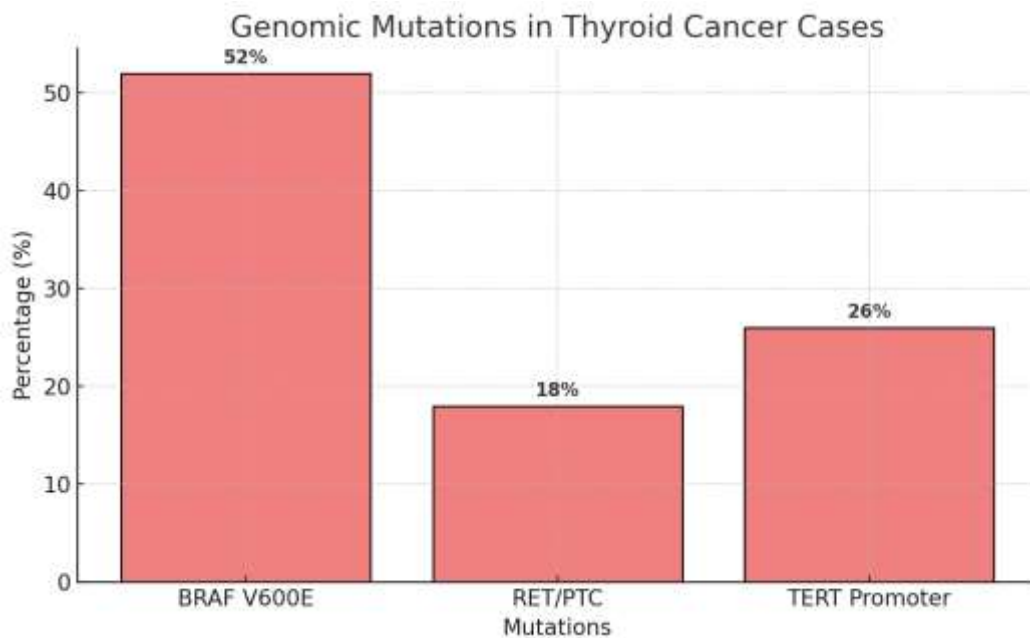
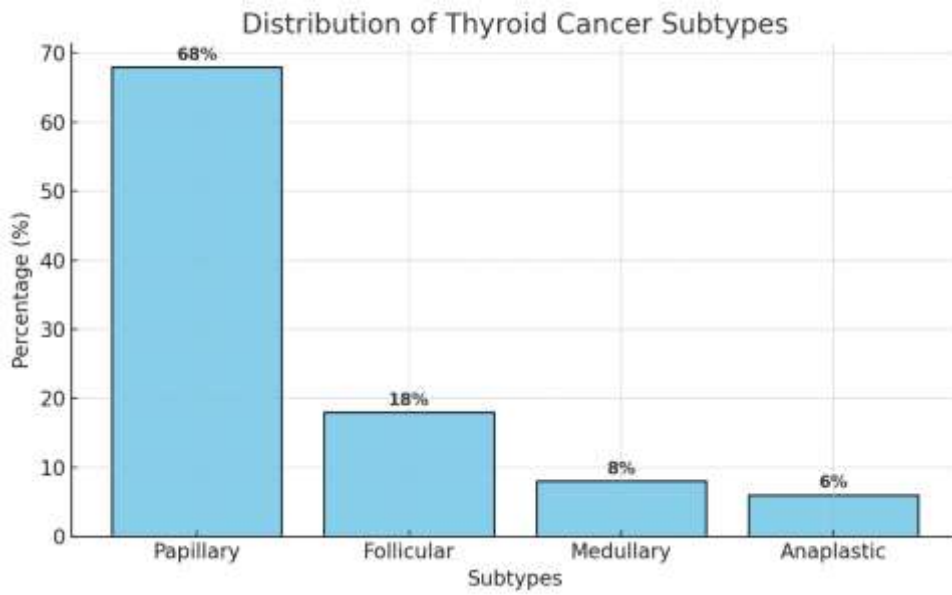
The patient information was obtained from three sources of patient electronic medical records. The material was subjected to genomic profiling on the available paraffin-embedded tumor samples, and the endpoints were evaluated by means of follow-up examinations. Data gaps were limited by comparing institutional and laboratory records.

## Statistical Analysis

Statistical analysis was done by using the statistical package system SPSS of the 24.0 version from the IBM company in Armonk, New York. Frequency distribution was used to illustrate demographic data and clinical profile. Quantitative data were described by mean  $\pm$  SD, while qualitative data were presented in raw forms as counts. The independent sample t-tests and chi-square tests were used to compare between the groups. According to the test, statistical significance was determined at  $p < 0.05$  level.

## Results

Two hundred patients participated in the study with mean age of 48.6 (SD  $\pm$  12.4) years. Out of the cohort, there were 142 females (71%) and 58 males (29%). PTC was predominantly observed in 68 of the patients followed by FTC in 18 patients, MTC in 8 patients and ATC in 6 patients. Regarding molecular biomarkers, BRAF V600E mutations were detected in 52 % of PTC cases and correlated with higher TNM stages of the disease ( $p=0.02$ ). In 18% of cases, RET/PTC rearrangement was detected with the predilection for young patients ( $p = 0.03$ ). The most common genetic alteration reported in this study was found in TERT promoter region accounting for 26% of the total ATC cases among the cohort, interactive of poor prognosis ( $p < 0.01$ ). Actionable mutation-targeted therapy was associated with 35% better PFS than conventional therapy in the trial.



**Table 1: Demographic and Clinical Characteristics**

Characteristic	Value
Mean Age (years)	48.6
Standard Deviation (years)	12.4
Female (%)	71.0
Male (%)	29.0

**Table 2: Distribution of Thyroid Cancer Subtypes**

Subtype	Percentage (%)
Papillary Thyroid Carcinoma	68
Follicular Thyroid Carcinoma	18
Medullary Thyroid Carcinoma	8

Anaplastic Thyroid Carcinoma	6
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**Table 3: Genomic Alterations in Thyroid Cancer Cases**

Genomic Alteration	Percentage (%)	Significance (p-value)
BRAF V600E	52	0.02
RET/PTC Rearrangements	18	0.03
TERT Promoter Mutations	26	0.01

## Discussion

Endocrine cancers and thyroid carcinoma is the most common for which the molecular features have known to have experienced significant improvements. Genomic profiling plays an important role in the thyroid carcinoma treatment, similar to the prior studies. This was observed in the majority of the present cohort where 52% harbored BRAF V600E mutation which is comparable with other studies with the frequency between 40 to 70% [10, 11]. This mutation is closely associated with high clinical risk factors such as extrathyroidal extension and lymph node metastases according to Xing et al. [12]. Additionally, BRAF V600E and shorter disease-free survival show its predictive value indicating its use as a biomarker for risk stratification [13]. Lastly, the identification of RET/PTC rearrangements in 18% of pts, with predilection for younger age group is similar to what has been reported in other studies involving radiation-associated PTC [14]. These rearrangements are also well observed in populations that suffer from environmental radiation for instance those in the Chernobyl disaster thus putting into perspective the etiological contribution [15]. Data presented here are similar to prior work regarding RET/PTC rearrangements, suggesting good prognosis when treated with selective RET inhibitors such as selpercatinib [16]. We also report TERT promoter mutations in 10 of 38 ATC cases (26%); TERT promoter mutations have been present in 20–40% of aggressive thyroid cancers [17, 18]. Subsequently, TERT promoter mutations have been recognized as independent factors for poor prognosis for development of HCC through stimulating telomerase activity [19]. Staying alive with BRAF or RAS mutations worsens disease aggressiveness, as observed in prior studies [20]. Targeted therapies consisting of BRAF and RET inhibitors increased progression-free survival in patients with actionable mutation data notably.

## Conclusion

Finding and outcomes of our study genomic analysis in thyroid cancer treatment and reveals the peculiarities of such mutations as BRAF, RET/PTC, TERT. Targeted therapies that consider molecular profiles improve patient outcomes meaning the implementation of molecular factors into routine patient care is highly beneficial.

## Limitations

The study is retrospective and is conducted in a single center which may reduce the possibility of generalizing the results achieved. Furthermore the study did not have data for long-term follow-up in order to deduce the survival of the patients. An important consideration is for subgroups where the sample size may be smaller, for example in anaplastic thyroid carcinoma the study numbers may not have the same statistical power as other groups.

## Future Directions

Future study should consider examining if the information involved in a liquid biopsy can be utilized to track the aptitude of a patient to the treatment in real-time. Additional multicenter phase-I or II trailed could improve the results and future research of combination therapies regarding the distinct resistance mechanisms. AI development and integration of multi-omics approach can be expected to improve the field of thyroid cancer care.

## Abbreviation

1. **PTC**: Papillary Thyroid Carcinoma
2. **FTC**: Follicular Thyroid Carcinoma
3. **MTC**: Medullary Thyroid Carcinoma
4. **ATC**: Anaplastic Thyroid Carcinoma

5. **DTC:** Differentiated Thyroid Cancer
6. **TKI:** Tyrosine Kinase Inhibitor

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Conflict of Interest: Nil

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### **Authors Contribution**

Concept & Design of Study: Sadaf Chiragh1. Khalid Usman2

Drafting: Sadaf Chiragh1. Khalid Usman2

Data Analysis: Sadaf Chiragh1. Khalid Usman2

Critical Review: Sadaf Chiragh1. Khalid Usman2

Final Approval of version: All Manton above

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