COMMENTARY

# Unveiling thyroid cancer precision: significance of molecular markers for risk stratification and management

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**Pakistan Journal of Nuclear Medicine**
Volume 14(2):45–48
DOI: 10.24911/PJNMed.175-1701839619



Pakistan Journal of Nuclear Medicine is the official journal of Pakistan Society of Nuclear Medicine

## ABSTRACT

This commentary delves into the significance of molecular markers, specifically BRAF and TERT mutations, in refining risk stratification (RS) and management strategies for thyroid cancer (TC), with a focus on optimizing radioactive iodine (RAI) doses. BRAFV600E mutation notably impacts risk classification in papillary TC (PTC), elevating it to intermediate-risk status and affecting recurrence rates. Additionally, the inclusion of TERT promoter mutation in risk assessment categorizes PTC larger than 1 cm as high-risk. The initial maximum permissible RAI dose, tailored to the respective risk group, targets heterogeneous tumor cell populations, including those with poor RAI uptake due to mutations, by utilizing the cross-fire effect of radiation, thereby reducing the risk of recurrence. BRAF mutational analysis aids in ruling out follicular neoplasms, while TERT mutational analysis facilitates tailored management, particularly in follicular tumors of uncertain malignant potential. Although current guidelines do not advocate RAI dose modification based solely on molecular markers, ongoing research emphasizes the need for exploration. Proactive integration of BRAF and TERT mutational analysis pre-RAI therapy enhances RS, facilitating personalized treatment decisions. It is recommended to conduct mutational analysis for BRAF and TERT genes before initiating RAI therapy in PTC and RAS+TERT in FTC for improved risk assessment and tailored RAI administration. As molecular insights advance, personalized approaches are vital for optimizing patient outcomes in TC management.

**Keywords:** TERT, BRAFV600E, molecular, thyroid cancer, risk.

**Received:** 06 December 2023 **Accepted:** 07 December 2024
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## "Influence of BRAFV600E and TERT Mutation (TERT) Status on Risk Stratification (RS) in Papillary Thyroid Cancer (TC)

Indeed, the presence of the BRAFV600E mutation introduces a pivotal shift in risk classification. For instance, intrathyroidal papillary thyroid carcinoma (PTC) less than 4 cm without BRAFV600E is categorized as low-risk. Contrastingly, when BRAFV600E mutation is detected in the same scenario, it elevates the classification to an intermediate-risk group. Similarly, multifocal papillary thyroid microcarcinoma with worrisome features like ETE and BRAF V600E mutation falls into the intermediate-risk category with a recurrence risk of 20% [1]. According to the 2015 American Thyroid Association (ATA) guidelines modification, the presence of a TERT promoter mutation in PTC larger than 1 cm categorically places it in the high-risk group, irrespective of other clinicopathological factors [1].

## Radioactive Iodine (RAI) Dose Escalation in Intermediate and High-Risk Papillary Thyroid Cancer Patients with BRAFV600E Mutation

In classical PTC or its follicular variant, the risk of recurrence in the BRAFV600E mutant group is approximately 20%, compared to 7% in the BRAFV600E wild-type group [2]. In the intermediate-risk group, patients with the BRAF V600E mutation face the maximum risk of recurrence. When considering a lower RAI dose based on other clinicopathological features, escalating the dose to the maximum permissible level in the intermediate-risk group in BRAFV600 mutant group becomes a prudent consideration [3].

While BRAFV600E alone might not suffice to justify maximum dose escalation in the high-risk group, the scenario changes when BRAF is co-present with other aggressive mutations such as TERT, tumor protein 53 (TP53), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), and so on. In the case of a TERT, the risk of recurrence soars to around 47%,

and with a genetic duet of TERT and BRAF mutations, this risk exceeds 60% [4]. Hence, in instances involving TERT alone or in combination with BRAF mutation, escalating the RAI dose to the maximum permissible level of the high-risk group becomes a justifiable consideration.

The rationale stems from the heterogeneous nature of tumor cells, each harboring distinct genetic clones. Cells with BRAF or TERT exhibit poor RAI uptake due to fewer sodium iodide symporters on the cell surface. Administering a high RAI dose initially facilitates targeting surrounding cancer clones with BRAF or TERT through the cross-fire phenomenon [5]. Furthermore, the high administered activity may enhance uptake in cell populations with BRAF or TERT due to the concentration gradient. Increasing the RAI activity to the maximum permissible level in the assigned risk group is advised to minimize the chance of recurrence [6].

As of 2015, the ATA guidelines do not explicitly recommend dose modification based solely on molecular markers. The guidelines advocate for further studies in this regard, reflecting the ongoing evolution in understanding the interplay between molecular markers and RAI response [1].

## Adequacy of BRAFV600E Mutational Analysis versus Comprehensive Genetic Panel for Risk Stratification in Thyroid cancer Patients

In the context of the 2015 ATA guidelines, the RS for papillary thyroid carcinoma (PTC) primarily relies on two key molecular markers, BRAF and TERT, owing to their high prevalence. Notably, the genetic combination of RAS and TERT also categorizes follicular neoplasms into the high-risk group [1,7]. To enhance the efficacy of RS, it is advisable to conduct mutational analysis for BRAF and TERT in PTC cases, while testing for RAS and TERT in follicular neoplasms.

While additional markers such as TP53, PIK3CA, AKT1, and others play a role in the management of thyroid disorders, their infrequent occurrence raises concerns about the financial feasibility for a majority of patients. The inclusion of these markers in routine testing may contribute to an increased overall cost, potentially surpassing the affordability threshold for many individuals. Therefore, a judicious approach to testing is recommended, focusing on the more prevalent and clinically impactful markers for cost-effective risk assessment and management of thyroid neoplasms.

## Potential Utility of BRAFV600E Mutational Analysis in the Management of Iodine-Refractory Thyroid Cancer

Currently, no existing guidelines recommend the utilization of BRAF mutational analysis for the selection of tyrosine kinase inhibitors (TKIs), unless no alternative option is available, i.e., unresectable or metastatic disease on progression with no other therapeutic option. Nevertheless, certain studies have explored the efficacy of the BRAF selective inhibitor Dabrafinib in BRAF mutant group, either as a standalone treatment or in combination with Trametinib, to induce redifferentiation in cases refractory to RAI. The double inhibition of the MAPK signaling pathway with Tramatinib (MEK inhibitor) and Dabrafenib in this group is more effective in inducing re-differentiation as appeared in preliminary small series clinical trials. In the case of BRAF wild-type disease, re-differentiation with MEK inhibitors alone might be sufficient. These studies have reported positive outcomes, such as partial response or stable disease, following RAI therapy [8]. The strategy of redifferentiation therapy has shown promise in slowing the progression of the disease and may serve as a viable option in the treatment of RAI-refractory differentiated TC before considering the initiation of long-term TKI treatment. While not yet formally recommended by guidelines, the potential benefits of redifferentiation therapy highlight its importance as a potential therapeutic avenue in cases where traditional treatment approaches have limited effectiveness [9].

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## BRAFV600E Mutational Analysis in the Management of Anaplastic Thyroid Carcinoma (ATC)

Due to the aggressive and rapidly progressing nature of ATC, early determination of BRAFV600E mutation (BRAF) status is crucial for effective tumor management. The Food and Drug Administration-approved BRAF/MEK inhibitor combination, dabrafenib and trametinib, is designated for ATC treatment; however, it is exclusively prescribed for patients with tumors carrying the BRAF V600E mutation. As a result, swift and accurate tests to identify the presence of the BRAF V600E mutation play a pivotal role in the optimal management of ATC [10].

## TERT Mutational Analysis in Assisting the Management of Follicular Tumors of Uncertain Malignant Potential (FT-UMP)

The incidence of TERT promoter mutation in follicular neoplasm of uncertain malignant potential is estimated to be around 15%. Conducting TERT mutational analysis has the potential to alter the classification of follicular neoplasm of uncertain malignant potential to malignant potential. Postoperative screening for TERT promoter mutations enables the identification of FT-UMP cases, a substantial proportion of which are prone to subsequent recurrence with distant metastases. Consequently, it is

advisable to incorporate TERT mutational screening into the assessment protocol for all FT-UMPs. The detection of a TERT promoter mutation not only justifies a shift in nomenclature to "malignant potential" but also suggests the consideration of adjuvant treatment. This proactive approach is crucial, given that the prognosis of TERT-promoter-mutated FT-UMPs align closely with those of TERT-mutated miFTCs [11]. On the other hand, TERT mutational analysis holds significance in the management of minimally invasive follicular thyroid carcinoma (MI-FTC)/encapsulated angioinvasive follicular thyroid carcinoma (EA-FTC) in a size-dependent manner. Specifically, MI-FTC/EA-FTC with a size ranging from 2 to 4 cm and harboring TERTs should be managed with the completion of thyroidectomy. In addition, the inclusion of radioiodine remnant ablation or adjuvant therapy may be warranted when a TERT promoter mutation is identified in thyroid nodules ranging from 2 to 4 cm in size, particularly in patients diagnosed with MI-FTC and EA-FTC. In contrast, the wild-type group can be safely managed with lobectomy. This distinction in management strategies based on TERT mutational analysis enhances the precision of decisions for MI-FTC/EA-FTC cases, contributing to more tailored and effective patient care [12].

## Conclusion

Conclusively, the incorporation of BRAF and TERT gene mutational analysis holds substantial merit, potentially modifying the risk group and thereby refining the management of aggressive TCs in nuclear medicine facilities. The inclusion of mutational analysis on FNAC samples have both diagnostic and prognostic implications regarding surgical decision making and subsequent management. However post-surgical BRAFV600E and TERT mutational analysis are also helpful in RS and management. While the current ATA guidelines do not endorse RAI dose modification based solely on molecular markers, the dynamic landscape of ongoing research underscores the necessity for continued exploration and validation of these associations. As molecular insights continue to shape the landscape of TC management, a nuanced and personalized approach appears increasingly essential for optimal patient outcomes.

### Recommendation

It is advisable to conduct mutational analysis for BRAF and TERT genes prior to initiating RAI therapy in PTC and RAS+TERT in follicular thyroid carcinoma (FTC). This pre-treatment genetic analysis serves to enhance RS and allows for tailored adjustments in the administration of RAI.

### List of abbreviations

| | |
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| ATA | American thyroid association |
| ATC | Anaplastic thyroid carcinoma |
| BRAF | BRAFV600E mutation |
| EA-FTC | Encapsulated angioinvasive follicular thyroid carcinoma |
| MI-FTC | Minimally invasive follicular thyroid carcinoma |
| PIK3CA | Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha |
| PTC | Papillary thyroid carcinoma |
| RAI | Radioactive iodine |
| RS | Risk stratification |
| TC | Thyroid cancer |
| TERT | TERT mutation |
| TKI | Tyrosine kinase inhibitors |
| TP53 | Tumor protein 53 |

### Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

### Funding

None.

### Consent to participate

Not applicable.

### Ethics approval

Not applicable.

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