Original Article

Clinicopathological features and outcome of thyroglobulin elevation and negative iodine scintigraphy (TENIS) patients with negative neck ultrasound: Experience from a thyroid carcinoma clinic in India

ABSTRACT

Management of differentiated thyroid carcinoma (DTC) patients with thyroglobulin (Tg) elevation and negative iodine scintigraphy (TENIS) and negative neck ultrasound scan causes considerable diagnostic and therapeutic dilemma, especially in resource-poor settings. The aim of this study was to evaluate clinicopathological features and outcome of TENIS patients with negative neck US attending a thyroid cancer clinic in India. From a DTC database of 722 containing 193 TENIS patients, subjects with negative neck US and negative Tg antibody (TgAb) were selected retrospectively and analyzed using appropriate statistical methods. The study group included 64 patients (male – 17, female – 47, mean age – 44.7 ± 12.8 years) with 54 papillary and 10 follicular thyroid carcinomas, American Thyroid Association (ATA) recurrence risk categorization (2009) – low – 16, intermediate – 28, and high – 2 0. Most of the patients became TENIS within 1 year of diagnosis with median Tg level of 6.5 ng/mL (1.2–996 ng/mL) and mean follow-up of 7.8 years. On follow-up, Tg dropped spontaneously in 27 patients, more among the low and intermediate-risk categories. For those with high or increasing Tg level, further imaging (fluorodeoxyglucose positron emission tomography/computed tomography) was done and 14 out of 18 were positive. Treatment included empiric radioactive iodine therapy-16, external beam radiation therapy (EBRT)-7, and lymph node dissection (LND)-10. A favorable outcome was seen in 36 patients and unfavorable in 28. Distant metastases were associated with unfavorable outcome and poor survival. Progression-free survival was significantly better in the Tg group of <10 at the time of TENIS (111 months) compared to the Tg group >10 (72 months). Tg level dropped spontaneously in nearly half the patients, especially if levels were <10 and more so among the low-risk category. Distant metastasis was predictive of unfavorable outcomes. Along with Tg level, the ATA risk category might help to predict clinical course and reduce unnecessary expensive imaging in resource-poor settings.

Keywords: TENIS, negative Thyroglobulin antibody, differentiated thyroid carcinoma, outcome, progression-free survival.

INTRODUCTION

During the management of differentiated thyroid carcinoma (DTC), it is not uncommon to come across cases with detectable or elevated thyroglobulin (Tg) and a negative diagnostic whole-body iodine-131 scan (DxWBS I). This is referred to as Tg elevation and negative iodine scintigraphy (TENIS) syndrome and is seen in 10%–27%.[1,2] This causes considerable diagnostic and therapeutic dilemma. In such patients, ultrasound (US) neck helps in identifying local disease which can be managed appropriately and may sometimes even eliminate the need for empiric radioactive

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iodine therapy (eRAI). However, when the neck US is negative, these patients might need further studies such as computed tomography (CT) of the chest, and fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT) to localize iodine nonavid disease and to decide on further treatment plans. These expensive imaging modalities may not be affordable to many.

Many such patients may undergo eRAI with high dose I131. The posttherapy scan (RxWBS I) after eRAI may show iodine avid disease or may be negative. The use of eRAI is controversial and all experts do not share the same view.[3-6] Moreover, this may add to the cost of treatment and may not be a feasible option in a resource-poor setting like ours. Hence, the management of TENIS patients, especially those with negative US neck, poses a challenge. We aimed at evaluating this group of TENIS patients (henceforth referred to as the TENIS subgroup) to see if factors contributing to the outcome could be predicted. The objective of the present study was to evaluate the prevalence of this TENIS subgroup in our population of DTC, their clinicopathological, treatment characteristics, and outcome.

SUBJECTS AND METHODS

This was a retrospective study conducted for which the institutional ethical committee approval (dated November 9, 2020; IEC-AIMS-2020-ENDO-188) was given. The patients were taken from the thyroid carcinoma database after taking their informed consent for data collection and its usage for research purposes. Consecutive patients were selected who fulfilled the following inclusion criteria and formed the study cohort (TENIS subgroup).

Patients with DTC who at first or any subsequent evaluation had

- A negative DxWBS I but had detectable stimulated Tg >1.0 ng/mL (when thyroid-stimulating hormone (TSH) after thyroxine withdrawal was >30 micro IU/mL) on the day of the scan, after having been on a low iodine diet for 3 weeks
- Negative Tg antibody (TgAb) defined as any value below the upper limit of the reference range of the assay used and
- Negative neck US.

Excluded were patients <18 years of age, those who had not received RAI ablation after total thyroidectomy, other thyroid cancers, and those with insufficient data for analysis. Out of this group, those who had at least three stimulated Tg on follow-up formed the study cohort.

The approach to the treatment of DTC at our Institute was published elsewhere.[7] Risk stratification for recurrence/persistence was performed using the American Thyroid Association (ATA) 2009 Guidelines.[8] The management of TENIS patients was based on histopathology reports, RxWBS I after ablation, patient preference, and affordability after discussion at the Thyroid Tumor Board, which comprised of all concerned specialists. The decision was made either for follow-up at regular intervals or for further imaging such as chest CT or FDG PET/CT to look for iodine nonavid lesions. If nonavid lesions were found, they were treated appropriately. If FDG PET/CT was negative, either an eRAI was given or the patients were kept under follow-up. If response to eRAI therapy was documented, additional doses were given till the uptake disappeared in the RxWBS I after therapy and/or Tg became undetectable. Further doses were withheld if the first eRAI treatment appeared ineffective.

Short-term response to eRAI therapy was defined as the change in Tg from before eRAI therapy to that of 6–12 months after treatment and the immediate RxWBS I findings as follows:

- Negative response: When RxWBS after eRAI was negative and Tg 6 to 12 months later, did not fall or rose
- Positive response: RxWBS after eRAI was positive or Tg dropped more than 50% in 6 to 12 months in those where RxWBS was negative
- Partial response: RxWBS negative after eRAI and Tg drop 6 to 12 months later was <50%.

To evaluate the outcome at the last follow-up, clinical endpoints were used to define five categories as recommended by Tuttle *et al*.[9]

No evidence of disease (NED), persistent biochemical disease (PBD), persistent structural disease (PSD), recurrent disease (RD), and indeterminate disease (ID).

These were then grouped into two for the sake of analysis: favorable response (NED and ID) and unfavorable response (PSD, PBD, and RD).

Laboratory assays

Tg level was determined by the Electrochemiluminescence Assay (ELECSYS 2010; Roche, Switzerland). TgAb was measured using the ARCHITECT anti-Tg assay (Abbott, USA) from 2010 to mid 2017. From July 2017, ELECSYS anti-Tg assay (Roche Laboratories) was used. TSH was assayed using the ARCHITECT TSH assay from 2010 to mid 2017. From then on, the testing used the Electrochemiluminescence Assay (Roche). The reference range was 0.005–100 μIU/mL with a functional sensitivity of 0.014 μIU/mL.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 software (IBM Corporation, Armonk, NY, USA). Categorical variables were expressed as frequency and percentage. Numerical variables were presented as median as well as mean and standard deviation. Chi-square test was used for the comparison of quantitative data between the two groups. Logistics analysis was used for univariate and multivariate analysis. Kaplan–Meier method was used to calculate progression-free survival (PFS) and a log-rank test was applied for calculating significance. Receiver operating characteristic (ROC) curve analysis was used to mark the Tg cutoff values above which, both the sensitivity and specificity for the unfavorable outcome reached an optimal value. The values of $P < 0.05$ were considered statistically significant with 95% of confidence interval.

RESULTS

From a DTC database of 722 patients, 193 (26.7%) with TENIS were identified. Among these, 101 patients had negative neck US and negative Tg antibody. From these, 64 patients with at least 3 subsequent Tg values and 2-year follow-up were included in the present study (TENIS subgroup). Baseline characteristics of the study cohort are described in Table 1.

More than 80% of the patients became TENIS by 1 year and almost half had Tg level <10 at that time. Majority of the tumor types (84.4%) were papillary thyroid carcinoma (PTC) and its variants and 43.8% belonged to the intermediate risk for recurrence (ATA 2009). The mean duration of follow-up was 7.8 ± 2.5 years and 75% had 5–10 years follow-up [Table 2].

Since half the cohort had Tg level below 10 ng/mL, these patients were divided into two groups, Tg <10 and Tg >10 for comparison [Figure 1]. The distribution of variables in the two Tg categories showed that basic variables were comparable except that the low-risk ATA category was more common in Tg <10 group.

Follow-up

During follow-up, spontaneous drop in Tg level was seen in 27/64 patients (42.2%). In the rest, distant metastases (DM) were detected in nine patients and lymph node (LN) metastases appeared in 20 patients [Table 2]. LN metastases were detected by US in 12 patients, FDG-PET/CT in five patients, posttherapy scan in one patient, and by both US and FDG-PET/CT in two patients. Further evaluation including FDG-PET/CT scan was done for 18 subjects with high or increasing Tg levels, out of which 14 were positive: LN metastasis in 7 and DM in 10 [Table 3]. Treatment constituted of LN dissection (LND-10), eRAI therapy (16), and external beam radiation therapy (EBRT-7).

Table 1: Baseline characteristics of thyroglobulin elevation and negative iodine scintigraphy subgroup (*n*=64)

Variable	*n* (%)
Gender	
Male	17 (26.6)
Female	47 (73.4)
Mean age at presentation (years)	44.7±12.8
Age category	
<30	7 (10.9)
30-50	35 (54.7)
>50	22 (34.4)
Type of tumor	
Classical PTC	30 (46.9)
Other variants of PTC	24 (37.5)
FTC	10 (15.6)
ATA 2009 risk stratification	
Low	16 (25)
Intermediate	28 (43.8)
High	20 (31.3)
Presence of distant metastasis prior to becoming TENIS	12 (18.8)
Bone	6
Lung	2
Bone and lung	3
Bone, lung, and liver	1
Median dose of RAI ablation (MBq) (range)	3330 (1850-7030)
Tg level at time of TENIS (ng/mL)	
Median	6.5 (1.2-996)
<10	35 (54.7)
>10	29 (45.3)
Distribution of Tg level (ng/mL)	
<2	11 (17.2)
2-10	24 (37.5)
10-20	8 (12.5)
20-50	8 (12.5)
50-100	6 (9.4)
>100	7 (10.9)
Time of becoming TENIS from diagnosis	
6 months	40 (62.5)
1 year	13 (20.3)
1.5 years	8 (12.5)
2 years	3 (4.7)
Time of becoming TENIS from the last dose of RAI therapy	
6 months	46 (71.9)
1 year	10 (15.6)
1.5 years	5 (7.8)
2 years	3 (4.7)

PTC: Papillary thyroid carcinoma, FTC: Follicular thyroid carcinoma, RAI: Radioactive iodine, TENIS: Thyroglobulin elevation and negative iodine scintigraphy, ATA: American Thyroid Association, Tg: Thyroglobulin

Empiric radioactive iodine therapy

In the TENIS subgroup of 64 patients, 16 (11 females and 5 males) were given eRAI therapy [Table 4]. Tg at the time of TENIS ranged from 1.2 to 996 ng/mL. Among these, 12 had FDG PET/CT Scan before eRAI therapy, of which 11 were

positive and showed lesions in thyroid bed and metastatic lesions in the neck nodes, lung, skeleton, and liver. Post eRAI therapy, I 131 scan was positive in four patients, two showing neck uptake only, one showing bone and other liver metastasis. Among the 12 who had single-dose eRAI only, six showed positive response, one had partial response, while the negative response was seen in five patients. Of the four patients who received two doses of eRIA, one showed partial response, while the remaining three had excellent response, however, with persistent high Tg.

Table 2: Follow-up and treatment modalities of thyroglobulin elevation and negative iodine scintigraphy subgroup (*n*=64)

Variables	*n* (%)
Mean follow-up (years)	7.6±2.5 (4-14)
Follow-up duration (years)	
<5	7 (10.9)
5-10	48 (75)
>10	9 (14.1)
PET CT scan done	18 (28.1)
Positive	14 (77.8)
Negative	4 (22.2)
Metastasis detected	
Lymph node metastasis	20 (31.3) (USG-12, FDGPET-5, both-2 and one by posttherapy scan)
Distant metastasis	9 (14.1)
Lung	6
Bone and lung	2
Bone, lung, and liver	1
Further treatment	
eRAI therapy	16 (25)
Salvage surgeries (LND)	10 (15.6)
EBRT	7 (10.9) (for distant mets-4 for thyroid bed-3)
Course of the disease	
Remaining TENIS	3 (4.7)
Tg dropping spontaneously	27 (42.1)
Tg dropped by treatment	6 (9.4) (3 LND and 3 RAI)
Tg increasing	28 (43.8)

eRAI: Empiric radioactive iodine, LND: Lymph node dissection, EBRT: External beam radiation therapy, TENIS: Thyroglobulin elevation and negative iodine scintigraphy, Tg: Thyroglobulin, RAI: Radioactive iodine, PET CT: Positron emission tomography computed tomography, USG: Ultrasonography, FDGPET: Fluorodeoxyglucose positron emission tomography

Outcome at last follow-up

When the outcome of these patients was assessed at the last follow-up, 33 (51.6%) had become NED. Spontaneous normalization of Tg was seen in 27 patients, whereas three became NED after further RAI therapy and three after LN excision. The mean time to become NED was 4.07 ± 1.99 years. Patients who had spontaneous drop in Tg were comparable to the rest in terms of age, gender, time

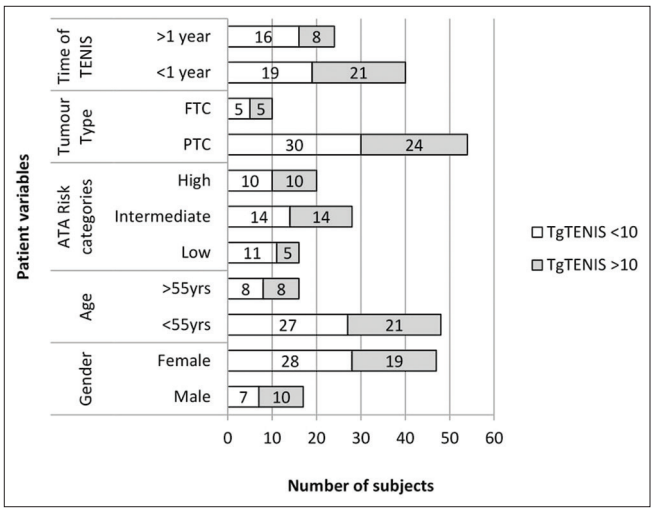

Figure 1: Comparison of the distribution of variables among Tg TENIS groups. Tg: Thyroglobulin, TENIS: Thyroglobulin elevation and negative iodine scintigraphy

Table 3: Details of thyroglobulin elevation and negative iodine scintigraphy patients with positive fluorodeoxyglucose-positron emission tomography/computed tomography scan (*n*=14)

Patient	Age (years)	Gender	FDG PET/CT findings	Interventions	Follow-up
1	68	Male	LN	None	Developed adrenal mass, sepsis, acute renal failure, and died
2	37	Male	LN	eRAI	Ultrasound positive
3	52	Female	Thyroid bed+LN	eRAI	Tg dropped
4	56	Female	LN+bone	Palliative EBRT and sorafenib	No significant change
5	78	Male	LN+lung	eRAI	Tg after 6 months not available
6	19	Female	LN+lung	eRAI	RxWBS showed right cervical node uptake
7	60	Female	LN+lung	none	
8	45	Male	Lung	eRAI	RxWBS negative, no Tg available
9	55	Female	Lung	eRAI	RxWBS right thyroid bed and neck node uptake
10	44	Female	Lung	eRAI	RxWBS negative, no drop in Tg
11	61	Male	Bone	None	
12	69	Female	Pleural nodule	eRAI	RxWBS negative, no drop in Tg
13	54	Female	Nonavid lesions	None	
14	30	Female	Nonavid lesions	None	

LN: Lymph node, eRAI: Empiric radioactive iodine, Tg: Thyroglobulin, RxWBS: Post therapy whole-body scan, EBRT: External beam radiation therapy, FDG PET CT: Fluorodeoxyglucose positron emission tomography computed tomography

Table 4: Characteristics and response of patients who received empiric radioactive iodine therapy (*n*=16)

Variables	*n* (%)
Gender	
Male	5 (31.2)
Female	11 (68.8)
Age (years)	
<55	8 (50)
>55	8 (50)
Type of tumor	
PTC	11 (68.8)
FTC	5 (31.2)
ATA risk category	
Low	1 (6.2)
Intermediate	7 (43.8)
High	8 (50)
Initial Tg at the time of TENIS (ng/mL)	
5-10	2 (10)
10-50	5 (25)
50-100	5 (25)
100-500	6 (30)
>500	2 (10)
DM±lymph node metastasis	10 (62.5)
Lymph node metastasis alone	5 (31.2)
Thyroid bed lesions	1 (6.3)
Number of eRAI therapy	
Once	12 (75)
More than once	4 (25)
Response (20 treatments)	
Positive	7 (35)
Partial	5 (25)
Negative	8 (40)

ATA: American Thyroid Association, DM: Distant metastasis, eRAI: Empiric radioactive iodine, Tg: Thyroglobulin, PTC: Papillary thyroid carcinoma, FTC: Follicular thyroid carcinoma, TENIS: Thyroglobulin elevation and negative iodine scintigraphy

of becoming TENIS, time from last RAI therapy, dose of RAI, and type of tumor. However, ATA high-risk category (4/27 vs. 16/37; *P* 0.004), Tg level >10 (4/27 vs. 25/37; $P < 0.01$), presence of distant metastasis (2/27 vs. 19/37: $P < 0.01$), and lymph node metastasis (9/27 vs. 25/37; *P* 0.007) were significantly lower in this group.

Of the 20 PSD patients, 16 showed DM and four had persistent LN metastasis. Among those with DM, 11 had progressive disease with increasing Tg and worsening structural disease. Among the eight PBD patients, one had bone metastasis but on follow-up, all showed a falling trend in Tg except one who showed a rise. The three ID patients showed a falling trend in Tg.

Empiric radioactive iodine therapy and outcome

Although the short-term response to eRAI was encouraging (of the 20 treatments, 12 showing some form of response with falling Tg level), only two became NED/ID on the last evaluation. Eleven continued to have PSD (two lymph nodal metastasis, two thyroid bed lesions, and seven lung/bone metastases) and three died from progressive disease. However, of these 16 patients, nine had undergone LN exploration and five had EBRT as well later in the course. All these additional treatments could have influenced the final outcome of these patients and hence, the independent impact of eRAI therapy on outcome could not be assessed.

Thyroglobulin level and outcome

When Tg level at TENIS was <10 ng/mL, almost 70% became NED, but only 40% did so when Tg was >10 ng/mL and this difference was statistically significant ($P = 0.007$). Among NED, spontaneous Tg drop was seen in 22/24 in Tg <10 compared to 5/9 patients in Tg >10, the difference being significant ($P = 0.017$). Moreover, DM was more common (41.4%) in Tg >10 compared to 17.1% in Tg <10 group and this difference was also statistically significant ($P = 0.03$). When Tg level was <2 ng/mL, all 11 patients became NED (10 patients Tg dropped spontaneously, while one patient had bone metastasis and Tg dropped after RAI treatment). On the contrary, all seven patients with Tg level >100 ng/mL had persistent disease, five with DM, and two with LN metastasis [Figure 2].

Univariate analysis showed all factors except gender, time of TENIS, and type of tumor associated significantly with unfavorable outcome [Table 5], but multivariate analysis showed that only DM was significantly associated with unfavorable outcome ($P = 0.002$).

Thyroglobulin level cutoff for predicting outcome

ROC curve analyses showed that the highest area under the curve in terms of best compromise between sensitivity and specificity for unfavorable outcome (sensitivity – 68.8%; specificity – 72.3%) was achieved at a stimulated Tg level >10.42 ng/mL [Figure 3]. Overall median survival was 112 months for this cohort. When PFS was calculated using Kaplan–Meier method [Figure 4], a significant difference was noted ($P = 0.03$), with better PFS in those with Tg <10 ng/mL group (111 months) compared to 72 months for Tg >10 [Figure 4].

American Thyroid Association risk category and outcome

ATA risk levels and Tg TENIS were used in combination for predicting the outcome on the last follow-up [Figure 5]. Best results were seen when initial risk was low and Tg at TENIS <10 ng/mL, ten out of 11 such patients having had spontaneous conversion to NED. One patient had PBD, but the Tg level showed falling trend. On the other hand, when patients initially fell into the high risk (20/64), the outcome was unfavorable even with a Tg of <10 ng/mL. Although NED

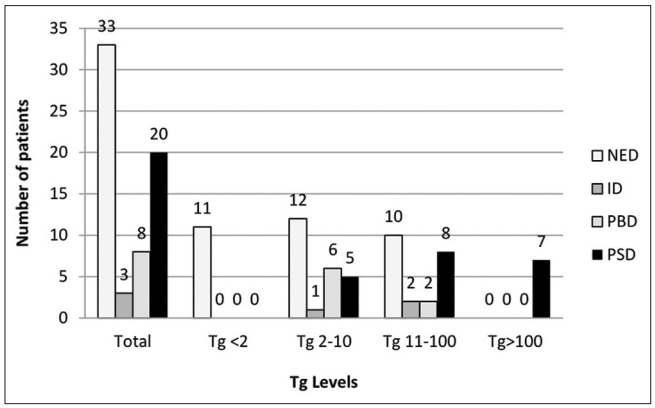

Figure 2: Thyroglobulin levels and outcome of thyroglobulin elevation and negative iodine scintigraphy subgroup

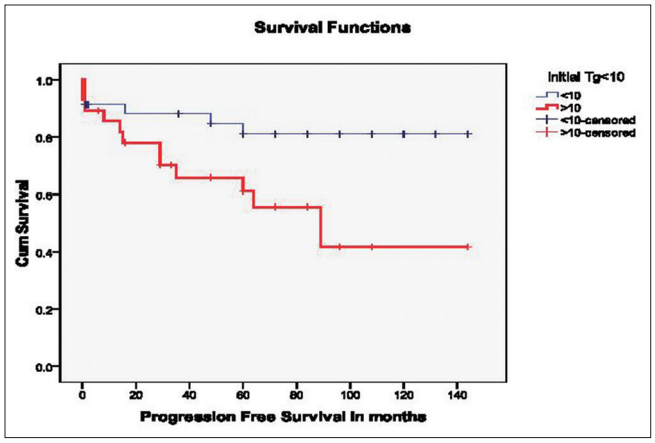

Figure 4: Comparison of progression-free survival in patients with thyroglobulin >10 and thyroglobulin <10

occurred spontaneously in one patient, four others required additional therapy. With high risk and Tg >10 ng/mL, only one patient became NED and the rest had persistent and progressive disease. This kind of difference in outcome was not very obvious in the intermediate-risk category.

DISCUSSION

The present study evaluated a subgroup of 64 patients with DTC and negative neck US, who had become TENIS at different periods of follow-up. The prevalence of this TENIS subgroup in this DTC cohort was comparable with that of TENIS from other publications. This study population, however, was different from conventional TENIS since, by a negative US, we largely eliminated local disease which could be managed differently. Patients showed similar age and gender distribution compared to our general DTC patients.[9] The distribution of tumor types was not different either. However, when ATA risk categories were compared with our general DTC cohort, more TENIS patients had high risk (29.5% vs. 8.9%) and less, low risk (24.5% vs. 41%).[9]

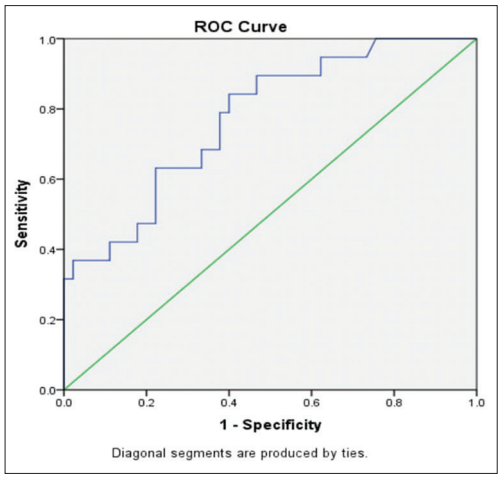

Figure 3: Receiver operating characteristic curve analysis demonstrating thyroglobulin cutoff for unfavorable outcome

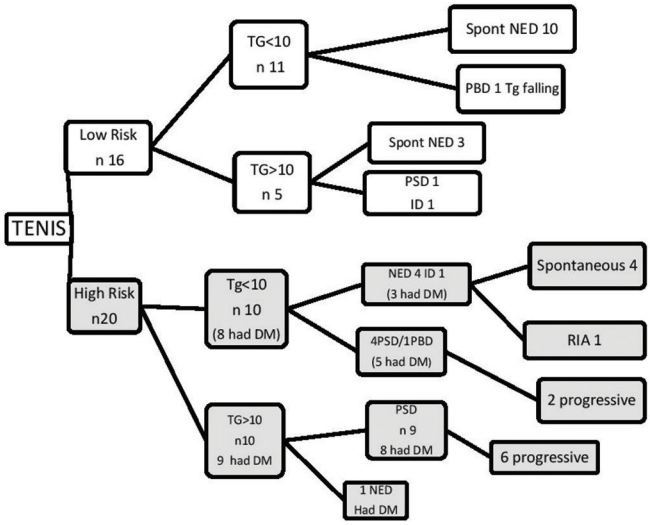

Figure 5: Comparison of Tg TENIS group and outcome among American Thyroid Association low- and high-risk categories. Tg: Thyroglobulin, TENIS: Thyroglobulin elevation and negative iodine scintigraphy

One important finding of this study is that normalization of Tg level is possible in nearly 50% of US neck negative TENIS patients and majority did so spontaneously. Although not from a similar TENIS subgroup, Pacini *et al*. found that 67.9% of untreated TENIS patients normalized Tg and no structural disease ever appeared in these patients on follow-up.[5]

In addition, the present study showed that a Tg cutoff at TENIS of 10.4 ng/mL can be helpful in predicting the long-term outcome in this subgroup. A value above this cutoff predicted the possibility of PSD and disease progression.The cutoff for Tg level of 10.4 ng/mL in the present study validates the ATA recommendation that one dose of eRAI can be given when Tg is >10 ng/mL and rising.[10] PFS in our patients is also significantly better with a Tg <10. However, the best prediction of outcome in our cohort was on combining

Table 5: Univariate analysis of factors associated with unfavorable outcome in thyroglobulin elevation and negative iodine scintigraphy subgroup

Variable category	*n*	Outcome		*P*
		Favorable NED/ID (*n*-36), *n* (%)	Unfavorable PSD/PBD (*n*-28), *n* (%)	
Age category				
<55	48	32 (66.7)	16 (33.3)	0.004
>55	16	4 (25)	2 (75)	
Gender				
Male	17	7 (48.1)	10 (52.7)	>0.05
Female	47	29 61.7)	18 (31.3)	
Risk stratification				
Low	16	14 (87.5)	2 (12.5)	0.003
Intermediate	28	16 (57.1)	12 (42.9)	
High	20	6 (30)	14 (70)	
Tg level				
<10	35	24 (68.6)	11 (31.4)	0.023
>10	29	12 (41.4)	17 (59.6)	
Time to TENIS (months)				
6	40	25 (62.5)	15 (37.5)	>0.05
>6	24	11 (45.8)	13 (54.2)	
Distant metastasis (12 preexisting+9 newly detected)				
Yes	21	4 (19)	17 (81)	<0.01
No	43	32 (74.4)	11 (24.6)	
LN metastasis (total)				
Yes	34	15 (44.1)	19 (55.9)	0.037
No	30	21 (70)	9 (30)	
Salvage surgeries (total)				
Yes	17	5 (29.4)	12 (70.6)	<0.01
No	47	31 (65.9)	16 (34.1)	
Tumor type				
PTC	54	33 (61.1)	21 (38.9)	>0.05
FTC	10	3 (30)	7 (70)	
eRAI therapy				
Yes	16	2 (12.5)	14 (87.5)	<0.01
No	48	34 (70.8)	14 (29.2)	
FDG PET/CT positive				
Yes	18	3 (16.6)	15 (83.3)	<0.01
No	4	1	3	

LN: Lymph node, Tg: Thyroglobulin, PTC: Papillary thyroid carcinoma, FTC: Follicular thyroid carcinoma, TENIS: Thyroglobulin elevation and negative iodine scintigraphy, FDG PET CT: Fluorodeoxyglucose positron emission tomography computed tomography, eRAI: Empiric radioactive iodine, NED/ID: No evidence of disease/indeterminate disease, PSD/PBD: Persistent structural disease/persistent biochemical disease

ATA risk category and Tg level [Figure 4]. This shows the importance of considering the initial risk category along with Tg level in determining the follow-up of this TENIS subgroup.

Compared to the general DTC cohort, where no patients died (236 patients with DTC with median follow-up 53 months), three disease-specific deaths occurred in this small cohort (4.6%) suggesting that our TENIS subgroup represents a form of aggressive DTC requiring meticulous follow-up and aggressive management.[9] Although eRAI therapy was associated with poor outcome in this cohort, it may be due to the fact that most of these patients fell in the high-risk category and had DM. We were unable to assess the independent effect of eRAI on the outcome as some of these patients underwent EBRT or further surgeries which could have influenced the outcome. This study, however, is not powered enough to make any strong conclusion because of the small sample size. Tyrosine kinase inhibitors (TKI) could not be used in many because of socioeconomic reasons.

Strengths and limitations

The strength of this study is the uniqueness of dealing with a rare clinical entity, with reasonable follow-up period without much dropouts. The addition of neck US before considering eRAI which was not done in many such studies helps to make management cost-effective in our resource-limited setting. The study findings have improved our understanding of the course and outcome of TENIS patients in this part of the

world. The added strength of this study is the use of ATA recurrence risk stratification along with Tg level in deciding the management strategy. Larger studies will be needed for confirmation.

Limitations include the retrospective nature and small sample size, especially those given eRAI which precluded subgroup analysis. Moreover, FDG PET/CT scans could not be performed for all patients due to socioeconomical reasons and hence, the PET positivity of TENIS and its influence on outcome could not be fully assessed.

CONCLUSION

The present study showed that patients with TENIS and a negative neck US who have Tg at TENIS <10 ng/mL should do well and can be maintained on follow-up, especially if they fall into the ATA 2009 low-risk category. On the other hand, when these patients belong to the high-risk category and with Tg >10 ng/mL, they need to be closely followed and periodically imaged for disease progression. DM portends unfavorable outcomes. eRAI given to such high-risk patients did not benefit the outcome. Other than the Tg cutoff of 10 ng/mL, the ATA risk category can possibly help to predict the outcome, but larger studies are needed for confirmation. In those who show poor response to eRAI, early consideration should be given for other modes of therapy such as TKIs, EBRT, and metastases resection.

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Conflicts of interest

There are no conflicts of interest.

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