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Clinicopathological Outcomes of TENIS Syndrome in Differentiated Thyroid Carcinoma: A Study from a Tertiary Center in South India

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ABSTRACT

Background: Thyroglobulin Elevated Negative Iodine Scintigraphy (TENIS) syndrome is an uncommon but clinically significant entity in differentiated thyroid carcinoma (DTC). It is characterized by persistently elevated serum thyroglobulin (Tg) despite negative radioactive iodine (RAI) scans. The condition poses diagnostic and therapeutic challenges, with limited data available from South India.

Objective: This study aimed to evaluate the clinicopathological features, treatment patterns, and outcomes of patients with TENIS syndrome managed at a tertiary care center in South India, with emphasis on factors influencing disease persistence and progression.

Methods: A retrospective descriptive analysis was conducted on adult patients with papillary thyroid carcinoma (PTC) or follicular thyroid carcinoma (FTC) who developed TENIS following total thyroidectomy and radioactive iodine (RAI) therapy. Data on demographics, histopathology, tumor stage, Tg levels, imaging, treatment modalities, and outcomes were extracted from medical records. Associations between clinicopathological variables and disease course were assessed using Chi-square and appropriate statistical tests, with significance defined at $p<0.05$.

Results: Thirty-three patients were included (12 males, 21 females; mean age 45.2±13.1 years). Classical PTC was the predominant subtype (60.6%). At diagnosis of TENIS, the median Tg was 8 ng/mL. Lymph node metastasis occurred in 36.4%and distant metastasis in 24.2%, most commonly involving lungs and bones. Empirical RAI was the most frequently used therapy (33.3%), while others underwent salvage surgery, combined therapy, or observation. Treatment responses varied; some patients achieved Tg decline, while others had persistent or progressive disease. Tumor stage ($p=0.031$) and nodal status ($p=0.018$) were significantly associated with persistence, whereas treatment modality showed no correlation ($p=0.79$). The mean follow-up duration was 6.5 years.

Conclusion: TENIS syndrome represents an aggressive subset of DTC with high rates of persistence and metastasis. Tumor stage and nodal involvement are important prognostic indicators, while treatment responses remain inconsistent. Individualized management, integration of advanced imaging, and long-term surveillance are essential. Further multicentric studies and novel targeted therapies are needed to improve patient outcomes.

Keywords: *Thyroglobulin Elevated Negative Iodine Scintigraphy (TENIS), Differentiated Thyroid Carcinoma (DTC), Papillary Thyroid Carcinoma, Radioiodine Refractory Thyroid Cancer.*

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1. INTRODUCTION

Thyroid carcinoma (TC) is the most common endocrine malignancy, though it carries a lower mortality than many other cancers【1,2】. Its incidence has risen steadily since 2000 and is projected to be among the most frequently diagnosed cancers by 2030, along with breast, prostate, lung, and melanoma【3,4】. Risk factors include iodine deficiency, radiation

exposure, obesity, family history, thyroid nodules or goiter, and female sex【5】.

Differentiated thyroid carcinoma (DTC), arising from follicular cells, accounts for ~90%of TC and includes papillary thyroid carcinoma (PTC, ~80%), follicular thyroid carcinoma (FTC, ~15%), and Hürthle cell carcinoma (HCC)【5】. Surgery followed by radioactive iodine (RAI) therapy provides good control in most patients without advanced disease. However, 1–4%present with distant metastases, and 7–23%develop them during follow-up【1】.

The radioactive iodine (RAI) whole-body scan (whole-body scan (WBS)) is central in DTC management【6,7】, but as disease progresses, ~10%develop distant metastases and two-thirds become RAI-refractory【8】. Once refractoriness occurs, prognosis worsens, with <15 months between metastatic events【9】, a 10-year survival under 10%, and average survival of only 3–5 years【10】.

A subset of patients develops Thyroglobulin Elevated Negative Iodine Scintigraphy (TENIS) syndrome, characterized by raised serum thyroglobulin (Tg) despite negative iodine scans【11】. Proposed mechanisms include dedifferentiation, sodium-iodide symporter dysfunction, competitive inhibition of uptake, and subclinical lesions【12】. Standard imaging often fails in this setting, and systemic therapies show limited benefit, making serial Tg monitoring essential until disease localization【13–15】.

Identifying TENIS is crucial for risk stratification and treatment planning. This study investigates the clinicopathological features and outcomes of TENIS patients at a tertiary center in South India, with focus on recurrence, metastasis, and factors influencing persistence.

2. MATERIALS AND METHODS

This retrospective descriptive study was carried out at a tertiary care center in South India to evaluate the clinicopathological outcomes of TENIS syndrome in patients with differentiated thyroid carcinoma (DTC).

Study Population
Eligible patients included adults (≥18 years) with papillary (PTC), follicular (FTC), or mixed DTC who had negative whole-body iodine scans but elevated stimulated thyroglobulin (Tg >1 ng/mL) with thyroid-stimulating hormone (TSH >30 μIU/mL) after thyroxine withdrawal. Only patients with negative anti-Tg antibodies and adherence to a three-week iodine-restricted diet were considered. Those who had not undergone total thyroidectomy with subsequent radioactive iodine (RAI) ablation, or who had medullary or anaplastic thyroid carcinoma, were excluded.

Data Collection
Information was obtained from hospital records, including histopathology reports, imaging (whole-body iodine scans, FDG PET/CT), serum Tg levels, treatment details, recurrence, and outcomes. TENIS syndrome was defined as persistent Tg elevation with negative RAI scans. Post-therapy whole-body scans (Rxwhole-body scan (WBS)) were used to assess residual or metastatic disease after RAI ablation. Response to empirical RAI (eRAI) was assessed by comparing Tg levels before treatment and 6–12 months afterward, along with Rxwhole-body scan (WBS) findings.

Statistical Analysis
Baseline characteristics, treatment modalities, and outcomes were summarized using descriptive statistics. Continuous variables were expressed as mean ± standard deviation or median values, and categorical data as frequencies and percentages. Group comparisons employed Chi-square tests for categorical variables and t-tests or non-parametric equivalents for continuous variables. Statistical significance was defined as $p < 0.05$.

3. RESULTS

A total of 33 patients were analyzed, comprising 12 males (36.4%) and 21 females (63.6%), with a mean age of 45.2 ± 13.1 years. Age distribution showed that 5 patients (15.2%) were under 30 years, 18 (54.5%) were between 30–50 years, and 10 (30.3%) were above 50 years. Classical papillary thyroid carcinoma (PTC) was the predominant histology in 20 cases (60.6%), while 8 (24.2%) had PTC variants and 5 (15.2%) had follicular thyroid carcinoma (FTC). Tumor staging revealed 7 patients with T1 disease, 12 with T2, 6 with T3a, and 3 with T3b. Based on ATA 2009 risk stratification, 10 patients (30.3%) were low risk, 15 (45.5%) intermediate, and 8 (24.2%) high risk.

Before TENIS diagnosis, distant metastasis was documented in 6 patients (18.2%): 3 with bone lesions, 2 with lung lesions, and 1 with combined bone and lung involvement. The median administered RAI ablation dose was 3700 MBq (range 1850–

7400 MBq). At the time of TENIS, median serum thyroglobulin was 8 ng/mL (range 1.5–500 ng/mL), with 20 patients (60.6%) recording <10 ng/mL and 13 (39.4%) ≥10 ng/mL. Most patients (25; 66.7%) developed TENIS within six months of their last RAI treatment, while 11 (33.3%) did so after six months.

The mean follow-up duration was 6.5 ± 2.8 years. Ten patients (30.3%) were followed for <5 years, 18 (54.5%) for 5–10 years, and 5 (15.2%) for more than 10 years. PET/CT was performed in 15 patients (45.5%), with positive findings in 10 (66.7%) and negative results in 5 (33.3%). Metastatic disease was identified in 12 patients (36.4%) with nodal involvement and in 8 patients (24.2%) with distant spread. Of the latter, 5 had pulmonary lesions, 2 had combined bone and lung metastases, and 1 showed dissemination to bone, lung, and liver.

With respect to further treatment, 11 patients (33.3%) received empirical radioactive iodine (RAI) (eRAI) therapy alone, 3 (9.1%) underwent salvage surgery, and another 3 (9.1%) had combined surgery and eRAI. Two patients (6.1%) were managed with eRAI plus external radiation, while 1 (3.0%) required revision neck dissection. Twelve patients (36.3%) were observed without additional intervention.

Among the 11 patients who received empirical radioactive iodine (RAI) therapy (eRAI) alone, 6 (54.5%) achieved a decline in thyroglobulin (Tg) levels, 2 (18.1%) remained in the TENIS state, 2 (18.1%) showed disease progression with rising Tg, and 1 (9.1%) was lost to follow-up. Of the 3 patients who underwent salvage surgery, 2 (66.6%) showed biochemical improvement, while 1 (33.3%) persisted in the TENIS state, with no cases of progression or follow-up loss. In the small subgroup treated with combined eRAI and external radiation (N=2), one patient (50%) showed Tg reduction, while the other (50%) continued in the TENIS state. The single case managed with revision neck dissection alone did not show Tg improvement and remained TENIS-positive.

In the observation group (N=12), 6 patients (50%) experienced spontaneous Tg decline, 4 (33.3%) remained in the TENIS state, 1 (8.3%) demonstrated disease progression, and 1 (8.3%) was lost to follow-up. These findings indicate variable responses across treatment modalities, with salvage surgery showing relatively favorable results in selected patients. (Figure 1)

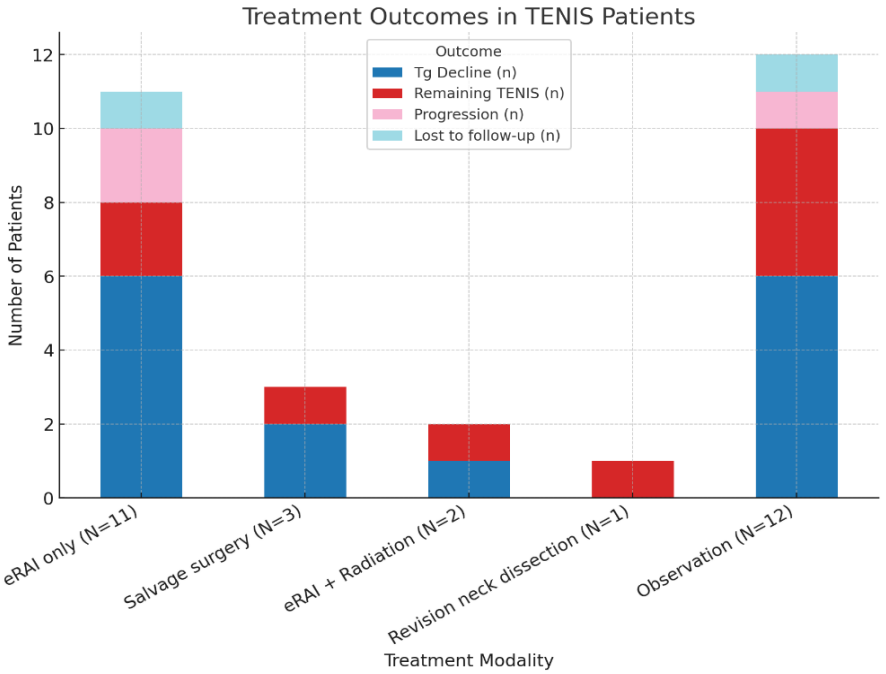

Figure 1: summarizes the treatment outcomes of patients with TENIS syndrome.

Table 4 shows Association between Clinicopathological Parameters and Course of TENIS Disease

Parameters	Chi-square test	p-value
Tumor stage	12.45	0.031
Nodal stage	15.89	0.018
Treatment modality	21.68	0.79

Tumor stage demonstrated a significant correlation with outcomes ($p = 0.031$), with higher stages more often linked to persistent or progressive disease. Nodal stage was also significant ($p = 0.018$), indicating that greater lymph node involvement increased the likelihood of disease persistence or progression. In contrast, treatment modality was not significantly associated with outcome ($p = 0.79$), suggesting that therapeutic response is influenced more by tumor biology and patient-related factors than by the type of intervention used. (Table 1)

4. DISCUSSION

Thyroglobulin Elevated Negative Iodine Scintigraphy Syndrome (TENIS) is a challenging clinical entity in the spectrum of differentiated thyroid carcinoma (DTC). In our series, nearly one-third of patients showed disease persistence or progression despite therapy, underlining its aggressive nature. This observation is consistent with earlier reports that DTC patients resistant to radioactive iodine (RAI) often present with difficult-to-detect and poorly controlled disease【16–18】.

The difficulty in identifying metastases in TENIS is well documented. Sweeney et al. demonstrated that advanced DTC frequently harbors distant metastases not visible on routine whole-body iodine scans【16】. Russo et al. highlighted that dedifferentiation, impaired sodium–iodide symporter function, or sub-centimeter lesions may explain negative scans despite active disease【17】. Our findings, showing TENIS in a significant proportion of patients with elevated Tg, are aligned with these mechanisms.

Empirical radioactive iodine (RAI) therapy in our cohort produced mixed results—some patients showed biochemical response, while others had persistent or progressive disease. This echoes Worden's findings that recurrent DTC with elevated Tg and negative scans often fails to respond to RAI, leading to poor outcomes【18】. Thus, our results reinforce the limited benefit of empiric RAI in advanced or dedifferentiated TENIS.

Tumor stage and nodal involvement were significantly associated with persistence in our study. This parallels observations in thyroid and breast cancers, where higher stage and nodal burden predict worse prognosis【19–21】. Elisei et al. also noted that late-stage disease with multiple nodal metastases correlates with poor survival in DTC【21】. Our findings confirm that tumor biology and disease burden strongly influence outcomes in TENIS.

With respect to treatment, salvage surgery offered favorable biochemical response in selected cases, supporting earlier evidence that surgery remains useful where disease is localized【22}. In contrast, revision neck dissection alone was ineffective, reflecting the need for multimodality approaches. The role of PET/CT was reaffirmed in our cohort, with positive findings in two-thirds of those scanned. This corroborates Asa et al., who emphasized its value in detecting metastases missed by iodine imaging【23】.

Overall, our findings align with prior studies in showing that TENIS is a biologically aggressive subset of DTC, often resistant to RAI. The integration of tumor stage, nodal status, and advanced imaging is critical for risk stratification. Management must be individualized, combining surgery, RAI, and systemic therapy where appropriate, while acknowledging that some patients may achieve spontaneous Tg decline without intervention. Future work should focus on targeted therapies and molecular profiling to improve outcomes in this high-risk group

5. CONCLUSION

This study demonstrates that TENIS syndrome represents an aggressive subset of differentiated thyroid carcinoma, with tumor stage and nodal involvement serving as key predictors of persistence. Metastatic spread, particularly to lymph nodes, lungs, and bones, was frequent. Overall, TENIS remains a difficult condition to treat, requiring individualized strategies tailored to disease burden and patient profile. Long-term surveillance is essential, as outcomes range from spontaneous Tg decline to relentless progression. Future multicentric studies and the incorporation of targeted therapies are needed to improve prognosis in this high-risk subgroup of thyroid cancer.

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