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RESEARCH ARTICLE

Thyroglobulin level before ablative radioactive iodine correlates with the clinical response and survival among patients with differentiated thyroid carcinoma

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ABSTRACT

Background: Thyroid carcinoma is the most common endocrine malignancy, accounting for 3–4% of all cancers. **Aim:** This retrospective study was designed to correlate stimulated thyroglobulin (sTG) levels before treatment with radioactive iodine (RAI) and the response in patients with differentiated thyroid cancer after thyroidectomy, as well as to evaluate sTG before RAI impact on disease free survival (DFS). **Patients and Methods:** This study included fifty-seven patients (43 females and 32 males). who had recruited in the period between January 2015 and April 2020 with the following criteria: first operated with total thyroidectomy with confirmed pathology of differentiated thyroid carcinoma (DTC) and then treated with RAI ablation. 91.2% of the patients had papillary thyroid carcinoma (PTC) and 44 (77.2%) were early-stage T1 and T2, while 13 (22.9%) were late stage T3 and T4. **Results:** The post ablation TG was <1 ng/ml in 52.6%, from 1-10 ng/ml in 36.8% and >10 ng/ml in 10.5% of patients. The univariate and multivariate analyses showed disease stage and RAI dose as two independent prognostic factors of DFS. However, factors as age, gender, histopathological type, T-stage, nodal status, and sTG level were of no statistical significance to DFS. In pairwise Fisher's exact tests statistical significance difference was irrelevant between all pairs (P=0.303) comparing intermediate vs. both excellent and incomplete. Also, there was a significant difference in the baseline level of sTG between the three levels of response (P=0.05). The low levels sTG was correlated with the most excellent response, while, most incomplete response showed high level (P=0.025). Comparing the level in excellent vs. intermediate and between intermediate vs. incomplete showed no statistical significance (P=0.145 and P=0.422), respectively. **Conclusion:** The sTG level is associated with risk stratification in patients with DTC. sTG is considered as response-to-initial therapy predictor, recurrence, and metastasis.

Keywords: Ablative RAI response; DTC; Differentiated thyroid cancer; Thyroglobulin; Thyroid cancer; sTG

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INTRODUCTION

The most prevalent endocrine malignancy is thyroid carcinoma, which has histological subtypes such as papillary and follicular. Both papillary and follicular are known as differentiated thyroid carcinomas (DTC) and represent 95 % of thyroid cancers (Chou, et al. 2022). Radioactive iodine (RAI) is highly concentrated in the thyroid follicular cells, is used to completely eradicate the post-operative thyroid remnant in DTC patients. The standard of care for DTC patients has been either a complete or nearly complete thyroidectomy followed by RAI therapy (Tarasova, et al. 2017). Patients with low-risk DTC who receive low-dosage RAI after a complete or nearly complete thyroidectomy showed no appreciable difference in the recurrence risk when compared with patients who received high-dose RAI (Kersting, et al. 2021).

In DTC, serum thyroglobulin (TG) is considered as the initial biochemical marker and an independent indicator for disease persistence and/or recurrence. A great response to treatment is indicated by undetectable TG measured, while patients under TSH

suppression following complete thyroidectomy and radio-iodine ablation. TG elevation, on the other hand, might signify disease recurrence (Guastapaglia, et al. 2021).

The main aim of this study was to correlate the levels of stimulated TG (sTG) before RAI therapy to the response to RAI in patients with DTC who underwent thyroidectomy. The study aimed also to evaluate the pretreatment levels of sTG and its impact on DFS.

METHODS and DATA

In silico Analysis

According to Kyoto Encyclopedia of Genes and Genomes (KEGG) (Last updated: September 23, 2022) integrated database consisting of sixteen databases (Accessed Feb. 2nd, 2023) thyroid cancer genetic alteration pathway https://www.genome.jp/entry/hsa05216 is presented in Figure 1. Normal thyrocytes via genetic alteration(s) give rise to follicular adenoma followed by carcinoma, which is together with papillary carcinoma constitutes undifferentiated thyroid cancer.

Cancer definition, types, stages, treatment of stages I, II, and III Papillary and Follicular Thyroid Cancer (Localized/Regional) relation to survival, gender, and age retrieved from https://www.cancer.gov/types/thyroid/patient/thyroid-treatment-pdq#_94. According to the National Cancer Institute (NCI) https://seer.cancer.gov/statfacts/html/thyro.html (Accessed Feb. 22nd, 2023) Thyroid Cancer - Cancer Stat Facts: Thyroid cancer is most frequently diagnosed among people aged 45–54. Age at diagnosis 45-55, with 5 years relative high survival, % of cases bystage; localized (65%) confined to primary site and regional (29%) spread to regional LNs from SEER 12 estimated of new cases and deaths in 2022.

Study type: This is a retrospective analytic cohort study.

PATIENTS

Fifty-seven patients with DTC treated with RAI ablation after total thyroidectomy were involved in the current study. All 57 patients were treated at Clinical Oncology and Nuclear Medicine Department at Mansoura University Main Hospitals, Egypt in the period between January 2015 to April 2020.

Ethical consent: Approval of the study was obtained from Mansoura University Academic and Ethical Committee. All patients had been informed with the study to agree and sign an informed consent (I.C) if accept of participate in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Demographic, clinical and pathological data: collected included age, sex, histologic subtypes, sTG, stage at diagnosis, treatment date, RAI dose, response to RAI, and DFS. All the following laboratory tests (serum T3, T4, TSH, baseline serum TG, thyroglobulin antibodies (anti-TG), complete blood count/picture (CBC), liver and kidney functions tests, serum calcium, and pregnancy test for female patients if they are in the childbearing period (CBP). Postoperative neck ultrasound and Chest x-ray were also done.

All female patients in the CBP were referred to Obstetrics and Gynecology Department, Mansoura University Hospitals, to confirm proper contraception, meanwhile, all patients were instructed to have a low-iodine diet for at least 2 weeks before starting treatment by the RAI.

https://www.genome.jp/pathway/hsa05216

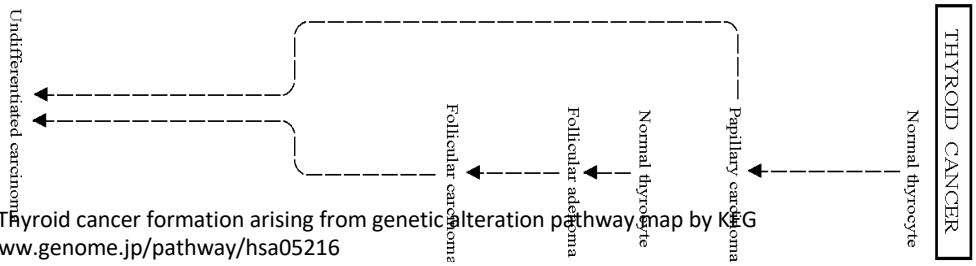

Figure 1. Thyroid cancer formation arising from genetic alteration pathway map by KEGG https://www.genome.jp/pathway/hsa05216

Therapy was total thyroidectomy then if remnant is there, ablation by RAI (I^{131}) administration is a must. Ablative RAI was received after withdrawal of thyroid hormone for 4-6 weeks to enable rising of serum TSH to the level of 25-30 mU/L. Following RAI, patients' isolation in the hospital is for doses > 80 mCi, while lower doses were directed to home isolation of 5-7 days.

A post RAT administration whole-body iodine scans were done 5-7 days later, where patients were divided into 3 types based on their radiologist report as "the response to RAI" as excellent response; defined when patients have a negative post therapeutic imaging along with low levels of TG <0.2 ng/ml or sTG <1.0 ng/ml, and absent anti-TG levels. Indeterminate response is defined when patients present any of the following; non-specific findings on imaging studies or faint uptake in thyroid bed on RAI scanning, in addition to suppressed TG detectable < 1 ng/ml, or sTG <10 ng/ml or stable or declining anti-TG levels. Finally, incomplete response is defined when patients' suppressed TG ≥ 1ng/ml or sTG ≥10 ng/ml or rising anti-TG levels, or biochemical incomplete response if negative imaging.

Pathological characteristics: differentiated thyroid cancer pathology papillary or follicular. TNM classification; T: T1-T4 and any N, M0, as defined by The American Joint Committee on Cancer (AJCC)

- T; T1 tumor size ≤2 cm in greatest dimension and is limited to the thyroid,
- T1a tumor ≤ 1 cm, limited to the thyroid,
- T1b tumor > 1 cm, but ≤ 2 cm in greatest dimension, limited to the thyroid,
- T2 tumor size > 2 cm, but ≤ 4 cm, limited to the thyroid,
- T3 tumor size > 4 cm, limited to the thyroid or any tumor with gross extrathyroidal extension invading only strap muscles,
- T3a tumor size >4 cm, limited to the thyroid,
- T3b any size tumor with gross extrathyroidal extension invading only strap muscles, eg, extension to sternothyroid, sternohyoid, thyrohyoid, or omohyoid muscles,
- T4a any size tumor with gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve,
- T4b any size tumor with gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels,
- While, for the nodal staging (N),
- N0a one or more cytologically or histologically confirmed benign lymph nodes (LN),
- N0b no radiologic or clinical evidence of locoregional LN metastasis,
- N1 regional LN metastasis,
- N1a metastases to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian or upper mediastinal) LN, either unilateral or bilateral disease,
- N1b metastases to unilateral, bilateral, or contralateral neck LN (levels I, II, III, IV, or V) or retropharyngeal LN.

Inclusion criteria: all patients with differentiated thyroid carcinoma undergoing total thyroidectomy.

Exclusion criteria: prior history of RAI administration, elevated anti-TG antibodies, and **m**etastatic thyroid carcinoma.

Statistical Analysis

Data collected, coded, processed, and analyzed using SPSS (Statistical Package for Social Sciences) version 26 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data to be tested for normal distribution using the Shapiro Walk test. Numerical data are expressed as mean ± standard deviation (S.D) or median (interquartile range; 25^{th}-75th) if appropriate. Qualitative data are expressed as n (%) frequency(percentage). The univariate analysis will be performed using the log-rank test. Multivariate analysis will be performed using Cox regression. Survival analysis will be done using the Kaplan-Meier method and a comparison between survival curves will be done using the log-rank test. Disease-free survival (DFS) will be calculated from the date of diagnosis to the date of disease progression. The prognostic factors determining response to RAI ablation to be tested by Fisher's Exact test. A *p*-value less than 0.05 will be considered statistically significant.

RESULTS

57 patients with DTC treated with RAI ablation after total thyroidectomy at the Clinical Oncology and Nuclear Medicine Department at Mansoura University Main Hospitals in the period between January 2015 and April 2020. Patients mean age ±S. D was 40.7 years ± 12.9. Most cases 43 (75.4%) were female gender. Although most of the cases were presented with early T-stage disease 44(77.2%), the majority of the cases (52.6%) were presented with positive LN. The most common TNM/AJCC stage was stage I; 93% and the most pathological type was PTC; 91.2%. 70% of cases had negative post-ablation whole body iodine scan, while 22.8% had faint uptake, and 7% had large residual. The median baseline sTG was 2. More than half of the cases, 52.6%, had successful ablation results (TG <1ng/ml), while 36.8% had post ablation TG (1-10ng/ml), 10.5% had post ablation TG > 10ng/ml, and positive serum anti-TG in 1.8%. Response to ablation 6-months after RAI was excellent in 43.9% of the cases, while intermediate response was found in 40.4% of them and an incomplete response in 15.8%. The median RAI dose patients received was 100 mci.

Recurrence or metastasis occurred only in patients who received RAI dose ≥ 100, so the DFS median was reported only for RAI dose ≥100 and was 71-months. For TNM/AJCC stage II DFS median = 31-months (Table 2). The univariate and multivariate analyses are represented in Table 2 which shows TNM/AJCC stage II vs. stage I, and RAI dose ≥100 vs. <100 as the most independent prognostic factors of DFS. The age, gender, histopathological type, T-stage, nodal status, and TG level were all without statistical significance. Survival analysis was done using the Kaplan-Meier method log-rank test. DFS calculated from the date of diagnosis to the date of disease progression. Figures 2 and 3 present the relation between TNM-stage or RAI dose (millicuries), respectively, to DFS. Time is presented in months and the event is disease recurrence.

Table 3 depicts the prognostic factors to determine response to post-RAI ablation, at 6-months as diagnosis treatment interval, which revealed a statistically significant difference by

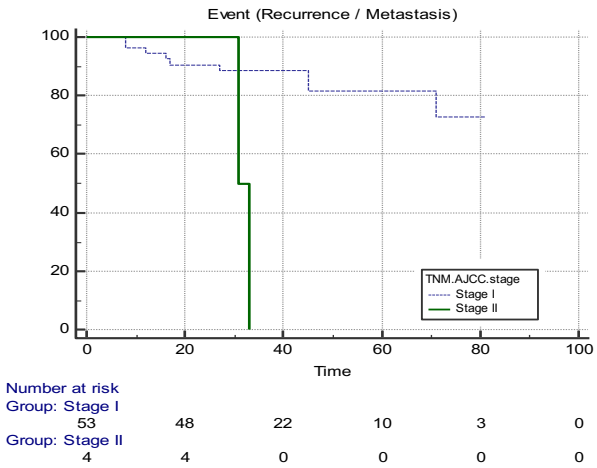

Figure 2. Kaplan Meier curve for the impact of tumor stage on DFS in the studied cohort (N=57), where 53 vs 4 patients were at risk for tumor stage I vs. II, respectively.

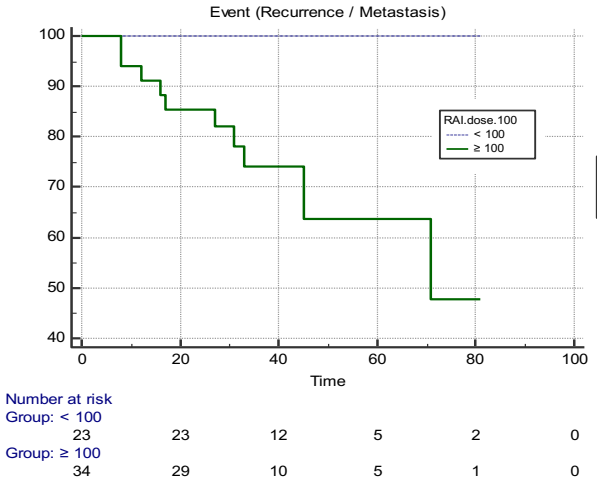

Figure 3. Kaplan Meier curve for the impact of RAI dose on DFS in the studied cohort (N=57), where 34 vs 23 patients were at risk for RAT dose ≥100 vs. <100 (millicuries), respectively.

Fisher's Exact test for TNM/AJCC stage between the 3 types of response (*P*=0.033). However, when the pairwise Fisher's Exact was used it revealed no statistically significant difference between all pairs (*P* = 0.303) comparing intermediate vs. both excellent and incomplete. Also, there was a significant difference in baseline sTG between the three responses (*P*=0.05). However, the excellent response has a low level, while the incomplete onees have a high level (*P* =0.025). Comparing the level in excellent vs. intermediate (*P*=0.145) and between intermediate vs. incomplete (*P*=0.422) showed no statistical statistically significant difference.

Table 1. Clinico-pathological characteristics of the study participants (N=57)

Characteristic	Statistic
Age* (years)	40.7 ± 12.9
Sex	
Male	14 (24.6%)
Female	43 (75.4%)
'T' stage	
T1	19 (33.3%)
T2	25 (43.9%)
T3	12 (21.1%)
T4	1 (1.8%)
'N' stage	
N0	27 (47.4%)
N1	30 (52.6%)
TNM /AJCC staging	
Stage I	53 (93%)
Stage II	4 (7%)
Histological type	
PTC	52 (91.2%)
FTC	5 (8.8%)
Post-ablation whole-body iodine scan	
Negative	40 (70.2%)
Faint uptake (minimal residual)	13 (22.8%)
Large residual	4 (7%)
Baseline sTG (ng/ml)	2 (0.85 – 2.95)
Post-RAI sTG (ng/ml)	
<1	30 (52.6%)
1-10	21 (36.8%)
>10	6 (10.5%)
Positive serum anti-TG	1 (1.8%)
Response to ablation 6-months after RAI	
Excellent	25 (43.9%)
Intermediate	23 (40.4%)
Incomplete	9 (15.8%)
RAI dose (millicurie)	100 (80 – 100)

Data are n(%) or median(Q1-Q3; 1st and 3rd quartiles; 25th and 75th percentiles). * Data are mean±S.D. [TG; Thyroglobulin, RAI; radio-active iodine, PTC; papillary thyroid carcinoma, FTC; follicular thyroid carcinoma.]

DISCUSSION

The current study involved 57 patients with DTC treated in the Clinical Oncology and Nuclear Medicine Department, Mansoura University. Patients' reported age mean (40.7 years) was almost 12 years lower than age reported by Cavalheiro et al. (2021), but equal to the study by Kabbash et al. (2019) which is in a comparable geographical area[6]. Male-to-female ratio is 1:3.07 which is almost equal to the results of Li et al. (2021), but higher than Slook et al. (2019) and Algamal and Aboelnaga (2015) ratios of 1:2. More than half of patients presented with early T-stage 44(77.2%) and nearly half of the patients presented with free cervical LN 27(47.4%). This copes with the results of Li et al. (2021) where 77.74% of patients were with T-stage ≤T2 (42,296 patients out of 54,405) but with a much higher % of patients with free cervical LN 78.4% for 31,438 out of 40,101 patients (Li, et al. 2021). Almost cases were PTC 52 (91.2%) which is in line with most studies which reveal that PTC is the most common subtype of DTC with an incidence range from 85% up to 93% (Seib and Sosa, 2019, Li et al., 2021, Truong et al., 2021).

All patients who received RAI with a dose less than 100 millicuries did not experience progression. This could be explained on the bases that those patients have no or low-risk factors according to the American Thyroid Association (ATA) stratification risk system for prediction of recurrence, according to which the decision of ablative RAI dose is taken.

Table 2. Uni and Multivariate analysis for comparisons of survival distribution of progression (recurrence/metastasis) based on pateints' (N=57) demographic and clinic-pathological characteristics

		Event		RMST at 24-months			Log-rank test		Hazard ratio (HR)	
Risk factor	**N**	N	**%**	Mean	95% CI	*P*-value	χ^2	*P*-value	HR	95% CI
Age						0.6249	2.3430	0.1258		
≤ 40 years	28	3	10.7%	23.2	22.1-24.3				r(1)	r(1)
> 40 years	29	7	24.1%	22.8	21.5-24.0				2.66	0.76-9.33
Sex						0.8995	0.9321	0.3343		
Female	43	6	14%	23.0	22.1-23.9				r(1)	r(1)
Male	14	4	28.6%	22.9	20.8-24.9				2	0.49-8.2
Histological type						0.0868	1.4302	0.1190		
PTC	52	8	15.4%	23.4	22.8-24.1				r(1)	r(1)
FTC	5	2	40%	18.4	12.7-24.1				6.7	0.61-74.2
'T' stage						0.2918	1.0896	0.2966		
T1-T2	44	7	15.9%	23.3	22.5-24.0				r(1)	r(1)
T3-T4	13	3	23%	21.8	19.3-24.4				2.4	0.46-12.5
'N' stage						0.6845	0.1355	0.7128		
N0	27	4	14.8%	23.1	22.0-24.3				r(1)	r(1)
N1	30	6	20%	22.8	21.6-24.0				1.3	0.36-4.4
TNM/AJCC stage						0.0161	4.6600	0.0309		
Stage I	53	8	15%	22.9	21.9-23.8				r(1)	r(1)
Stage II	4	2	50%	24.0	24.0-24.0				22.9	1.3-393.5
Diagnosis-treatment interval ≥ 6 months						0.1406	0.0030	0.9562		
< 6 months	28	4	14.3%	22.3	20.8-23.8				r(1)	r(1)
	29	6	20.7%	23.6	22.9-24.3				1.04	0.29-3.7
RAI dose (millicuries)						0.0135	7.8853	0.0050		
<100	23	0	0%	24.0	24.0-24.0				r(1)	r(1)
≥100	34	10	29.4%	22.3	20.9-23.6				-	-
Response							3.1567	0.2063		
Excellent	25	2	8%	23.7	23.1-24.2				r(1)	r(1)
Intermediate	23	5	21.7%	22.8	21.3-24.3	0.2742			3.3	0.83-12.9
Incomplete	9	3	33.3%	21.4	18.3-24.6	0.1730			4.1	0.72-23.9
Baseline stimulated TG						0.0704	3.4992	0.0614		
≤ 2	29	3	10.3%	23.7	23.3-24.1				r(1)	r(1)
> 2	28	7	25%	22.2	20.6-23.8				3.4	0.94-12.2

[RMST; restricted mean survival time, C.I; confidence interval, r(1); reference category, TG; Thyroglobulin, RAI; radio-active iodine, PTC; papillary thyroid carcinoma, FTC; follicular thyroid carcinoma.] Univariate analysis was performed using the log-rank test and multivariate analysis was performed using Cox regression. *P*-value less than 0.05 is statistically significant.

However, the median DFS was 71-months in patients received RAI dose ≥100 millicuries, which is much higher than the results by Trimboli et al. (2020) study, whose DFS median was 44-months. This could be related to the patients older age and higher risk features observed in the Trimboli study.

The multivariate analysis of DFS prognostic factors revealed disease stages and RAI doses were the most independent prognostic factors of DFS with *p*-values 0.0309 and 0.005, respectively. These results go parallel to the results of Jukkola et al. (2004) where disease stage was significantly related to DFS. Amui et al. (2019) confirmed the significance of RAI dose DFS [13&14]. Comparing the current study and Wahba et al. (2018), both revealed that patients' gender and the histopathological subtypes had no statistical significance on the DFS. Regarding significance of age, T-stage, nodal status, and sTG level as prognostic factors, the current study attempted different classifications in regard to patients' characteristics. Patients' age cutoff is either ≤ 40 years or > 40 years vs 40 and 45 years for Jukkola et al. (2004) and Wahba's study[15], respectively, who gave insignificant vs significant results, respectively.

Table 3. Patients' (N=57) demographic and clinicopathological characteristics as prognostic predictors of response to post-RAI ablation as either excellent, intermediate, and incomplete at 6-months as diagnosis treatment interval

Characteristic	Response to ablation post-RAI at 6-months (N)			*P*-value
	Excellent (25)	Intermediate (23)	Incomplete (9)	
Age				0.199
≤ 40 years	14 (56%)	8 (34.8%)	6 (66.7%)	
> 40 years	11 (44%)	15 (65.2%)	3 (33.3%)	
Sex				0.415
Male	4 (16%)	7 (30.4%)	3 (33.3%)	
Female	21 (84%)	16 (69.6%)	6 (66.7%)	
Histological type				0.293
PTC	23 (92%)	22 (95.7%)	7 (77.8%)	
FTC	2 (8%)	1 (4.3%)	2 (22.2%)	
'T' stage				0.912
T1-T2 (Early)	20 (80%)	17 (73.9%)	7 (77.8%)	
T3-T4 (Advanced)	5 (20%)	6 (26.1%)	2 (22.2%)	
'N' stage				0.829
N0	13 (52%)	10 (43.5%)	4 (44.4%)	
N1	12 (48%)	13 (56.5%)	5 (55.6%)	
TNM/AJCC stage				0.033
Stage I	25 (100%)	19 (82.6%)	9 (100%)	
Stage II	0 (0%)	4 (17.4%)	0 (0%)	
Diagnosis-treatment interval				1.000
< 6 months	13 (52%)	12 (52.2%)	4 (44.4%)	
≥ 6 months	12 (48%)	11 (47.8%)	5 (55.6%)	
RAI dose (millicuries)				0.764
<100	11 (44%)	8 (34.8%)	4 (44.4%)	
≥100	14 (56%)	15 (65.2%)	5 (55.6%)	
Baseline sTG				0.05
≤ 2	17 (68%)	10 (43.5%)	2 (22.2%)	
> 2	8 (32%)	13 (56.5%)	7 (77.8%)	

Data are N(%). The test of significance is Fisher's exact test. *P*-value less than 0.05 is statistically significant

Amui et al. (2019) results go parallel with the current study and showed age, gender, T-stage, histopathological subtype, and nodal status were not prognostic or related factors for DFS. In regard to the relapsed and non-relapsed cases Zahra et al. (2021) TG levels did not differ significantly in-between. Multivariate analysis of predictive factors of ablation post-RAI revealed that the disease stage and sTG level are the most independent predictive factors with *p*-values of 0.033 and 0.05, respectively. While other factors like (age, gender, histopathological subtype, T-stage, nodal status, and RAI dose) were statistically insignificant. These results contradict in regard to age (p =0.041), T-stage (p=0.017) according to Kersting et al. (2021) and for the nodal status impact (p=0.001) and T-stage (p=0.15) according to Alzahrani et al (2020).

Alzahrani et al. (2020) and Campennì et al. (2021) cope with our results in regard to gender (p = 0.16, 0.748, respectively) and T-stage (p = 0.09, 0.197, respectively) [17&18]. Campennì et al. (2021) and Kwon et al. (2020) [19] reported non-significant impact of gender and histopathological subtype. Liu et al. (2022a and b) confirmed the impact of disease stage (p=0.000 and < 0.001, respectively). Strength in the current research resides in that it clarifies the significant impact of post-operative sTG, as a prognostic factor of response on RAI ablation treatment.

SUMMARY

Results of the current study suggested that sTG before RAT is associated with dynamic risk stratification 1-year (12-months) after therapy in patients with DTC. Higher TG levels were found in patients that had an indeterminate, and in particular, incomplete response. Therefore, sTG before RAT, can serve as a response predictor to initial treatment.

RECOMMENDATION

Relying on sTG before RAT, as a response predictor, would provide a mean to reduce treatment cost via tailoring the RAI dose according to patients' sTG levels (the link of clinical application to pharmaco-economics and personalized follow-up).

CONCLUSION

Routine measurement of sTG post-surgery, before ablation with RAI, to evaluate response to RAI ablation and during follow-up, if recurrence or metastasis to be expected. One of the main constraint/limitations in the current study was the sample size (N=57) for more significant results.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION

Authors contributed equally in the study.

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