RESEARCH ARTICLE

Baseline Stimulated Thyroglobulin Level as a Good Predictor of Successful Ablation after Adjuvant Radioiodine Treatment for Differentiated Thyroid Cancers

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Abstract

Background: To determine the predictive value of the baseline stimulated thyroglobulin (STg) level for ablation outcome in patients undergoing adjuvant remnant radioiodine ablation (RRA) for differentiated thyroid carcinoma (DTC). Materials and Methods: This retrospective study accrued 64 patients (23 male and 41 female; mean age of 40±14 years) who had total thyroidectomy followed by RRA for DTC from January 2012 till April 2014. Patients with positive anti-Tg antibodies and distant metastasis on post-ablative whole body iodine scans (TWBIS) were excluded. Baseline STg was used to predict successful ablation (follow-up STg <2 ng/ml, negative diagnostic WBIS and negative ultrasound neck) at 7-12 months follow-up. Results: Overall, successful ablation was noted in 37 (58%) patients while ablation failed in 27 (42%). Using the ROC curve, a cut-off level of baseline STg level of ≤14.5 ng/ml was found to be most sensitive and specific for predicting successful ablation. Successful ablation was thus noted in 25/28 (89%) of patients with baseline STg ≤ 14.5 ng/ml and 12/36 (33%) patients with baseline STg >14.5 ng/ml ((p value <0.05). Age >40 years, female gender, PTS >2 cm, papillary histopathology, positive cervical nodes and positive TWBIS were significant predictors of ablation failure. Conclusions: We conclude that in patients with total thyroidectomy followed by I-131 ablation for DTC, the baseline STg level is a good predictor of successful ablation based on a stringent triple negative criteria (i.e. follow-up STg < 2 ng/ml, a negative DWBIS and a negative US neck).

Keywords: Successful ablation - stimulated thyroglobulin - radioiodine remnant ablation

Asian Pac J Cancer Prev, **15 (15)**, 6443-6447

Introduction

Differentiated thyroid carcinomas (DTC; including papillary and follicular varieties) are the most common endocrine malignancy with 10 years survival around 90% (Lin et al., 2011; Budak et al., 2013). This outcome is ensured by total thyroidectomy, radioiodine-131 remnant ablation (except in patients with unifocal or multifocal lesion≤1 cm in size) and lifelong thyroxin suppressive therapy (Pacini et al., 2006; Cooper et al., 2009). 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 (RRA) after surgery (Vaisman et al., 2001). Rationales for RRA are (a) to destroy any residual macroscopic and microscopic disease; (b) to enhance sensitivity of diagnostic whole body iodine scan (DWBIS) 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 (TWBIS) which is more sensitive than DWBIS for detection of nodal or distant functioning metastases (Robbin and Schlumberger, 2005).

Stimulated Tg level (STg) after complete thyroid ablation (follow-up) is a reliable and sensitive marker for detecting tumor persistence and recurrence (Schlumberger, 1998; Mazzaferri et al., 2003). Similarly baseline (pre-ablation) STg is considered to have an indirect correlation with residual functioning thyroid tissue over thyroid bed in low risk patients (adequacy of thyroidectomy) (Zaman et al., 2013). Various researchers have used either baseline STg or STg/TSH ratio for predicting the ablation outcome with variable inference (Lee et al., 2007; Hussain et al., 2014). Similarly TWBIS not uncommonly reveal more focal uptake that had not been highlighted on a corresponding low-dose DWBIS and this certainly alters patient's prognosis (Souza et al., 2004).

The aim of this study was to determine the predictive value of the baseline (pre-ablative) stimulated serum thyroglobulin (STg) level for ablation outcome in

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patients who had adjuvant RRA for differentiated thyroid carcinoma.

Materials and Methods

Study Design and Protocol: This was a retrospective study conducted at Nuclear Medicine Departments of Dr. Ziauddin University Hospital and KIRAN Hospital Karachi, Pakistan. From January 2012 till April 2014, medical records of patients who had had total thyroidectomy for DTC and were referred from endocrine section of Aga Khan University Hospital (AKUH), Karachi for ablation with I-131 (RRA). The study was duly approved by ethical review committees of institutes. All patients were treated as per following protocol: (1) after total thyroidectomy patients remained off-thyroxin for 3-4 weeks; (2) advised to have low iodine diet for at least 2 weeks prior to RRA; (3) 2-3 days prior RRA they had , baseline stimulated TSH (sTSH), STg, and Anti-Thyroglobulin antibodies (anti-Tg-ab); (5) I-131(as sodium iodide) in liquid form (mean dose: 105±24 mCi) was administered orally and patients were kept in isolation as per local statutory guidelines; (6) TWBIS was performed 3 to 5 days after RRA; (7) they were started on thyroxin 72 hours after RRA to suppress TSH; (8) 7-12 months after RRA, they had their sTSH, STg, anti-Tg-ab, neck ultrasound, and DWBIS after stopping thyroxin for 18-24 days. Patients with inadequate surgeries, positive anti-Tg-ab or with distant metastases were excluded. Successful ablation was defined as STg<2 ng/ml with negative anti-Tg-ab and no evidence of tumor on DWBIS and neck ultrasound 7-12 months after RRA.

Imaging Methods: WBIS (post-ablative and diagnostic) was acquired using digital gamma cameras fitted with high energy parallel holes collimators (single head Ecam, Siemens, Germany and dual head GCA-7200, Toshiba, Japan) and a scan speed of 5-10 cm/minute was used. The results of these scans were categorized as no uptake, uptake over thyroid bed or node or both and distant metastases (on follow-up diagnostic WBIS).

Measurement of Stimulated Thyroglobulin (STg), Anti-Tg antibody, and stimulated TSH (sTSH): Serum TSH was measured using chemiluminescent assays with analytical sensitivity of 0.008 uIU/ml, functional assay sensitivity of 0.008 uIU/ml, and reportable range of 0.008 to 150 uIU/ml. Thyroglobulin was measured using chemiluminescent assays with analytical assay sensitivity of 0.2 ng/ml and functional assay sensitivity of 0.9 ng/mL interassay for values higher than2 ng/ml. Anti-Tg antibodies were measured using chemiluminescent assays with analytical assay sensitivity of 2.2 IU/ml, interassay precision of 4.6-5.8%, and intra-assay precision of 3.2-4.9% with reportable range of 20-3000 IU/ml and normal range<40 IU/ml.

Statistical analysis: Data were analyzed using commercially available packages such as the Medcalc statistical software (MedCalc Software, Ostend, Belgium), version 11.3.10 and the statistical package for social sciences (SPSS version 17; SPSS Inc., Chicago, Illinois, USA). Comparisons between patient groups were made using the Student t-test for continuous variables and the χ^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: The study cohort included 64 patients (23 male and 41 female) with a mean age of 40±14 years. Mean primary tumor size (PTS) was 2.440±1.190 cm with papillary carcinoma in 55 (86%), follicular in 07 (11%) and follicular variant of papillary carcinoma in 02 (03%). In 27 (42%) patients nodal status was positive

Table 1. Patients' Demographic Characteristics

Variables		Total (n=64)	≤14.5 Tg (n=28)	>14.5 Tg (n=36)	X^2/t-test	P values
Age (mean ±SD) years		40±14	42±11	39±15	-0.888	0.377
Gender (Male: Female)		23:41 (36:64%)	11:17 (39:61%)	12:24 (33:67%)	0.0548	0.815
PTS (mean ±SD) cm		2.440±1.190	2.106±1.043	2.701±1.251	2.027	0.047*
Baseline Nodal status	Nx	02 (03%)	00 (00%)	02 (06%)	0.386	0.535
	N0	35 (55%)	21 (75%)	14 (39%)	6.85	0.009*
	N1a	12 (19%)	04 (14%)	08 (22%)	0.243	0.622
	N1b	15 (23%)	03 (11%)	12 (33%)	3.116	0.077
Type of WDTC	PC	55 (86%)	25 (89%)	30 (83%)	0.102	0.749
	FC	07 (11%)	02 (07%)	05 (14%)	0.237	0.627
	FVPC	02 (03%)	01 (03%)	01 (03%)	0.545	0.46
Baseline TSH status (post-op stimulated)		62±33	69±30	56±34	-1.596	0.115
Baseline STg (post-op) median (range)		16.9 (<0.2-65)	3.65 (<0.2-14.5)	62.65 (15-650)	7.788	<0.0001*
Average I-131 ablative dose in mCi Post ablative scan		105±24	102±21	109±26	1.16	0.25
Negative		07 (11%)	03 (11%)	04 (11%)	0.162	0.687
Thyroid bed		50 (78%)	23 (82%)	27 (75%)	0.135	0.714
+ Lymph nodes		07 (11%)	02 (07%)	05 (14%)	0.237	0.627
Successful ablation		37 (58%)	25 (89%)	12 (33%)	17.985	<0.0001*
(F/up STg <2 ng/ml with negative DWBIS and US)						
Ablation Failure (F/up STg <2 ng/ml with positive DWBIS)		04 (06%)	03 (11%)	01 (03%)	0.603	0.437
Ablation Failure (F/up STg>2.0 ng/ml with positive DWBIS and US)		23 (36%)	00 (00%)	23 (64%)	25.291	<0.0001*

*p<0.05; PTS=Primary Tumor size; PC=Papillary Carcinoma;FC=Follicular Carcinoma; FVPC=Follicular variant Papillary Carcinoma; TSH=Thyroid Stimulated Hormone; STg=Stimulated Thyroglobulin; FU=Follow up; DWIB= Diagnostic whole body iodine scan; US= ultrasound

Table 2. Predictive Values for Ablation Failure for cut off 14.5 ng/ml of Baseline Stimulated Thyroglobulin (STg) with Confounding Factors

Confounding factors >14.5 STg : ≤14.5 STg	True Positive cases of ablation Failure >14.5 STg: ≤14.5 STg	Odd ratios for ablation Failure(lower-Upper limits) >14.5 STg : ≤14.5 STg	95% CI	Z statistics	p values
Age >40 (n=14:18)	9:02	14.4	2.305-89.934	2.854	0.0043*
Female gender (n=24:17)	16:03	9.333	2.065-42.184	2.902	0.0037*
PTS >2.0 cm (n=25:14)	18:01	33.428	3.654-305.776		
PC (n=30:25)	22:03	14.667	3.526-60.998	3.693	0.0002*
Nodes positive (n=20:07)	15:01	18	1.722-188.091	2.414	0.0158*
Positive post ablative scan (n=32:25)	21:02	21.955	4.351-110.788	3.74	0.0002*

*p<0.05; PTS=Primary Tumor size; PC=Papillary Carcinoma; STg= Stimulated Thyroglobulin

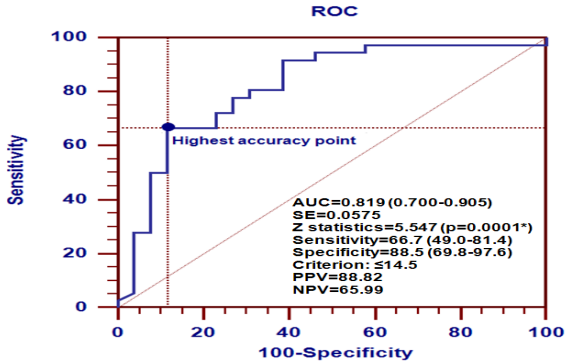

Figure 1. Receiver Operating Characteristics (ROC) Curve of Baseline Stimulated Thyroglobulin (STg) as Predictor of Successful Ablation

[N1a: 12 (19%) and N1b: 15(23%)] and in 35 (55%) patients no evidence of nodal metastasis reported (N0). Mean baseline sTSH and STg levels were 62±33 uIU/ml and 16.9 (range:<0.2-65) ng/ml respectively.

Average ablative dose of radioiodine-131 used was 105±24 mCi and TWBIS revealed residual functioning tissue over thyroid bed only in 50 (78%), thyroid bed plus cervical node(s) in 07 (11%) and no uptake (i.e. negative TWBIS) in 07 (11%) patients.

Clinical Outcomes: Over-all successful ablation (i.e. STg <2 ng/ml with negative DWBIS and U/S neck at follow-up) was seen in 37 (58%) patients. Overall ablation failure was seen in 27 (42%) patients [23 (36%) with follow-up STg>2 ng/ml and 04 (06%) with STg<2 ng/ml but with positive DWBIS]. To find out most sensitive and specific ablation baseline STg 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 STg level <14.5 ng/ml as the most sensitive and specific level for predicting successful ablation with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 66.7%, 88.5%, 88.82% and 65.99% respectively (Figure 1). On basis of baseline STg level, patients were grouped into 28 patients with baseline STg≤14.5 ng/ml and 36 patients with baseline STg >14.5 ng/ml. Comparative analysis revealed that patients with baseline STg >14.5 ng/ml had significantly larger primary tumor size with lower incidence of N0 status than patients with baseline STg≤14.5 ng/ml (p value <0.05). Successful ablation was noted in 25 (89%) of patients with baseline STg≤14.5 ng/ml and 12 (33%) patients with baseline STg >14.5 ng/ml ((p value <0.05). Ablation failure was noted in 03 (11%) patients with baseline≤14.5 ng/ml [follow-up STg<2 ng/ml with positive DWBIS) and 24 (67%) of patients with baseline STg >14.5 ng/ml [1 with follow-up STg <2 ng/ml and positive DWBIS and 23 patients with follow-up STg >2 ng/ml and positive DWBIS and US, p value significant] (Table 1).

Predictors of Ablation Failure: Multivariate analysis for ablation failure revealed that age >40 years, female gender, PTS >2 cm, papillary histopathology, positive cervical nodes and positive TWBIS were significant predictors of ablation failure (Table2).

Discussion

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 (Edward et al., 2002). Total thyroidectomy and RRA (in tumors>1cm in size) are considered as major therapeutic measures (Mazzaferri and Kloss, 2001). Successful ablation induced by I-131 has been shown to reduce recurrence and improve disease free survival (Verburg et al., 2005) although ablation failure has been observed in 20-30% patients after higher ablative doses of I-131 (Karam et al., 2003). A repeat ablative dose is associated with inconvenience to patients, increase financial burden and possible higher odds of second primary malignancy (Iyer et al., 2011). In this regards various researchers have explored different variables as predictor for successful ablation.

In this study we have evaluated predictive value of baseline STg (just before ablation) for successful ablation in 64 patients with total thyroidectomy for DTC followed by RAA. The overall successful ablation was 58% with a median baseline STg level 16.9ng/ml. This is significantly lower than 82.7% achieved by Lee at al (2010). Possible explanation for this discordance is significantly lower baseline median STg level of 2.6 ng/ml in their study and it is an established fact that baseline STg 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 (Giovanella et al., 2005). Researchers have failed to prove association between mRNA based marker oncofetal fibronectin (onfFN mRNA) with thyroid metastases (Sritara et al., 2012). Although our cohort had no evidence of distant metastasis (M0) and 55% had N0 status, a median baseline STg level of 16.9 ng/ml 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 (Beierwaltes et al., 1984) while recent data claim cervical uptake is a predictor of successful ablation (Rosario et al., 2004).

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 STg level (2-69.7 ng/ml) has been suggested (Lee et al., 2007). In this study we used ROC curve to find out a cut-off value of STg with highest diagnostic strength which was 14.5 ng/ml. On the same note, 89% of patients with baseline STg≤14.5 ng/ml had successful ablation while only 33% of patients with baseline STg >14.5 ng/ml could achieve successful ablation. This fact has recently been elaborated that the post-operative STg levels prior RAA had a complementary role for predicting the persistence or recurrence of thyroid carcinoma during the 6-12 month postoperative period (Kim et al., 2005). 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 STg level 10 ng/ml with a successful ablation rate of 96.6% and 47.8% in patients with STg≤10 and>10 ng/ml respectively. The basic reason for this difference is use of unstimulated (or suppressed) Tg<2 ng/ml as biochemical criteria for successful ablation in their study while we used stimulated Tg<2 ng/ml. This is an established fact as undetectable serum Tg levels after withdrawal of thyroxin (i.e. stimulated Tg or STg) during follow-up would guarantee complete remission and DWBS could be avoided (Pacini et al., 2002). Here we would like to mention that smaller value of baseline STg 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 (Mallick et al., 2012; Schlumberger et al., 2012). 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 in patients with STg >14.5 ng/ml, age (>45 years), PTS (>2 cm), nodal metastases and positive TWBIS were strong predictors for ablation failure and this is in accordance with published data (Lim et al., 2012). Our data also revealed female gender as a confounding factor for ablation failure whom baseline STg was marginally but not significantly higher (16.45 ng/ml) than males (14.5 ng/ml). This is not in accordance with published data (Lee et al., 2007; Lim et al., 2012) and we have no plausible explanation too. Similarly our results show patients with papillary carcinoma had more ablation failure than patients with follicular carcinoma and this is not in accordance with published studies (Verburg et al., 2005; Lee et al., 2007). However, we feel that bias sampling error is the possible reason for this observation.

Our study has some limitations and the first one is retrospective nature of study although all accrued individuals had same pathology (differentiated thyroid cancers) and were treated according to a well-designed protocol. 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 STg 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 DWBIS and negative US (i.e. stringent triple negative criteria). In fact this is the major strength of our study as negative predictive value of STg is better than non-stimulated Tg level (Pacini et al., 2002). 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.

We conclude that in patients with total thyroidectomy followed by I-131 ablation for DTC, baseline STg level is a good predictor of successful ablation based on a stringent triple negative criteria (i.e. follow-up STg<2 ng/ml, a negative DWBIS and negative US neck).

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