RESEARCH ARTICLE

Importance of Postoperative Stimulated Thyroglobulin Level at the Time of ^{131}I Ablation Therapy for Differentiated Thyroid Cancer

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Abstract

Background: Serum thyroglobulin detection plays an essential role during the follow-up of thyroid cancer patients treated with total/near total thyroidectomy and radioiodine ablation. The aim of this retrospective study was to evaluate the relationship between stimulated serum thyroglobulin (Tg) level at the time of high dose ^{131}I ablation and risk of recurrence, using a three-level classification in patients with differentiated thyroid cancer (DTC) according to the ATA guidelines. Also we investigated the relationship between postoperative stimulated Tg at the time of ablation and DxWBS results at 8-10 months thereafter. Materials and Methods: Patients with radioiodine accumulation were regarded as scan positive (scan+). If there was no relevant pathological radioiodine accumulation or minimal local accumulation in the thyroid bed region, this were regarded as scan negative (scan-) at the time of DxWBS. We classified patients in 3 groups as low, intermediate and high risk group for assessment of risk of recurrence according to the revised ATA guidelines. Also, we divided patients into 3 groups based on the stimulated serum Tg levels at the time of ^{131}I ablation therapy. Groups 1-3 consisted of patients who had Tg levels of ≤2 ng/ml, 2-10 ng/ml, and ≥10 ng/ml, respectively. Results: A total of 221 consecutive patients were included. In the high risk group according to the ATA guideline, while 45.5% of demonstrated Scan(+) Tg(+), 27.3% of patients demonstrated Scan(-) Tg(-); in the intermediate group, the figures were 2.3% and 90.0% while in the low risk group, they were 0.6% and 96.4%. In 9 of 11 patients with metastases (81.8%), stimulated serum Tg level at the time of radioiodine ablation therapy was over 10, however in 1 patient (9.1%) it was <2ng/mL and in one patient it was 2-10ng/mL (p=0.005). Aggressive subtypes of DTC were found in 8 of 221 patients and serum Tg levels were ≤2ng/ml in 4 of these 8. Conclusions: We conclude that TSH-stimulated serum thyroglobulin level at the time of ablation may not determine risk of recurrence. Therefore, DxWBS should be performed at 8-12 months after ablation therapy.

Keywords: Thyroid carcinoma - radioiodine therapy - thyroglobulin - I-131

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Introduction

Total thyroidectomy is the primary treatment of thyroid cancer. Therapy with radioiodine (^{131}I) after surgery has been used in the treatment of patients with papillary and follicular thyroid carcinoma, both to ablate any remaining normal thyroid tissue and to treat the carcinoma. Postoperative ^{131}I ablation is also provide destruction of occult foci of neoplastic tissue. Thyroglobulin (Tg) is a high molecular weight glycoprotein which is released only by normal or neoplastic thyroid follicular cells. After total thyroidectomy and ^{131}I ablation of residual normal gland it can be used as a highly sensitive and reliable marker of recurrence and/or metastatic foci in differentiated thyroid cancer (DTC) (Kucukalić-Selimović et al., 2012). The presence of anti-thyroglobulin antibodies (anti-TgAb) can result in falsely low levels on thyroglobulin test (Durante et al., 2013). According to the revised guidelines of American Thyroid Association (ATA), the first diagnostic whole body scan with ^{131}I (DxWBS) should be performed 6-12 months after ablation therapy (Cooper et al., 2009). Cut-off level of unstimulated serum Tg is 2ng/ml in patients with total thyroidectomy and ^{131}I ablation. Serum thyroglobulin level was more sensitive in patients with stimulated TSH level. However, discordant results of Tg levels and whole body scan (WBS) can be seen (Koh et al., 2003).

The aim of this retrospective study was to evaluate the relationship between stimulated serum Tg level at the time of high dose ^{131}I ablation and for assessment of risk of recurrence, a three-level classification in patients with DTC according to the ATA guideline. Also we investigated

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the relationship between postoperative stimulated Tg level at the time of ablation and DxWBS results at 8-10 months after ablation therapy.

Materials and Methods

Patients

In this retrospective study, 221 patients who were diagnosed with DTC, treated with total and/or near-total thyroidectomy, with or without lymphadenectomy and ^{131}I ablation therapy and 8-10 months after ^{131}I ablation therapy referred for low dose diagnostic ^{131}I whole body scan (DxWBS) were included in our study. Clinical, imaging and laboratory data were recorded at the time of ^{131}I ablation therapy and DxWBS. This study was performed in accordance with the principles of the Declaration of Helsinki. In all patients, L-thyroxine (L-T4) treatment was started for TSH suppresion after surgery and ablation therapy with ^{131}I. Patients with anti-TgAb positive, without clinical follow-up and without low-dose diagnostic ^{131}I whole body scan were excluded from the study. Also we excluded patients who had ablation therapy given in another hospital.

Radioiodine ablation therapy was given after L-thyroxine (L-T4) withdrawal in all patients. Post-ablation whole-body scan (RxWBS) was performed 8th and 9th days after the administration of ^{131}I. After ^{131}I ablation therapy, all patients began taking L-T4 preparation. Serum Tg, TSH and anti-TgAb levels were simultaneously measured before ^{131}I administration. In all patients, low iodine diet were recommended for 2 weeks before ablation therapy and DxWBS. It was known that, ablation therapy and DxWBS requires TSH stimulation. For stimulated TSH level, L-T4 preparation was stopped 4 weeks before ^{131}I administration (THW-thyroid hormone withdrawal) during ablation therapy. For stimulated TSH level, L-T4 preparation was stopped 4 weeks before ^{131}I administration or recombinant TSH was administered (0.9 mg) by two intramuscular injections on successive days with the ^{131}I being given on the third day during DxWBS. At 2nd and 6th months, the initial clinical follow-up evaluation was performed after ^{131}I ablation therapy in all patients. Clinical follow-up was included that; a physical and neck ultrasonographic examination and, serum Tg, anti-TgAb, TSH, freeT4 level measurements. Diagnostic WBS with approximately 185 MBq of ^{131}I, neck ultrasonography and chest plain radiography or if necessary neck and/or chest computed tomography examinations were performed and serum Tg, anti-TgAb and TSH levels were measured 8-10 months after ^{131}I ablation therapy. Diagnostic WBS was performed 24th ve 48th hours after administration of ^{131}I.

Scintigraphic images were obtained with the use of a single-headed gamma camera (Toshiba GCA-7100A) that was equipped with a "high energy parallel hole" collimator and interfaced to a dedicated computer. For image acquisition, a peak energy setting at 364 keV with a 20% window was used. The scan speed was 7cm/min for all WBS. Whole body scan with anterior and posterior views was acquired, and local static images were obtained. Patients with radioiodine accumulation which was thyroid bed outside (in the cervical region or in other areas of the body) or apparent accumulation in the thyroid bed region were regarded as scan positive [scan(+)]. If there was no relevant pathological radioiodine accumulation or minimal local accumulation in the thyroid bed region, this were regarded as scan negative [scan (-)] at the time of DxWBS.

We classified patients in 3 groups for assessment of risk of recurrence according to the revised ATA guidelines; Low-risk patients have the following criteria: no local or distant metastases, all macroscopic tumor has been resected, there is no tumor invasion of locoregional tissues or vascular invasion, the tumor does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma) and, if ^{131}I is given, there is no ^{131}I uptake outside the thyroid bed on the post ablation treatment whole body scan (RxWBS). Intermediate-risk patients have any of the following criteria: microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery, cervical lymph node metastases or ^{131}I uptake outside the thyroid bed on the RxWBS carried out after thyroid remnant ablation or tumor with aggressive histology or vascular invasion. High-risk patients have the following criteria: macroscopic tumor invasion, incomplete tumor resection, distant metastases, and thyroglobulinemia disproportionate to what is seen on the posttreatment whole body scan.

Also, we divided patients into 3 groups based on the stimulated serum Tg levels at the time of ^{131}I ablation therapy. Group 1 consisted of patients who had Tg level ≤2ng/ml, Group 2 patients with Tg level 2-10 ng/ml, and Group 3 patients with Tg level ≥10 ng/ml.

Statistical analyses

SPSS 15.0 software was used for statistical analysis. Descriptive quantitative data are expressed as the mean values and standard deviation, and qualitative data are expressed as percentages. Fisher's exact test and chi square test was used to compare variables. It was assumed that the observed differences were statically significant at the p≤0.05 levels. Independent Sample T test was used to assess the relationship between risk groups and levels of Tg.

Results

Two hundred twenty one consecutive patients were included in the present study. They were consisted of 189 (85.5%) females and 32 (14.5%) males with a mean age of 46±13 years (range; 16-80yrs). The clinical characteristics of the patients are reported in Table 1. Mean size of primary thyroid tumor was 18.5±14 mm (range 1-90 mm, median 15 mm). Thyroid carcinomas were classified as papillary in 168 (76%) patients, follicular in 32 (14.5%), thyroid tumors of uncertain malignant potential 14 (6.3%), poorly differentiated in 4 (1.8%), aggressive histology (tall cell and insular variant) in 2 (0.9%), and anaplastic cancer in 1 (0.5). Hundred three patients (46.6%) were under the age of 45 years and 118 patients (54.4%) were over 45 years. Postoperative stimulated Tg levels at the time of ablation therapy were ≤2ng/ml in 75 patients (33.9%) and these patients were categorized as Group 1. Postoperative

Tg levels were 2-10 ng/ml in 67 patients (30.3%) and these patients were categorized as Group 2. Postoperative Tg levels were ≥10 ng/ml in 79 patients (35.7%) and these patients were categorized as Group 3. Additionally, TSH-stimulated serum Tg level measurements were obtained at the time of DxWBS performed 8-12 months after ablation in all patients. Median of the stimulated serum Tg level was 0.2ng/ml.

One hundred sixty six (75.1%) of 221 patients belonged to the low risk group according to ATA risk classification system, while 44 (19.9%) patients were intermediate group and 11 (5%) patients were high risk group. Table 2 demontrates the results of postoperative Tg levels and patients risk groups. Postoperative stimulated Tg levels were ≥10 ng/mL in 10 of 11 patients in high risk group (p=0.001).

Table 3 demonstrates the results of DxWBS and stimulated Tg levels at the time of first radioiodine therapy. Two patients have lymph node metastases, one patient has lung metastases, 2 patients have obvious residue mass in thyroid bed in Scan(+) Tg(-) group. Another patient in this group had lung uptake but, it was thought that this was related to the known bronchiectasis. So, this finding was not accepted as metastasis.

Four patients have lymph node metastases, one patient has lung metastasis, one patient has bone metastasis and one patient has apparent residue mass in thyroid bed in Scan(+) Tg(+) group.

One patient has lymph node metastasis, one patient has lung metastasis, one patient has bone metastasis and 2 patient have mimimally residue mass in thyroid bed in Scan(-) Tg(+) group.

A second ^{131}I treatment was administrated all these metastatic patients.

In the high risk group according to the ATA guideline, while 45.5% of patients demonstrated Scan(+) Tg(+), 27.3% of patients demonstrated Scan(-) Tg(-); in the intermediate group, while 2.3% of patients demonstrated Scan(+) Tg(+), 90.0 % of patients demonstrated Scan(-) Tg(-); and while in the low risk group, 0.6% of patients demonstrated Scan(+) Tg(+), 96.4% of patients demonstrated Scan(-) Tg(-) (p=0.0001) (Table 4).

In 9 of 11 patients with metastases (81.8%), stimulated serum Tg level at the time of radioiodine ablation therapy was over 10, however in 1 patient (9.1%) it was <2ng/ml and in one patient it was 2-10ng/mL (p=0.005).

In 154 patients with tumor size ≤20 mm, stimulated serum Tg level was found as 16.3±45, in 45 patients with tumor size 20-40 mm, stimulated serum Tg level was found as 35.11±93, and in 17 patients with tumor size >40mm, stimulated serum Tg level was found as 80±217 (p>0.05).

Aggressive subtypes of DTC were found in 8 of 221 patients and serum Tg levels were ≤2ng/ml in 4 of 8 patients (not statistically significant).

Table 1. Demographic and Clinicopathologic Characteristics

Characteristics		No. of patients (%)
Gender	Female	189 (85.5%)
	Male	32 (14.5%)
Age (years)	Mean (range)	46 years (16-80)
	<45 years	103 (46.6%)
	≥45 years	118 (53.4%)
Histopathologic classification		
Papillary		168 (76%)
Follicular		32 (14.5%)
Thyroid tumors of uncertain malignant potential		14 (6.3%)
Poorly differentiated		4 (1.8%)
Agressive histology (tall cell and insular)		2 (0.9%)
Anaplastic		1 (0.5%)
Tumors size (mm)	Mean (range)	18.5 mm (1-90 mm)

Table 2. Results of Postoperative Stimulated Tg Levels at the Time of Ablation Therapy and Patients Risk Group (p=0.001)

Risk group	≤2 ng/mL (n=75)	2-10 ng/mL (n=67)	>10 ng/mL (n=79)
Low	55 (33.1%)	55 (33.1%)	56 (33.7%)
Intermediate	20 (45.5%)	11 (25%)	13 (29.5%)
High	-	1 (9.1%)	10 (90.9%)

Table 3. Results of Tg Levels at the Time of Radioiodine Therapy and DXWBS with 5mCi 131I (p=0.001)

		<2ng/mL (n=75)	2-10ng/mL (n=67)	>10 ng/mL (n=79)
Scan-	Tg-	73 (36%)	65 (32%)	65 (32%)
	Tg+	0	0	5 (100%)
Scan+	Tg-	2 (33.3%)	2 (33.3%)	2 (33.3%)
	Tg+	0	0	7 (100%)

Table 4. Comparison of Results of Diagnostic WBS with 5 mCi ^{131}I at 8-12 Months after Ablation Therapy and Risk Groups (p=0.0001)

Risk Group (n=221)	DXWBS Results (n=221) Scan+Tg- (n=6)	Scan-Tg- (n=203)	Scan+Tg+ (n=7)	Scan-Tg+ (n=5)
Low	4 (2.4%)	160 (96.4%)	1 (0.6%)	1 (0.6%)
Intermediate	1 (2.3%)	40 (90.9%)	1 (2.3%)	2 (4.5%)
High	1 (9.1%)	3 (27.3%)	5 (45.5%)	2 (18.2%)

Discussion

Differentiated thyroid cancer is related with a good prognosis, especially in patients less than 45 years old who have no evidence of distant metastases and have no agressive histology. The patients who had total thyroidectomy and ablation therapy, serum Tg measurements can be used as an indicator of residual or metastatic cancer. Postoperative RAI ablation is routinely used at some institutions to destroy residual thyroid tissue and occult foci of neoplastic cells. Therefore, postoperative RAI ablation therapy and diagnostic WBS with ^{131}I is performed 8-10 months after ^{131}I ablation are routinely used in our department. Although, there is a general agreement that post operative RAI may not be use for low risk patients, because these patients have low risk of recurrence (Durante et al., 2013) , in our study, lymph node metastases could not be noticed with ultrasonographic neck examination was detected by DxWBS in 1 patient among 166 patients in low risk group (0.6%).

Low serum Tg level at the time of ablation has negative predictive value for absence of residual disease, and the risk of persistent disease increases with stimulated Tg levels (Pacini et al., 2002). Recently, some researchers reported that, postoperative stimulated Tg level is used in predict of prognosis (Kim et al., 2005; Nascimento et al., 2011). Ibrahimpasic et al. (Ibrahimpasic et al., 2012) reported that, low risk patients ≤45 yrs with pT1 tumors and intermediate risk patients >45 yrs, small T1-T2 tumors, and who have negative neck examination findings can be safely managed without RAI after total thyroidectomy if they have an undetectable postoperative Tg. Also, Lee et al. (2013) reported that, when high-dose ^{131}I remnant ablation is performed after total thyroidectomy, the stimulated Tg measurement and DxWBS that are usually performed 6-12 months after ^{131}I ablation therapy may be skipped in low-and intermediate-risk patients with postoperative stimulated Tg level of <2ng/ml and negative neck ultrasonography findings. Similarly, Baudin et al. (2003) reported that, DxWBS with ^{131}I has a limited interest for the follow-up of thyroid cancer patients. Whereas, we demonstrated that, in 2 of 55 patients with low risk and Tg level of <2ng/mL DxWBS was scan(+) Tg(-) in our study. In one of these patients has lymph node metastasis and the other patient has residue mass.

Postoperative stimulated Tg level is primarily related to success of surgeon and the presence of persistant disease or normal thyroid remnant. Even after successful total thyroidectomy by applied experienced surgeons, absence of residual thyroid tissue is extremely rare. Low serum Tg levels(<2ng/ml) predict successful ablation and remaining no residual tumor tissue after ablation, but it may always not predict tumor aggressiveness and presence of metastasis. Otherwise, postoperative stimulated Tg level would be expected to be high in all tumors that have aggressive histology. Aggressive subtypes of DTC were found in 8 of 221 patients and Tg was ≤2ng/ml in 4 of 8 patients in our study. Also, if tumor size is larger than 2 cm, it exhibites more aggressive biological characteristics than the tumor size which is 2 cm or less (Ito et al., 2012). Besides, thyroglobulin levels were above 10 ng/ml when tumor size was both above 2 cm and below 2 cm in our study.

In reality, there is no gold standard for neck recurrence imaging. DxWBS may be insufficient to show the small tissue. Besides ultrasonography is high sensitive for detection of neck recurrence but this examination is operator dependent (Frasoldati et al., 2003; Leenhardt et al., 2013). Despite this, the entire body can be viewed with DxWBS. Combination of DxWBS, neck ultrasonography and stimulated Tg level were valuable than serum Tg level measurement and neck ultrasonography alone. Also, stimulated Tg level is more sensitive (Francis et al., 2008).

Castagna et al. (2011) reported that, the clinical outcome of DTC patients in clinical remission after initial treatment is not correlated with initial risk classification according to ATA and ETA (Europan Thyroid Association) guidelines. Also they reported that, re-classification should be performed at the time of 8-12 months after ablation therapy, especially in intermediate and high risk patients. In another study, although patients risk classification made according to the first ATA guide predicted recurrent / persistent disease it was suggested to perform modified risk classification again during patients two years of follow-up and performing the patient management according to this dynamic risk classification. Similarly, Berger et al. (Berger et al., 2011) reported that, risk classification is more effective at the 9 month after ablation therapy for long-term follow-up.

We think that, TSH-stimulated serum thyroglobulin level at the time of ablation may not be determine risk of recurrence. Therefore, DxWBS should be performed at 8-12 months after ablation therapy. If no residual disease and metastases is detected on the DxWBS that is performed after the first 8-12 months, subsequent follow-up should be primarily based on serum Tg concentration and neck ultrasonography.

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