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Pre-ablative Stimulated Thyroglobulin (sTG) versus sTG/TSH Ratio in Prediction of Ablation Outcome in Patients with Papillary Thyroid Cancer.

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ABSTRACT:

Radioactive iodine (131-I) ablation is employed post-operatively for patients with papillary thyroid cancer. Actually, there are many factors that can affect ablation outcome including stimulated TG (sTG). The latter was reported to be a good predictor of response to first 131-I ablation dose, yet, it is influenced by serum TSH level. So, it is postulated that sTG/TSH ratio can be a more accurate predictor of ablation outcome post first 131I ablative dose. Aim: to compare the role of sTG and sTG/TSH ratio as predictors of ablation outcome post first ablative 131-I dose in patients with papillary thyroid cancer together with looking for other factors that owe significant impact on ablation outcome. Patients and methods: Data of 126 patients with papillary thyroid cancer presented post-operatively for 131-I ablation were retrospectively analyzed. These data included age, gender, histopathological data, pre-ablative laboratory and sonographic data, disease stage , risk stratification, given 131-I ablation dose , and post ablative 131-I whole body scan (WBS), 6-9 months post ablation follow up sonographic, laboratory and WBS results as well as ablation outcome were collected and statistically analyzed. Results: Pre-ablative sTG, TSH and sTG/TSH ratio had a range of 2.9-59.8, 31.4-127.9 and 0.027-1.97 together with a median value of 7.41, 61.3 and 0.089 respectively. Follow up sTG and diagnostic WBS confirmed successful complete ablation in 94 patients (74.6 %) with partial ablation in the remaining 32 patients.

The measured cutoff value for prediction of successful ablation outcome of sTG and sTG/TSH ratio was 8.25 and 0.105, with sensitivity of 77.6% and 72.3% and specificity of 47% and 75% respectively, with statistically significant difference in the latter in favor of sTG/TSH. Positive postoperative neck US, positive lymph node (LN) involvement, multi-focality and lower 131-I ablative dose together with sTG and sTG/TSH above reported cutoff values are significantly associated with ablation failure post first 131-I dose.

Conclusion: sTG level and sTG/ sTSH ratio have comparable sensitivity in prediction of ablation outcome post first ablation dose of 131-I. Yet, the sTG/ sTSH ratio has significantly higher specificity, raising the additive value of sTG/TSH ratio in clinical practice for prediction of ablation outcome. Positive baseline post-operative neck US , Positive LN involvement, multi-focality, low dose of I-131 (30mCi), sTG level >8.25 and sTG/sTSH ratio >0.105 are predictor factors associated with significantly higher incidence of ablation failure post first I-131 ablation dose**.**

Key words: sTG level, TG/TSH ratio, radioactive iodine, thyroglobulin.

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INTRODUCTION:

Well differentiated thyroid cancer (WDTC), mainly papillary type, has been increasing in incidence for several decades and is expected to be the fourth leading cancer diagnosis by the year 2030. Most of this rise in incidence is explained by diagnosis of small, low risk cancers. These low-risk cancers are associated with an excellent long-term survival [(1)]. The mainstay of treatment of papillary thyroid cancer is surgical resection. Although the prognosis is generally excellent with 10-year survival rate exceeding 90%,yet,around 6-30% recurrence occurred during follow-up, being recognized as an important contributor to increased morbidity and mortality [(2)].

Most patients with papillary are treated with ablative dose of radioiodine 131-I (RAI) after initial surgery (total or near total thyroidectomy), aimed to destroy residual normal or microscopic tumoral thyroid cells and to facilitate early detection of tumor recurrence based on serum stimulated thyroglobulin (sTG) level and 131-I whole-body scan (WBS) during follow-up [(3)]. Successful remnant ablation is usually defined as an absence of visible radioactive iodine (RAI) uptake on a diagnostic WBS scan together with an undetectable stimulated sTG level [(4)]. Stimulated TG is a well-recognized marker in follow-up of patients with WDTC post thyroidectomy and 131-I ablation therapy for assessment of ablation outcome, for detection of persistent disease as well as for evaluation of development of disease recurrence either in the form of loco-regional recurrence or distant metastasis. Pre-ablation sTG level was reported to be a good predictor of successful ablation post first dose of I-131 in patients with WDTC. Yet, as sTG level can be influenced by TSH level in addition to other factors, therefore, it was postulated that the ratio sTG/TSH can be a more accurate predictor of ablation outcome in response to first ablative dose of I-131[(5)].

PATEINTS AND METHODS:

The current study was performed retrospectively by analysis of data from patients' files who presented for RAI ablation post total/near total thyroidectomy in the period from January 2016 to December 2020 to Nuclear Medicine unit, Faculty of Medicine, Cairo University, Egypt. Inclusion criteria:

(1) Adult patients with papillary thyroid cancer;

(2) Patients who underwent total/near thyroidectomy;

(3) Assessment of stimulated TSH (TSH), sTG, and Anti-TG antibodies (Anti-TG) 3-4 weeks post- thyroidectomy and few days pre 131I ablation;

(4) Patients who received RAI ablation therapy, with 131I dose ranging from 30 to 120 mCi according to ATA risk stratification;

(5) Patients with post-therapeutic WBS done 5-10 days post 131I ablation therapy;

(6) Patients who performed diagnostic WBS, and sTG; and Anti-TG with or without neck US 6-9 months after RAI ablation.

We excluded patients with (1) Subtotal thyroidectomy or lobectomy; (2) Diagnostic WBS before RAI ablation; (3) Elevated Anti-TG prior to RAI or in the 6-9 months follow up assessment; (4) those with 131I avid lesions outside thyroid bed in post ablation WBS or in first diagnostic 131-I WBS;(6) Patients with properly documented ablation outcome by results of sTG , diagnostic WBS and neck ultrasound , if its result is available, performed 6–9 months after RAI ablation; (7) pregnancy in women of childbearing age.

Ablation outcome was reported to be either successful complete ablation (both sTG < 1 ng/mL and complete disappearance of I-131 avid lesion in the thyroid bed with free neck US if done) or incomplete ablation outcome (either persistent smaller residual 131-I avid lesion in the neck or partial diminution of sTG level, yet it is still >2 ng/ml).

Statistical analysis:

Statistical software version 24 SPSS. A P value less than 0.05 was defined as statistically significant in all tests. Bivariate relationship was displayed in cross tabulations and Comparison of proportions was performed using the chi-square and Fisher's exact tests where appropriate. T-independent was used to compare normally distributed quantitative data and Mann-Whitney for skewed data. . Cut off values were calculated from ROC curve.

RESULTS:

Our study included 126 patients (105 females, 21 males), with 75 (59.5%) patients less than 45 years. All patients presented for post-operative (total/near total thyroidectomy) RAI ablation with histopathologically proven papillary thyroid cancer. Out of them 94 patients (74.6 %) achieved successful complete ablation post first I-131 ablative dose, while 32 patients (25.4) were partially ablated, calling for a second ablative dose.

There was no significant difference as regards age, and gender between those who achieved successful complete ablation and those who were partially ablated.

As regards histopathology, all included patients had papillary thyroid cancer with variable size of the primary lesion ranging from 0.7 cm up to 5.6, being less than 4 cm in diameter in 86% of patients, with capsular invasion in only 21 patients (16.7%), mainly in those with larger primary tumor.

Vascular invasion and extra-thyroidal extension were reported in 7 (5.6%) and 10 (7.9%) patients respectively. Multi-focality and cervical lymph node (CLN) involvement were reported in around one third and one fourth of patients respectively.

For TNM staging, 96 patients were stage I and the remaining 30 patients were stage II. Size of primary tumor and capsular invasion showed no statistically significant correlation with ablation outcome. On the other hand , patients with mutli-focality and those with positive CLN involvement showed statistically significant ablation failure compared to those with unifocal primary lesion and those with absent CLN involvement, with 82% versus 62% (p<0.021) and 80% versus 58% (p<0.015) for ablation failure and successful ablation respectively.

Concerning risk stratification, low and intermediate risk patients were evidently more commonly encountered, found in 55 (43.7%) and 69 (54.8%) patients respectively with only 2 (1.5%) patients in the high-risk group.80% of low-risk patients and 71% of intermediate risk achieved successful complete ablation. These data denote significant more successful ablation outcome in both risk groups. Yet, no statistically significant difference in ablation outcome between both groups was found (P>0.05). 86% of patients (77/90) with negative baseline neck US achieved successful complete ablation after first ablative dose, this figure decreased to 31% (11/36) for those with positive thyroid bed neck US (P value <0.001) .

As for 131I ablative dose, the incidence of successful ablation after first ablation dose increased from 33.3% (2/6 patients) in patients who received 30 mCi to 82% (41/50 patients), 85% (28/33 patients) and 62.2% (23/37) for those who received 80,100 and 120 mCi respectively, with significant p value (P: 0.005) in favor of those who received higher RAI ablation doses ***(Table 1)***.

Baseline stimulated serum TG level was elevated for all patients ranging from 2.9 to 59.8 ng/ml, with a mean and median values of 16.3± 9.76and 6.41 respectively. Serum TSH level was ranging from 31.4 to 127.9 mIU/L with mean and median values of 44.7± 21.3 and 61.3 respectively. The range of stimulated serum TG level/ stimulated TSH ratio level was from 0.027 to 1.9 with mean and median values of 0.529± 0.61 and 0.089. The calculated cutoff values for sTG and sTG /TSH ratio were 8.25 ng/ml and 0.105 respectively (Table 2).The sensitivity of having sTG and sTG/TSH below this cutoff levels in prediction of successful ablation outcome was comparable, being 77.6% and 72.3% .On the other hand, specificity was significantly higher for sTG/sTSH ratio compared to sTG, being 75% and 47% respectively ***(Table 2)***.

Table (1): Correlation between baseline characteristics with ablation outcome post first I-131 ablation.

Characteristic	Complete ablation [*n* (%)]	Incomplete ablation [*n* (%)]	*P* value
Gender			
Female	81(77%)	24(23%)	0.143
Male	13(62%)	8(38%)	
Age 45 or less	51(68%)	24(32%)	0.059
> 45	43(84.3%)	8(15.7%)	
Histopathological features			
Tumor size			
<4cm	79(73%)	29(27%)	0.559
>4cm	15(83%)	3(17%)	
Lymph nodal			
Yes	18(58%)	13(42%)	0.015
No	76(80%)	19(20%)	
Capsular invasion			
Yes	18(85.7%)	3(14.3%)	0.210
No	76(72.4%)	29(27.6%)	
Multi-focality			
Yes	26(62%)	16(38%)	0.021
No	69(82.1%)	15(17.9%)	
Baseline Neck US			
Free	81(90%)	9(10%)	<0.001
Residual in thyroid bed	13(36%)	23(64%)	
ATA risk			
Low	44(80%)	11(20%)	0.016
Intermediate	49(71%)	20(29%)	0.041
High	1(50%)	1(50%)	0.445
Ablative dose			
30	2(33.3%)	4(66.6%)	0.005
80	28(84.8%)	5(15.2%)	
100	41(82%)	9(18%)	
120	23(62.2%)	14(37.8%)	

Table (2): Cutoff values of sTG and sTG/sTSH ratio with their sensitivity and specificity in papillary thyroid cancer.

Area	Cut-off	P value	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
sTG 0.825	8.25	<0.001	77.6%	47%	0.732	0.918
sTG/TSH 0.809	0.1050	<0.001	72.3%	75%	0.713	0.906

Patients were divided according to the sTG cutoff level of 8.25ng/ml into two groups, 90 patients have sTG level below this value (71.4%) and 36 patients (28.6%) with sTG above this level. Patients with sTG lower than cut off value showed significant successful ablation, found in 73 patients (81%), with ablation failure in 17 patients (19%) with a p value of <0.001.While for sTG /TSH ratio, patients with this ratio below 0.105 were 76 patients and those having this figure above this cutoff value were found to be 50 patients Again, those with sTG/TSH ratio < 0.105 showed significant outcomes of successful ablation, reported in 89.5% of patients and with incomplete ablation in only 10.5% with a significant p value ***(Table 3)***.

Table (3): Number and % of patients above and below cutoff levels of sTg and sTg/TSH ratio papillary thyroid cancer.

		Number of patients	%	Complete ablation	Partial ablation	p
sTG	< 8.25ng/ml	90	71.4%	73(81.1%)	17(18.9%)	<0.001
	> 8.25ng/ml	36	28.6%	21(58.3%)	15(41.7%)	(>0.05)
	Total	126	100.0%	94(74.6%)	32(25.4%)	
sTG/TSH ratio	< 0.105	76	60.3%	68(89.5%)	8(10.5%)	<0.001
	> 0.105	50	39.7%	26(52%)	24(48%)	(>0.05)
	Total	126	100.0%	94(74.6%)	32(25.4%)	

DISCUSSION:

Successful I-131 ablation therapy significantly reduces loco-regional recurrence, distant metastasis, and disease-specific death rates. Response to I-131 ablation therapy varied significantly among well differentiated thyroid cancer (WDTC) patients according to many factors that are still not completely well defined, leading to evident variable efficacy of I-131 thyroid remnant ablation across published studies [(6)].

To our knowledge, no single study reported 100% successful ablation outcome post-operatively in response to first I-131 ablation dose. Ablation outcome ranging from 43 to 87.2% was reported [(7)]. In patients with papillary thyroid cancer this figure was reported to be 76-79.3% post low ablation dos [(8)]. ***El Rasd et al***, reported an overall successful ablation of 59.4% in patients with WDTC, with a median baseline stimulated TG level of 16.9 ng/ml [(9)].

The successful ablation figure is evidently higher as reported by ***Lee et al***, being 82.7% with a median baseline sTG level of 2.6 ng/ml [(10)]. In the current study we reported a successful ablation rate of 74.6% with a median sTG level of 7.41 ng/ml.

The difference in successful ablation outcome figures can be explained by the difference of sTG level, as the latter is a direct indicator of bulk of residual functioning tissue in the thyroid bed, reflecting the adequacy of thyroidectomy, which was described as one of the factors that affect ablation outcome [(7)]. This is in agreement with the report of ***Rosario et al,*** who stated that total ablation is achieved with >80% success rate in patients who have undergone total thyroidectomy with minimal thyroid remnant (<2% thyroid bed uptake) than in patients with larger thyroid remnants with 67% success rate [(11)].

Variable factors influencing initial ablation outcome are described by many authors. ***Lin et al,*** identified age, clinical stage, extent of surgery and the one-month post-operative serum thyroglobulin (TG) level as the main factors influencing response to initial ablative I-131 dose. In 2017, ***Claimon et al,*** stated that prognostic factors for ablation success were female gender, absence of lymph nodal involvement or distant metastases [(12)], absence of multi-focality, free surgical margins, age <45 years and post-operative sTG level < 20 ng/dl at ablation time.

The latter two factors were proved to be independent significant risk factors ($p<0.001$) for ablation success using multivariate analysis [12]. Also, **Wang et al,** in 2018, on multi-variate logistic regression analysis showed that tumor size, pre-ablation sTG together with lymph node and distant metastases were independent factors affecting the efficacy of the first I-131 ablation outcome [7]. While in 2021, ***Lubin et al,*** found that factors such as tumor multi - focality and lymph node invasion at surgical resection were significantly associated with initial treatment failure following RAI. They reported also that elevated serum thyroglobulin (TG) and TG antibody levels following surgery but before RAI were also associated with treatment resistance with $P < 0.0001$ and P: 0.011 respectively. They stated that clinical outcomes following RAI can be suggested by identifying factors that are associated with initial treatment failure. These findings can help rest ratify patients for RAI treatment and change patient management in some patients, helping to optimize successful treatment outcomes and improve patient quality of life [13].

In the current study demographic factors has no effect on ablation outcome, including both gender and age, with no statistically significant difference in ablation outcome between males and females as well as between patients <45 years and those > 45 years. Also, ***Wang et al,*** showed that age has no significant difference [7], indicating the heterogeneity caused by age stratification is negligible in predicting ablation outcome. Some unfavorable prognostic pathological factors were encountered in the current study, which may have an impact on ablation outcome post initial ablative dose of I-131. These factors include primary tumor size more than 4 cm, lymph nodal involvement, multi-focality, capsular invasion, vascular invasion and extra-thyroidal extension. The latter two factors were found only in few patients and cannot be statistically assessed. Out of the remaining factors significant more incidence of unsuccessful ablation outcome post initial I-131 ablation dose was found in patients with lymph nodal involvement and in those with multi-focality. This goes with the reports of ***Claimon et al,*** and ***Lubin et al,*** about lymph nodal involvement and multi-focality, as both reported that their presence had significant negative impact on initial ablation outcome [12, 13].

As regards risk stratification, only two patients were in the high risk group, representing only 1.5% of the whole patient population.

The remaining 98.5% were in the low risk (43.7%) and the intermediate risk group (54.8%). Both groups showed successful ablation outcome in 80% and 71% of patients, respectively. Though this high positive ablation outcome, no significant difference depicted between these two risks groups, denoting lack of significant influence of stage of the disease on ablation outcome. This is in agreement with the aforementioned report of ***Wang et al***, they stated that risk stratification was not a factor independently affecting the efficacy of 131-I thyroid remnant ablation in DTC patients; While other reports did not state the stage of the disease per se as a predictor of ablation outcome [(6)]. The absence of significant number patients in the high risk group in the current study may mask the significant effect of this factor as a predictor of ablation outcome between high risk group patients and the other two groups, if any. Post-operative neck US was positive for residual functioning thyroid tissue in 36 patients, representing 28% of studied patients, being free in the remaining 90 patients, yet all patients had variable sized remnant in thyroid bed in post-operative WBS. Though neck US is operator dependent and providing that it was performed for all our patients by experienced staff, positive neck US points to relatively larger remnant thyroid tissue. Those patients with sonographically detected residual thyroid tissue in the thyroid bed showed significantly higher failure of ablation outcome compared to those in whom the residual thyroid tissue was not detected by US (p:<0.001). Most studies did not report that post-operative neck US can be used as a predictor of ablation outcome [(7, 12, 13)]. The present study support this finding that sonographically detected residual thyroid tissue means presence of relatively larger remnant thyroid tissue compared to those with free US that was detected only in I-131 WBS,. This larger residual thyroid tissue had subsequently higher sTG level; the latter was reported to have a significant positive correlation with ablation outcome failure post first I-131 dose. The current study showed that there is significant difference in ablation outcome in favor of patients who received a higher I-131 ablation doses, considering the I-131 dose a critical factor to effectiveness and outcome of I-131 ablation.

Also, ***Karam et al,*** and ***Kim et al,*** stating that higher dose of I-131 is associated with higher success rate of 131-I ablation.

They reported that their data was consistent with other meta-analysis stated that the ablation success rate was greater in the high-dose group than in the low-dose group [14, 15]. Despite these reports, some studies indicated that low-dose ablation is not inferior to high-dose ablation for low or intermediate-risk patients, similar to risk stratification of patients in our study.

However, the proportional decrease in thyroglobulin levels was significantly greater after a high dose than after a low dose, even when successful ablation could not be accomplished, suggesting that a higher dose may be more effective than a lower one, especially in those with high thyroglobulin levels [16]. Many studies reported that high sTG level before the first I-131 ablation is associated with lower success rate of the given I-131 ablation therapy and sTG has an important predictive value for successful ablation outcome [14,15]. Also, ***Watanabe et al,*** stated that thyroglobulin levels were significantly different between ablation success and failure groups [16]. In addition, they reported that thyroglobulin levels greater than 10 ng/ml were significantly associated with ablation failure after multivariate analysis for patients negative for anti-thyroglobulin anti-bodies. Their data mandates that sTG levels should rank among the most important factors for successful ablation. Previous similar data were reported by ***Tamilia et al,*** and ***Bernier et al,*** who reported that postoperative sTG values greater than 5–6 ng/ml were associated with increased rates of failed ablation after the administration of either 1110 or 3700 MBq of I-131[17,18]. Different cutoff values were reported for pre-ablative sTG level with the highest sensitivity and specificity for achievement of successful ablation outcome below this level. Furthermore, ***Tamilia et al,*** and ***Hussain et al,*** reports showed that the cutoff values of sTG for prediction of successful or unsuccessful thyroid remnant ablation were 6 and 18 ng/ml [17, 19], respectively. In these two studies, the sensitivity of sTG of both cutoff levels to predict thyroid remnant ablation were 67% and 76.7%, and the specificity of both cutoff levels were 79% and 79.1%, respectively. The aforementioned reports indicate the proper performance of sTG level is a good predictor of successful ablation outcome post first I-131 ablation dose with acceptable levels of sensitivity and specificity of variable cutoff values.

The cutoff figure in our study was reported to be 8.25 ng/ml with sensitivity 77.4% and specificity of 47% for prediction of ablation outcome. The sensitivity seems to be more or less comparable to figures stated in many other reports with slight differences. Yet, the specificity appears to be evidently lower in comparison to most other reports. This difference may be attributed to presence of associated other factors affecting ablation outcome, in addition to sTG level, owing a significant influence on the result of ablation success. So, despite the sTG level is below the cutoff level , yet, presence of other factors as multi-focality, LN involvement, low dose of I-131and more importantly relatively lower sTSH level can hamper successful ablation post first I-131 ablation dose in some patients.

It is well known that sTG is influenced by serum TSH level. Zhao et al 2016 (20) stated that no appreciable significant difference in sTG levels obtained with sTSH values between 30-60 mIU/L in patients with either excellent or incomplete response to first I-131 ablation dose. They reported that higher concentration of TSH seems to result in more significant elevations in sTG, postulating that higher levels of sTSH, between 60 and 90 mIU/L, would be more reliable for evaluating sTG as a predictor marker for ablation outcome with better differentiation between both complete and incomplete responders to first I-131 ablation dose considering TSH effect on sTG level. In the present study, 17 patients with sTG level <8.25 and incomplete ablation outcome are supposed to be out of those 50%. So, the presence of sTSH level in the range of 30-60 mIU/L in around 50% of patients in our study can be strongly accused for the low specificity of sTG. All these data raises the value of sTG/TSH ratio that could have a greater potential for better predictor of ablation success than isolated sTG level. In a study by Lin et al, they considered a higher TG/TSH ratio as a predictive factor for treatment failure in patients with WDTC [(21)]. In 2021, ***Zheng et al,*** reported that a cutoff value of sTGg/TSH < 0.11 predicts a better prognostic therapeutic effect, stating that sTG/TSH ratio can be considered as another predictor of I131 ablation effect [(22)]. In the current study the sTG/TSH ratio cutoff value was found to be 0.105, which is more or less comparable to this figure in some other reports.

The difference may be related to difference in sTSH level due to variable patients' proper maintaining a strict low I-131 diet for two weeks and even for their incompleteT4 withdrawal for at least the whole four weeks as instructed by their physician, affecting the increase in sTSH to the optimal level, with subsequent impact on the sTG/TSH ratio as well with sensitivity of (77.6%) in prediction of successful ablation. On the contrary, the reported specificity of the present study of STG/TSH was 75%, which is significantly of only more compared to specificity of sTG 47%. This confirms the effect of the addition of sTSH to sTG level to predict ablation outcome, with significant improvement of specificity on applying the sTG/sTSH ratio rather than sTG level alone in this particular issue.

CONCLUSIONS:

In patient with papillary thyroid cancer, sTG level and sTG/ sTSH ratio with cutoff values of 8.25 and 0.105 respectively have comparable sensitivity in prediction of post-operative ablation outcome post first ablation dose of I-131. The sTG/ sTSH ratio has significantly higher specificity, for prediction of ablation outcome-Positive post-operative neck with positive, multi-focality, low dose of I-131, sTG level >8.25 and sTG/sTSH ratio >0.105 are predictor factors associated with significantly higher incidence of ablation failure following first I-131 ablation dose.

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