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The Value of Postoperative Baseline Serum Thyroglobulin in Prediction of the Outcome of Radioactive Iodine-131 Thyroid Ablation in differentiated thyroid carcinoma

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Abstract:

Background: Thyroglobulin is commonly used to monitor patients with differentiated cancer thyroid. It has also become an excellent biological marker for tumor persistence or recurrence. **Aim of study:** To study the relation between the level of baseline serum thyroglobulin (TG) and thyroid remnant ablation outcome using radioactive iodine-131 (RAI-131) in patients with differentiated thyroid cancer after surgical treatment. **Methods:** A prospective study involved 64 patients (age 20-77 years) with differentiated thyroid cancer, referred for post-surgical ^{131}I ablation. All patients performed baseline serum TG, anti-TG-Ab's under TSH stimulation as well as neck ultrasonography, before receiving RAI-131ablation dose 1110 - 3700 MBq (30 -100 mCi). Follow-up was performed 6-8 months later. Successful ablation was determined by negative whole body ^{131}I scan, negative neck ultrasonography and stimulated serum thyroglobulin level less than 2 ng/mL. **Results:** Successful ablation was reported in 38 out of 64 cases (59.4 %). Baseline serum thyroglobulin level was significantly predictive of ablation outcome. ROC analysis showed AUC (area under curve) of 0.66 (CI: 0.53 - 0.78; P = 0.03). A cutoff value of 4.4 ng/ml showed sensitivity of 79 % and specificity of 68% in predicting ablation outcome. Patients were divided into high (n = 32) and low (n = 32) baseline TG groups using this cut-off point. Successful ablation significantly higher in low TG group (25/32 vs. 13/32; P=0.002). There was no significant difference between the two groups regarding their clinical and pathological data. **Conclusion:** Baseline serum thyroglobulin is associated with ablation outcome. Serum TG> 4.4 is linked to significantly higher rates of unsuccessful ablation.

Key words: Differentiated thyroid cancer, radioactive iodine-131, ablation, Serum Thyroglobulin.

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INTRODUCTION:

Differentiated thyroid carcinomas (DTC; including papillary and follicular varieties) are the most common endocrine malignancy with 10 years survival around 90%[1,2]. This outcome is ensured by total thyroidectomy, radioiodine-131 remnant ablation (except in patients with uni-focal or multifocal lesion≤1 cm in size) and lifelong thyroxin suppressive therapy [3, 4]. Interestingly in recent years, >80% of patients diagnosed with DTC are low risk with a primary tumor size <2cm with controversies about the role of radioiodine-131 remnant ablation after surgery[5]. Rationales for radioiodine-131 remnant ablation are (a) To destroy any residual macroscopic and microscopic disease; (b) To enhance sensitivity of diagnostic whole body iodine scan and specificity of serum thyroglobulin (TG) which facilitates follow-up and early detection of recurrence and metastatic disease; and (c) To use post-therapy whole body iodine scan which is more sensitive than diagnostic whole body iodine scan for detection of nodal or distant functioning metastases [6]. Stimulated TG level after complete thyroid ablation (follow-up) is a reliable and sensitive marker for detecting tumor persistence and recurrence[7, 8]. Similarly baseline (pre-ablation) Stimulated TG is considered to have an indirect correlation with residual functioning thyroid tissue over thyroid bed in low risk patients (adequacy of thyroidectomy) (9). Various researchers have used either baseline stimulated TG or stimulated TG /TSH ratio for predicting the ablation outcome with variable inference (10-13). **The aim** of this study was to determine the predictive value of the baseline (pre-ablative) stimulated serum thyroglobulin level for ablation outcome.

MATERIAL AND METHODS:

Study Design and Protocol: This was a prospective study conducted at Nuclear Medicine Unit, Faculty of Medicine, and Cairo University, Egypt. From January 2013 till January 2015, Approval was obtained from the national research ethics panel. All patients provided written informed consent to participate in the study. Eligibility criteria were an age of 16 to 80 years., histological confirmation of differentiated thyroid cancer, tumor stage T1 to T3 with or without regional lymph-node involvement in surgical specimen but with no distant metastasis, total or Near total thyroidectomy with or without resection of cervical lymph nodes, no evidence of residual malignancy. Exclusion criteria were pathological cervical lymphadenopathy foundon postoperative ultrasonography, distal metastasis, and incomplete surgical resection of the tumor, anaplastic or medullary thyroid carcinoma,

pregnancy, severe coexisting conditions, and previous cancer with limited life expectancy, previous iodine-131 pre-ablation scanning, and previous treatment for thyroid cancer except surgery.

All patients were treated as per following protocol: (a) after total thyroidectomy, the Eltroxin stopped for 3-4 weeks; (b) advised to have low iodine diet for about 3 weeks prior to radioiodine-131 remnant ablation; (c) 2-3 days prior RAI^{131} therapy, they had baseline stimulated TSH (sTSH), stimulated serum TG and Anti-Thyroglobulin antibodies (anti-TG-ab); (d) RAI^{131} therapy dose of 1.1-3.7 GBq (30-100 mCi) in a capsular form was administered orally, Patients receiving higher doses were in hospital isolation in shielded rooms until the dose rate at 1 m is less than 0.07 mSv/hr (7.0 mrem/hour) and clinical conditions permitted discharge. Patients received low ablative dose will be discharged on the day of ^{131}I administration with the usual written instructions for radiation protection. Pre and post- ablative dose administration Instructions were given in a written form; (e) Post-therapy RAI-131 whole body scan was performed at 5 day later using dual-head gamma camera fitted with high-energy collimators and a bed speed of 8cm/min for simultaneous anterior and posterior whole body images. The energy window was set at 15 % centered on 364 Kev with a 256×1024 size matrix. Ten minutes spot views of the head and using the same collimator and the same energy window as for the whole-body images were also obtained in a 128×128 matrix size and images were interpreted qualitatively by visual assessment of the size & tracer uptake intensity of the residual uptake. (f) LT4 suppressive therapy was resumed after completion of the imaging. (g) 6-8 months after RAI^{131} therapy, all patients they performed stimulated TSH, TG, anti-TG-ab, neck ultrasound, and diagnostic RAI^{131} whole body scan, all patients were prepared in the same way for the administration of radioiodine by withdrawal of LT4 medication 4 weeks before administration of 3 mCi of ^{131}I (TSH level > 30 uIU/mL) and were asked to follow a low iodine diet 2-3 week before dose. Blood samples were taken to measure TG levels on the same day (just before) administration of diagnostic radio iodine dose using radioimmunoassay. Whole body scan was performed using dual-head gamma camera fitted with high-energy collimators and a bed speed of 6 cm/min for simultaneous anterior and posterior whole-body images. The energy window was set at 15 % centered on 364 kev with a 256×1024 size matrix. Ten minutes spot views of the head and neck with radioactive markers on the suprasternal notch using the same collimator and the same energy window as for the whole body images were also

obtained in a 128×128 matrix size with a 15 % energy window.

Study End Points: The primary end point was the success rate for ablation, which was defined as absence of any significant ^{131}I uptake at the thyroid bed, no abnormal iodine uptake elsewhere in the body, stimulated serum TG level less than 2 ng/mL, neck ultrasonography doesn't show any LN's or cervical mass or thyroid residue.

Statistical Analysis: Data was analyzed using commercially available packages such as the SPSS win statistical package version 17 (SPSS Inc., Chicago, IL). Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. Comparisons between patient groups were made using the Student t-test for continuous variables and the $\chi 2$-test for categorical variables. Continuous variables were described by mean ± SD. Receiver-operating characteristic curves (ROCs) were plotted for predictive strength of stimulated TG for successful ablation. Odd ratios were calculated by multivariate analysis for various confounding factors with stimulated TG levels for ablation failure. P-values less than 0.05 were considered significant.

RESULTS:

Patients' Characteristics (table 1): The study cohort included 64 patients [17 (26.6%) males and 47 (73.4%) females] with a mean age of the mean age was 40 years (range 20–77 years). Most patients were treated for papillary carcinoma 57 cases (89%) versus 11 (11%) cases with follicular cancer thyroid.In 5 (7.8%) patients nodal status was positive [N1a: 3 (4.7%) and N1b: 2 (3.1%)] and in 6 (9.4%) patients no evidence of nodal metastasis reported (N0), the remaining 53 (82.8%) cases LN metastasis was unknown (Nx). Mean stimulated TG levels were 16.9 (range :< 0.2-65) ng/ml. ***Clinical Outcomes:*** Over-all successful ablation was seen in 38 (59.4%) patients & ablation failure in 26 (40.6%) patients. To find out most sensitive and specific ablation baseline stimulated TG value (i.e. cutoff value) for the discrimination of successful ablation and ablation failure, a receiver operating characteristic (ROC) curve was used. The ROC curve revealed baseline stimulated TG level < 4.4 ng/ml as the most sensitive and specific level for predicting successful ablation with sensitivity of 79 % and specificity of 68% in predicting ablation outcome (figure 1).On basis of baseline stimulated TG level, patients were divided into high (n = 32) and low (n = 32) TG groups using this cut-off point (4.4 ng/ml). The two groups assumed equal regarding

most of the clinical and pathological features including ATA risk category and received ablation doses (Table 1). Exceptionally, the associated pathology showed significant association with baseline TG. When excluding patients with normal thyroid tissue, the low-TG group showed significantly higher number of multi nodular goiter (10 vs. 2), while the high TG group showed significantly higher patients with Hashimoto's thyroiditis (4 vs. 0) (P = 0.006).Comparative analysis revealed that patients with baseline stimulated TG< 4.4 ng/ml had significantly higher rates of successful thyroid remnant ablation 25/32 cases vs. 13/32 cases of the group with baseline stimulated TG > 4.4 ng/ml with significant difference (P-value = 0.002) .

Table 1: Characteristics for the patients and distribution between the two groups of the study**.**

Total	BL TG ≤ 4.4	BL TG > 4.4	Total	P-value
Number of cases	32 (50.0%)	32 (50.0%)	64 (100%)	
Males	6 (18.8%)	11 (34.4%)	17 (26.6%)	0.157
Females	26 (81.3%)	21 (65.6%)	47 (73.4%)	
Age >45	10 (31.3%)	13 (40.6%)	23 (35.9%)	0.434
Age ≤ 45	22 (68.8%)	19 (59.4)	41 (64.1%)	
PATHOLOY OF DIFFERENTIATED CANCER THYROID				
Papillary	26 (81%)	31 (97%)	57 (89%)	0.88
Follicular	6 (19%)	1 (3%)	7 (11%)	
ASSOCIATED PATHOLOGY				
Hashimoto thyroiditis	0 (0.0%)	4 (12.5%)	4 (6.3%)	0. 012
MNG	10 (31.3%)	2 (6.3%)	12 (18.8%)	
Plumber Disease	1 (3.1%)	0 (0.0%)	1 (1.6%)	
Normal thyroid	21 (65.6%)	26 (81.3%)	47 (73.4%)	
FOCALITY				
Unifocal	20 (62.5%)	23 (71.9%)	43 (67.2%)	0.424
Multifocal	12 (37.5%)	9 (28.1%)	21 (23.8%)	
INVASION				
Tumor capsule +ve	7 (21.9%)	8 (25.0%)	15 (23.4%)	0.768
Tumor capsule –ve	25 (78.1%)	24 (75.0%)	49 (76.6%)	
Vascular invasion	3 (9.4%)	2 (6.3%)	5 (7.8%)	0.641
No vs. invasion	29 (90.6%)	30 (93.8%)	59 (92.2%)	
T-STAGING				
Tx	1 (3.1%)	0 (0%)	1 (1.6%)	0.429
T1a	9 (28.1%)	4 (12.5%)	13 (20.3%)	
T1b	8 (25.0%)	11 (34.4%)	19 (29.7%)	
T2	11 (34.4%)	11 (34.4%)	22 (34.4%)	
T3	3 (9.4%)	5 (15.6%)	8 (12.5%)	

N-STAGING				
Nx	25 (78.1%)	28 (87.5%)	53 (82.8%)	0.160
N0	5 (15.6%)	1(3.1%)	6 (9.4%)	
N1a	2 (6.3%)	1 (3.1%)	3 (4.7%)	
N1b	0	2 (6.3%)	2 (3.1%)	
Postoperative TG				
TG< 2 ng/ml	22 (68.8%)	0 (0.0%)	22 (34.4%)	< 0.001
TG 2-10 ng/ml	10 (31.3%)	9 (28.1%)	19 (29.7%)	
TG >10 ng/ml	0 (0.0 %)	23 (71.9%)	23 (35.9%)	
Risk				
Low	11 (34%)	9 (28%)	20 (31%)	**0.18**
Intermediate	21 (66%)	23 (72%)	44 (69%)	
Ablation dose				
Low	17 (53%)	14 (44%)	31 (48%)	**0.45**
High	15 (47%)	18 (54%)	33 (52%)	

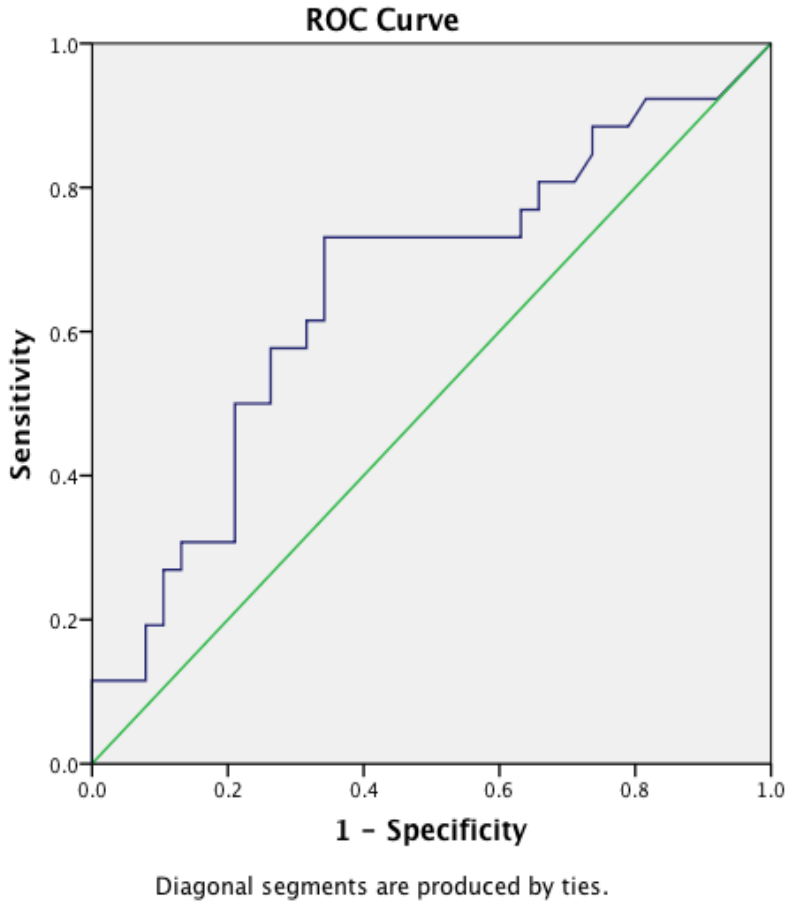

Figure 1. Receiver Operating Characteristics (ROC) Curve of Baseline Stimulated Thyroglobulin (STG) as Predictor of Successful Ablation.

A binary logistic regression model was built using the variables known to affect the ablation outcome (risk group, ablation dose, associated pathology) in addition to the factor under

investigation (baseline TG group). The most significant factor was the baseline TG (P = 0.001; Hazard's ratio = 8.7) (Table 2).

Table 2 : Binary egression model for factors affecting first dose ablation outcome

	P	Exp (B)*
Risk group	.053	.278
Baseline Tg	.001	8.763
Ablation group	.030	.253

* **Exp (B)** represents the expected increased hazard in relation to the baseline group.

DISCUSIONS:

In last two decades there has been a staggering incidence of DTC and importantly 87% and 49% of diagnosed tumors are either ≤2cm or ≤1cm in size respectively (14). Total thyroidectomy and radioiodine-131 remnant ablation (in tumors>1cm in size) are considered as major therapeutic measures (15). Successful ablation induced by I-131 has been shown to reduce recurrence and improve disease free survival (16) although ablation failure has been observed in 20-30% patients after ablative doses of I-131 (17). Repeat ablative dose is associated with inconvenience to patients, increase financial burden and possible higher odds of second primary malignancy (18). In this regards various researchers have explored different variables as predictor for successful ablation. In this study, we have evaluated predictive value of baseline stimulated serum TG level (just before ablation) for successful ablation in 64 patients with total/near total thyroidectomy for DTC followed by radioiodine-131 remnant ablation. The overall successful ablation was 59.4% with a median baseline stimulated TG level 16.9 ng/ml. This is significantly lower than 82.7% achieved by ***Lee et al (2010) (11)***. Possible explanation for this discordance is significantly lower baseline median stimulated TGlevel of 2.6 ng/ml in their study and it is an established fact that baseline stimulated serum TG level is a direct indicator of bulk of residual functioning tissue in low risk patients and residual tissue over neck and functioning nodal and distant metastasis in high risk patients (19). The higher median baseline STG level in our study draws our attention about adequacy of total thyroidectomy in studied patients. As a matter of fact prior studies revealed a negative impact of cervical uptake as a

successful ablation (20) while recent data claim cervical uptake is a predictor of successful ablation (21). In this work, we did not quantitatively assess the residual neck uptake; however, all our patients had post-surgery neck ultrasound documenting small thyroid residue if any. As we are cognizant of the fact that available data is quite variable regarding the normal TG levels in post-thyroidectomy patients and broad range of stimulated serum TG level (2-69.7 ng/ml) has been suggested [(12)]. In this study we used ROC curve to find out a cut-off value of stimulated serum TG with highest diagnostic strength, which was 4.4 ng/ml. On the same note, 78.1% of patients with baseline stimulated serum TG ≤4.4 ng/ml had successful ablation while only 40.6% of patients with baseline stimulated serum TG>4.4 ng/ml could achieve successful ablation. This fact has recently been elaborated that the post-operative stimulated serum TG levels prior radioiodine-131 remnant ablation had a complementary role for predicting the persistence or recurrence of thyroid carcinoma during the 6-12 month postoperative period[(22)]. However, incidence of successful ablation in both groups of our study is lower than Lee JH et al (2007) who had a cut-off value of baseline stimulated serum TG level 10 ng/ml with a successful ablation rate of 96.6% and 47.8% in patients with stimulated serum TG ≤10 and >10 ng/ml respectively. The basic reason for this difference is use of un-stimulated (or suppressed) TG<2 ng/ml as biochemical criteria for successful ablation in their study while we used stimulated TG<2 ng/ml. It is known that undetectable serum TG levels after withdrawal of thyroxin (i.e. stimulated TG or STG) during follow-up would guarantee complete remission and diagnostic RAI^{131} whole body scan could be avoided [(23)]. Here we would like to mention that smaller value of baseline stimulated serum TG level also ensures comparable successful ablation in patients treated with low or high doses of I-131. This has been observed in two landmark trials where baseline STG was <2ng/ml in 21-59% of patients treated in a randomized way with either 30 or 100 mCi of I-131 with comparable outcomes[(24, 25)]. These facts elucidate the importance of adequacy of thyroidectomy and role of high volume surgeons as in low risk patients good surgical-ablation ensures best radio-ablation. Multivariate analysis of our cohort revealed that patients with STG>4.4 ng/ml were having 8 times risk for ablation failure. This comes in accordance with published data[(26)]. The clinical impact of these results is still evolving. Data from Memorial Sloan Kettering define normal post-op TG as non-stimulated TG< 5 ng/mL or stimulated TG< 10 ng/mL with negative anti-TG antibodies. They recommended the use of more

radioiodine dose for patients with elevated post-operative TG[27]. However, this recommendation was not studied in our work and future clinical trials are warranted to further assess the possible clinical impact of these results. Our study has some limitations and the first one is the lack of accurate detection of the post-operative thyroid residual size or quantification of residual uptake. We also did not check serum thyroglobulin level between ablation and follow-up period but we are sure that this is a common and cost effective strategy which is being practiced at many centers and predictive value of a single TG level is high. Finally, our data showed a lower ablation rate which is due to use of stimulated TG (rather than suppressed TG) level along with a negative diagnostic ^{131}I whole body scan and negative US (i.e. stringent triple negative criteria). Another limitation is shorter follow-up period and keeping in view the indolent course of DTC, late recurrence of the disease in patients labeled as disease free could not be assessed in this study. However, we have been following these patients at our Centre to monitor disease status.

CONCLUSION:

In patients with total thyroidectomy followed by I-131 ablation for DTC, baseline stimulated serum TG level is a good predictor of successful ablation based on a stringent triple negative criteria (i.e. follow-up stimulated TG<2 ng/ml, a negative diagnostic ^{131}I WBS and negative US neck). Serum TG> 4.4 is linked to significantly higher rates of unsuccessful ablation.

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