

## Prognostic Value of Postoperative and Post-ablative Serum Thyroglobulin Levels in Patients with Differentiated Thyroid Cancer

\*Raef H, \*Malabu U H, \*Alfadhli E, \*Al-Hajjaj A, \*\*Al-Sobhi S, \*\*\*Rifai A, \*Al-Nuaim A

Departments of Medicine\*, Surgery\*\*, Radiology\*\*\* King Faisal Specialist Hospital & Research Center Riyadh, Saudi Arabia

### Abstract

**Background:** The study was designed to examine the value of post-operative and post-ablative serum thyroglobulin levels and diagnostic whole body scan in predicting remission in patients with differentiated thyroid carcinoma.

**Methodology:** Serum TG levels and diagnostic iodine-123 whole body scans performed prior to and 6-12 months after  $^{131}\text{I}$  ablation for DTC were evaluated in 100 consecutive patients at King Faisal Specialist Hospital Riyadh. Patients were followed up for a period of 7.6 years (range 7-10 years). All patients underwent total thyroidectomy prior to  $^{131}\text{I}$  ablation.

**Results:** Patients with serum TG levels  $< 8$  ng/ml post thyroidectomy (50 patients) also maintained low TG  $< 8$  ng/ml after  $^{131}\text{I}$  ablation and had better outcome (60%) remission. On the other hand DTC subjects with higher TG  $> 8$  ng/ml post thyroidectomy (50 patients) 40% remained in remission  $\chi^2 = 4.00$ ,  $p = 0.046$ . For the group with initial high post-operative TG, it became  $< 8$  ng/ml in 34/50 (68%) patients after ablation with  $^{131}\text{I}$  and in this subgroup, remission was seen in 16/34 (47%) of patients in contrast to 4/16 (25%) remission rate in those who continue to have TG  $> 8$  ng/ml after ablation. At the end of follow up,  $^{123}\text{I}$ -WBS was positive in 4% and 10% of patients with initial TG  $< 8$  ng/ml and TG  $> 8$  ng/ml respectively;  $\chi^2 = 1.38$ ,  $p = 0.24$ .

**Conclusion:** Post-operative and post-ablative serum TG levels -but not follow up diagnostic WBS- have predictive values and permit selection of patients with higher risk for persistent/recurrent disease.

**Keywords:** differentiated thyroid carcinoma, post-thyroidectomy, thyroglobulin, remission

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### Introduction

Standard treatment of differentiated thyroid cancer consists of total or near-total thyroidectomy, followed by ablation of residual thyroid tissue with high-dose  $^{131}\text{I}$ , and

levothyroxine therapy in sufficient doses to maintain low or suppressed thyrotropin levels.<sup>1,2</sup> Long term follow-up surveillance is usually based on  $^{123}\text{I}$  or  $^{131}\text{I}$  whole-body scan (WBS) and the determination of serum thyroglobulin (TG) after suspension of levothyroxine during a period sufficient enough to allow for substantial increment of thyroid stimulating hormone (TSH) levels, to detect any possible persistence of thyroid tissue either locally or the presence of distant metastases.<sup>3-7</sup> Recently, the availability of recombinant human TSH alleviated the need of withdrawal of levothyroxine.<sup>8-10</sup> The sensitivity of TG as a marker for the presence of residual thyroid tissues have caused various groups to propose the withdrawal of WBS in the follow-up of patients who have low TG levels and a prior negative scan, given that it does not provide any additional clinical information to that obtained from the determination of TG levels alone.<sup>11-16</sup> Nonetheless, few authors have reported the value of the TG level measured in the postoperative or post-ablative period as a prognostic factor for persistent or recurrent disease mainly in the West where treated DTC is known to have excellent outcome.<sup>11, 17</sup> In contrast previous reports have shown Saudi subjects with DTC to have resistant disease with high recurrence and persistence.<sup>18, 19</sup>, yet until now no study designed to find out prognostic value of TG in the local population.

The aim of the study was therefore to examine the value of post-operative and post-ablative TG levels in predicting the outcome in our patients with relatively higher rate of persistent/recurrent DTC and therefore in selecting those with higher risk for further evaluation.

### Materials and Methods

One hundred subjects diagnosed consecutively with DTC were studied and followed up for a period of 7.6 years. Patients were treated by total thyroidectomy with cervical lymph node dissection performed for the patients on the basis of known lymph node involvement prior to surgery or an abnormal finding at the time of surgery. This was followed by remnant ablation with

Correspondence to Usman Malabu, Email: [umalabu@yahoo.com](mailto:umalabu@yahoo.com)

100-150 (mean 137) mCi of <sup>131</sup>I according to the Thyroid Cancer Unit protocol of King Faisal Specialist Hospital (KFSH) Riyadh. The study was approved by the ethical committee of the hospital and consent was sought from all subjects. Patients diagnosed with anaplastic or medullary thyroid carcinoma were excluded from the study.

Initial assessment of such patients included verification of diagnosis for patients whom initial biopsy done outside KFSH, through reviewing the pathology reports and slides. The following information was obtained: type of thyroid cancer; pathologic primary tumor size; staging and lymph node involvement; clinical assessment; history and physical examination. Biographical data included all Saudis, gender and age at diagnosis, and family history of thyroid cancer.

Laboratory and radiologic work-up including serum TG, TSH, free thyroxine (FT4), thyroid autoantibodies, and anti-thyroglobulin antibodies were determined. TG was measured by a chemiluminescent immunometric assay with a lower limit of 0.2 ug/liter (Immunlite Kit, EURO/Diagnostic products). TG autoantibodies were measured using a solid phase, two-step, chemiluminescent enzyme immunometric assay with a calibration range up to 3000 IU/ml (Immunlite Kit, EURO/Diagnostic Products).

Histologic examination was conducted for all the patients. Patients were staged according to the pathologic tumor-node-metastasis (pTNM) classification.<sup>17</sup> Other histopathologic characteristics were also recorded: tumor size, multifocality, extrathyroidal extension, and vascular invasion. Shortly after surgery, LT4 was withdrawn, and LT3 was given for 2-3 weeks and then withdrawn for 2 weeks. Serum TSH was then measured and exceeded 30 uU/ml in all patients followed by measurement of serum TG levels. Diagnostic <sup>123</sup>I scanning was done 24 h after oral ingestion of 370-555 MBq of the radioiodine. Following the diagnostic scan, 100-150 mCi of <sup>131</sup>I was administered. A whole body scan (WBS) was performed 4 days after the administration of <sup>131</sup>I. T4 treatment was then initiated with the aim of decreasing serum TSH to low levels (< 0.1 uU/ml) without inducing clinical thyrotoxicosis. Repeated <sup>123</sup>I WBS was done 6-12 months after initial treatment using the same protocol. A second ablative dose of <sup>131</sup>I was then given to those with continuous positive uptake on WBS.

During the follow-up period, a clinical examination and neck ultrasound were carried out every six months. In the first 3 years of follow-up, diagnostic <sup>123</sup>I-WBS and measurement of TG levels off L-thyroxine were carried out every year. Afterward determinations were done at

longer intervals. When TG levels off thyroxine were detected but <sup>123</sup>I WBS negative, other radiologic methods such as ultrasound, computed tomography (CT) scan, magnetic resonance imaging (MRI), and positron emission tomography (PET) were used to determine the localization of tumor. If the TG levels persistently above 2 ng/ml with negative WBS or other diagnostic radiology, patient would be observed on suppressive thyroxine therapy and would have repeated imaging studies to identify the focus of persistence or metastatic disease. On the other hand, if the persistently high serum TG levels were accompanied by positive WBS uptake or recurrent tumor localized by ultrasound, CT, MRI or PET, patient would be subjected to repeat surgery to be followed by ablative radiotherapy.

Remission of the disease was defined as negative clinical examination, negative <sup>123</sup>I WBS uptake, TG level < 2 ng/ml off L-thyroxine, and no other clinical or radiological evidence of the disease. Persistence was defined as absence of remission as defined above. Recurrence was defined as evidence of disease after at least one year of remission. Active disease was defined as presence of any one of the following: positive clinical examination, positive <sup>123</sup>I WBS uptake, TG level > 2 ng/ml off L-thyroxine, or presence of disease demonstrated by other imaging methods.

Patients were grouped into 2 based on post-operative TG values. The patients' data were used to determine the most suitable discriminating concentrations for the two groups of patients by using receiver operator characteristic (ROC). Analyses were performed using the Statistical Package for the Social Sciences 7.5 (SPSS, Inc., Chicago, IL). Stepwise logistic regression for multivariate analysis was used to determine predictive value for remission. As significant effects were found, the Student's t-test or the X<sup>2</sup> was used as appropriate to examine prognostic value of post-surgical and post-ablative TG levels in the study population. Mean and standard deviation were determined by quantitative data and frequency was determined for categorical variables. A level of  $\alpha=0.05$  was used as indicator of statistical significance.

## Results

A total of 100 patients with differentiated thyroid carcinoma were studied in 7.6-year period (range 6-10 years). The mean age at diagnosis was  $36 \pm 12.5$  years 80 females and 20 males with female to male ratio 4:1. According to the pathologic tumor-node-metastasis (pTNM) classification (17), 78 patients (78%) had stage

I, 5 patients stage II, 15 patients stage III, and 2 patients stage IV. Thyroid mass was the commonest presentation (90%), while pathological examination showed papillary thyroid cancer (PTC) in 76%, follicular variant of PTC in 14%, other variants of PTC (tall cell and sclerosing types) in 3%, Hurthle cell carcinoma in 3% and follicular thyroid cancer in 4%. The tumors showed multifocality in 26% and soft tissue invasion in 32%. Cervical lymph node (CLN) metastases were present in 33%. Thirty-six patients had late presentation more than 3 years of having first symptom. All patients received <sup>131</sup>I therapy once (mean dose 137 mci) and 25% received twice (mean dose 178 mci). The remission rate and ablation rate were 50% and 93% respectively.

Using ROC analysis of TG serum levels measured while patients were off thyroxine with elevated TSH levels after total thyroidectomy were under 8 ng/ml in 50 patients (50%) and above 8 ng/ml in another patients (50%). Table 1 shows status of patients with initial post-surgical TG level below 8 ng/ml 60% had remission compared to 40% in those with initial post-operative TG level > 8 ng/ml. Persistent and recurrent diseases representing non-remission group were higher (60%) in patients with higher initial post-surgical serum TG level than those with lower initial values (40%), X<sup>2</sup> = 4.00; p = 0.046. On the other hand, of the 50 patients with TG levels less than 8 ng/ml post surgery, 2 (4%) showed positive uptake at the thyroid bed after WBS, while patients with TG above 8 ng/ml, 5 (10%) showed positive radioactive uptake, X<sup>2</sup> = 1.38; p = 0.24 (Table II).

**Table I. Differentiated thyroid carcinoma patients' disease status after 7.6-year of follow-up**

Post surgery TG	Remission	Persistent	Recurrent	Non-Remission
< 8 ng/ml	30 (60%)	14 (28%)	6 (12%)	20 (40%)
≥ 8 ng/ml	20 (40%)	27 (54%)	3 (6%)	30 (60%)

X<sup>2</sup> = 4.00; p = 0.046 for post-operative TG in predicting remission

**Table II. Status of differentiated thyroid cancer patients' whole body scan during follow up after ablative therapy**

Status	Patients with initial TG <8 ng/ml	Patients with initial TG > 8 ng/ml *
Patients with final WBS negative	48	45
Patients with final WBS positive	2	5
Total number of patients	50	50

\*X<sup>2</sup> = 1.38; p = 0.24

**Table III: Outcome in DTC patients with initial low post-operative TG**

		Outcome	
TG Post surgery	TG Post ablation	Remission	Persistent/Recurrent
TG <8 ng/ml (50/100)	TG <8 ng/ml (50/50)	60%	2 (-) scans ↓ TG 16 (-) scans ↑ TG 1 (+) scan ↑ TG 1 (+) scan ↓ TG

**Table IV: Outcome in DTC patients with initial high post-operative TG**

		Outcome	
TG Post-surgery	TG Post-ablation	Remission	Persistent/Recurrent
TG ≥ 8 ng/ml (50/100)	<8 ng/ml 34/50 ≥ 8 ng/ml 19/50	16/34 (47%) 4/16 (25%)	20/50 (40%) (Combined) 24 (-) scans ↑ TG 5 (+) scans ↑ TG 1 (-) scan ↓ TG

TG post ablation was also predictive of remission. All the 50 patients with TG < 8 ng/ml postoperatively maintained same TG levels after ablative therapy (Table III). Whereas among the 50 patients with a TG ≥ 8 ng/ml postoperatively, 34 (68%) had TG <2 ng/ml during follow up after completed ablation (once or twice) with remission in 16/34 (47%), while 16/50 had TG ≥ 8 ng/ml post-ablation, with remission in only 4/16 (25%) as shown in Table IV.

## Discussion

We studied 100 patients diagnosed consecutively with differentiated thyroid carcinoma and treated with total or near-total thyroidectomy followed by high-dose thyroid ablation once or twice and been followed for an average of 7.6 years. Clearly, post-surgical serum TG levels separated our patients into two prognostic groups with a cut-off value of 8 ng/ml determined by ROC in our study population. Overall, 60% of patients with initial TG levels < 8 ng/ml remained disease free, in keeping with earlier reports (13, 14). Conversely, patients with initial high TG levels had worse prognosis. For instance, of the 50 patients with initial post thyroidectomy serum TG concentrations higher than 8 ng/ml, persistent or recurrent disease was noted in 60%, similar to previous observations.<sup>20-22</sup> Thus, serum TG level after initial surgery prior to <sup>131</sup>I ablation proves to be valuable index of a disease-free in the long term in the majority of patients in our series as well as others finding.<sup>23, 24</sup> Interestingly, we recorded lower remission in our patients with DTC at 50% in a relatively short duration of follow-up compared to 75-85% in Caucasian series as

reported by DeGroot et al and Mazzaferri et al in longer period of 10 years.<sup>11, 25</sup> Most of the non-remission cases in our report were those with persistent disease (41 patients), while 9 subjects had recurrences and may indicate locally aggressive disease at presentation.

Several studies have reported that high TG levels at the time of ablation can be related to initial metastasis or recurrence. In these studies, significant relationship between TG levels and the chance of successful ablation was observed where elevated serum TG levels shortly after administration of I-131 is correlated with a lower chance of successful ablation.<sup>12, 15, 16</sup> Furthermore, the value of post-ablative TG in predicting outcome is also seen in our patients. Subjects with low post-ablative TG had better prognosis in keeping with similar findings in earlier series.<sup>26, 27</sup>

A closer look at our study revealed lack of relationship between serum TG level and likelihood of WBS uptake in the thyroid bed. The WBS was positive in only 10% of subjects with high initial TG levels and in 4% who had low serum TG with no significant differences between the 2 groups. The study shows reliance of WBS alone in post-ablative follow-up of patients with DTC can be misleading

since majority of those with persistent disease were missed, similar to Cailleux et al's observation.<sup>13</sup> Distinctively, TG levels alone not only separated patients into 2 prognostic groups as indicated above, but detected subjects with recurrence or persistent disease. Thus, it has been suggested that follow-up of patients with low or undetectable TG should be carried out by periodic determinations of serum TG levels alone in the presence of high TSH achievable by thyroxine withdrawal or recombinant TSH supplementation.<sup>27, 28</sup>

Our results confirm the reliability of TG levels in predicting remission or persistence/recurrence of differentiated thyroid carcinoma after thyroidectomy and 131I ablation even in a relatively high risk DTC population. We believe -as others had suggested-that follow-up of patients with low or undetectable postoperative and post-ablative TG levels can be carried out by periodic determinations of stimulated serum TG levels only.<sup>28, 29</sup> More stringent follow up and diagnostic tests can be reserved for those with elevated stimulated TG especially those who continue to have elevated stimulated TG after adequate ablation.

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