

# Radioactive Iodine Uptake in Response to Recombinant Human Thyrotropin Stimulation for Thyroid Remnant Ablation in Patients with Differentiated Thyroid Cancer

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## ABSTRACT

**Purpose:** Thyroid hormone withdrawal (THW) is required for the preparation of differentiated thyroid cancer (DTC) patients referred for thyroid remnant ablation. Alternatively, recombinant human thyrotropin (rhTSH) treatment may be performed. We aimed to evaluate whether pre-ablation radioiodine uptake (RAIU) measurement is affected by the performance of rhTSH preparation, particularly with regard to the outcome of the ablation therapy.

**Methods:** We retrospectively studied 139 DTC patients (117 females, mean age 46.3 years). Eighty-four patients discontinued thyroxine or triiodothyronine treatment (group A), whereas 55 received 2 doses of rhTSH, without THW (group B). Pre-ablation RAIU values were recorded for all patients. In patients with RAIU >9%, a lower RAI activity was administered. Patients were followed up based on whole-body imaging and stimulated thyroglobulin levels in 12-18 months post-ablation.

**Results:** Mean RAIU value for group A was 2.41% and for group B 1.53%. Eight group A patients had RAIU measurement >9%. In total, 123/139 patients found to be disease-free in the follow-up; 73/84 group A and 50/55 group B patients (ablation rates 86.9% and 90.9%, respectively).

**Conclusion:** rhTSH preparation was associated with RAIU underestimation in DTC patients. However, the management of these patients was not influenced by the recorded variations in RAIU values.

## Introduction

The vast majority of differentiated thyroid tumours arise from thyroid follicular epithelial cells; papillary cancer corresponds to approximately 85% of cases, whereas about 12% of tumours have follicular histology, including Hürthle cell carcinomas [1]. Initial therapeutic management aims to remove the primary tumour with as low surgery-related morbidity as possible [2]. Total thyroidectomy (TT) has been indicated as the primary surgical treatment option for nearly all differentiated thyroid

lesions >1cm, independently of the presence of loco-regional or distant metastases [3]. When performing TT, the surgeon aims to remove as much thyroid tissue within the operative bed as possible. However, in a significant number of patients, a small amount of thyroid tissue may remain. Complete thyroid tissue removal is demonstrated based on a negative post-operative whole-body scan (TxWBS), radioactive iodine uptake (RAIU) <1%, and undetectable levels of thyroglobulin (Tg). In a large study sample, Salvatori et

al. demonstrated the presence of thyroid remnant (TR) in 93.1% of the patients who underwent TT due to differentiated thyroid cancer (DTC) [4]. Incomplete thyroid tissue removal may lead to the performance of radioactive iodine (RAI) therapy for TR ablation [5,6].

In general, RAIU measurements provide valuable information for the therapeutic management of DTC patients. Residual RAI-avid disease can be detected, and TR uptake is evaluated through RAIU testing. As previously mentioned, RAIU data are employed, in combination with TxWBS findings and Tg levels, in the decision-making process regarding the need for RAI ablation. Interestingly, Holsinger et al. reported that post-operative RAIU <0.2% is associated with the highest likelihood of undetectable Tg levels after TT, resulting in an even smaller need for TR ablation [7]. Moreover, Zerva et al. reported that the ratio of Tg levels to RAIU values, during the immediate post-surgical period, can be used as a tool for the identification of patients with metastatic disease [8]. In these patients, higher initial RAI therapy doses may be selectively administered in order to obtain a better outcome. On the other hand, the tailoring of RAI activities based on RAIU values was not found more advantageous compared to the fixing dosing, in terms of the success of TR ablation [9-11]. A dose of approximately 1,110MBq (30mCi) is generally favoured over higher administered activities that may be considered only if a large TR is suspected [5].

In DTC patients considered to be at low risk of recurrence or mortality, previous management guidelines advocated selective performance of RAI ablation, due to its side-effects [3,6,12,13]. More recently, according to the American Thyroid Association (ATA) guidelines task force on thyroid nodules and DTC, TT may be performed in patients with tumour size 1-4 cm, but it is strongly indicated only in patients with tumour >4 cm, or gross extra-thyroidal extension, or clinically apparent metastatic disease [5]. These recommendations are formulated in international centres of excellence; however, they may not be fully applicable in other institutions where TT remains the primary surgical procedure in DTC patients [14-16]. Therefore, especially in countries with few specialized thyroid cancer centres, such as Greece, RAIU measurements continue to have a significant role in making therapeutic decisions, in most patients with regard to the need for RAI ablation.

A goal thyroid-stimulating hormone (TSH) concentration of  $\geq 30$  mIU/L is generally adopted in RAI therapy preparation, since TSH levels above this threshold are required for incompletely resected thyroid tissue to significantly concentrate  $^{131}\text{I}$  [17]. According to the recent ATA guidelines, preparation with recombinant human thyrotropin (rhTSH) stimulation is an acceptable alternative to thyroid hormone withdrawal (THW) for achieving TR ablation in ATA low-risk DTC patients, ATA intermediate-risk DTC patients, especially in those without extensive lymph node involvement, and DTC patients of any risk level with significant co-morbidity that may

preclude THW prior to RAI administration. rhTSH preparation is also advocated for attaining TSH elevation in DTC patients, referred for RAI ablation, based on the European Association of Nuclear Medicine (EANM) guidelines [6]. In the present study, we aimed to investigate the presence of variations in RAIU measurements after either rhTSH preparation or THW in DTC patients referred for TR ablation, and to examine whether these potential discrepancies could influence the efficacy of TR ablation.

## Methods

The influence of rhTSH preparation on RAIU measurements was retrospectively investigated in patients with DTC referred for TR ablation to the Department of Nuclear Medicine, Bioclinic General Hospital in Piraeus, Greece. All patients who underwent this procedure between January 2013 and December 2015 were considered as potential participants. Exclusion criteria included

- Histological component of low differentiated thyroid carcinoma,
- Established metastatic disease (M1),
- Patients presenting with incomplete histopathological data,
- Locoregional tissue invasion or macroscopic extrathyroidal extension,
- Patients who had not (at least) undergone central neck lymph node dissection, and
- Patients who missed follow-up appointments. Based on these criteria, 134 patients were enrolled in the study (Table 1).

**Table 1:** Patient Characteristics.

	Study Sample	Group A	Group B
Patient number (n)	139	84	55
Mean age (years)	46.3+/-13.3	45.1+/-12.9	50.5+/-13.7
Males	22	13	9
Females	117	71	46
Tumour size $\leq 1$ cm	71	44	27
Tumour size $>1$ cm	68	40	28
METE	104	67	37
Multifocality	56	34	22
Bilaterality	46	27	19
Node metastasis	56	36	20

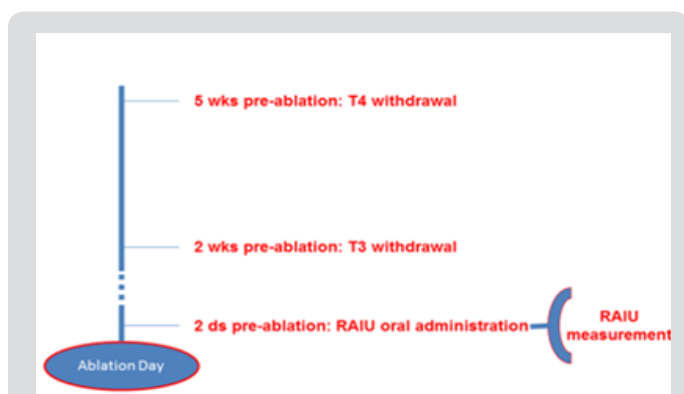
Note: METE: microscopic extra-thyroidal extension.

Group A: thyroid hormone withdrawal group.

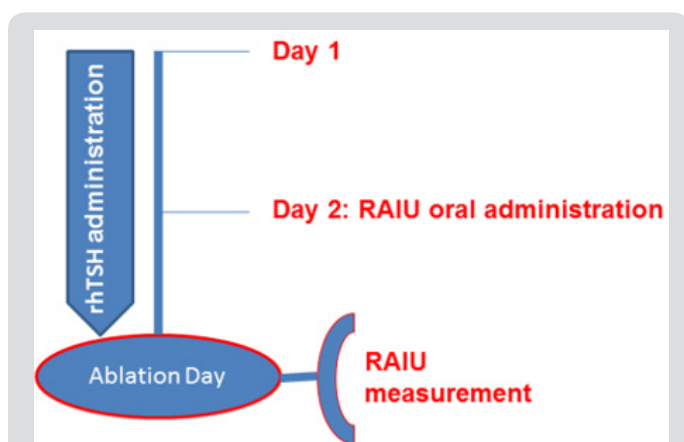
Group B: recombinant human thyrotropin treatment group.

The sample consisted of 117 females and 22 males (age 46.3+/-13.3 years, range 20-82). Thyroxine or triiodothyronine treatment was discontinued in 84 patients (group A), whereas two rhTSH doses were administered in 55 patients without THW (group B).

Serum TSH levels were measured prior to RAI administration in order to evaluate the degree of hormone elevation, requiring TSH levels in excess of 30 mIU/L. The measurements were performed using immunoradiometric assays (IRMA, Immunotech, Beckman Coulter co., Prague Czech Rep.) with a sensitivity of 0.025 IU/mL. Serum Tg levels were measured by immunoradiometric assays (IRMA, Immunotech, Beckman Coulter co., Prague, Czech Rep) with a sensitivity of 1ng/mL. Antithyroglobulin antibodies were measured by IRMA (Immunotech, Beckman Coulter co., Prague, Czech Rep.) with an analytical sensitivity of 5 IU/mL.



**Figure 1:** Thyroid hormone withdrawal (group A). RAIU measurement was performed 2 days prior ablation, following an oral <sup>131</sup>I administration of 60-80 μCi. RAIU: radioiodine uptake.



**Figure 2:** Recombinant human (rh) thyrotropin treatment (group B). RAIU measurement was performed at the day of ablation, 1 day after RAIU oral administration. RAIU: radioiodine uptake.

All patients started a low-iodine diet 2 weeks before RAI administration. In group A patients, thyroxine was withdrawn for 5 weeks prior to RAI treatment and was substituted by triiodothyronine administration during the first 3 weeks of thyroxine withdrawal. Triiodothyronine was withdrawn for at least 2 weeks before RAI therapy. RAIU was performed 2 days prior ablation, after an oral <sup>131</sup>I administration of 2,220-2,960MBq (60-80μCi) (Figure 1). In group B patients, <sup>131</sup>I was administered at

the second day of rhTSH administration and RAIU was performed 24h later, at the day of ablation (Figure 2). The pre-treatment RAIU value in the neck region was assessed using a standard collimated probe. This probe measures the percentage of a dose in the thyroid bed with the subtraction of a neck equivalent background level measured over the patient’s thigh, in comparison to a standard of equal value to the administered dose. Patients received 30-120 mCi of <sup>131</sup>I at the day of ablation. Particularly, a dose of 30-40 mCi was administered to patients with RAIU >9.0% and no evidence of RAI-avid tissue outside the thyroid bed, in order to avoid potential side-effects associated with higher activities. Tg levels were recorded in all participants on the day of RAIU measurements. Successful ablation was defined as no visible or faint uptake on the follow-up WBS after 12-18 months, in combination with undetectable stimulated Tg levels.

**Results**

The mean age of patients treated under THW (group A) was 45.1+/-12.9 years, whereas the mean age of rhTSH-prepared patients (group B) was 50.5+/-13.7 years (P=0.1). The number of female patients was higher but similar in both groups (85% in group A and 84% in group B). No statistically significant differences were observed between the two groups regarding administered dose and retained activity. Histologically, all patients suffered from papillary thyroid cancer. Table 1 summarizes information for the sample, group A and group B patients. In group A, mean RAIU measurement was 2.41+/-2.63% (range 0.1-14.3%), whereas the corresponding value for rhTSH-prepared patients was 1.53+/-1.30% (range 0.2-6.3%) (P=0.01) (Figure 3). RAIU values over 9% were observed in eight group A patients. Mean Tg concentration was 4.84+/-8.29 ng/mL (range 0.1-48.3 nh/mL) in group A patients and 6.31+/-6.79 ng/mL (range 0.1-32.6) in group B patients (P=0.27) on the day of RAIU measurement (all patients with TSH>30 ng/mL). RAI administered activity was 92.2+/-23,3 mCi in group A patients and 93.1+/-25.5 mCi in group B patients (P=0.57). Patients showing RAIU>9% received a smaller RAI dose of 34+/-5.5 mCi (Table 2). Moreover, these eight patients underwent a second RAI treatment. There was no other patient receiving second RAI therapy, either in group A or B. After 12-18 months, 88.5% (123/139) of patients were found to be disease free; successful ablation was demonstrated in 86.9% (73/84) of group A patients and in 90.9% (50/55) of group B patients (P = n.s.).

**Table 2:** Mean administered activity (AA) in group A and group B patients with respect to the radioiodine uptake (RAIU) values.

	Group A		Group B	
	RAIU <9%	RAIU >9%	RAIU <9%	RAIU >9%
Number of patients (n)	76	8	55	0
Mean AA (mCi)	92.2+/-23.3	34+/-5.5	93.1+/-25.5	-

Note: Group A: thyroid hormone withdrawal group.

Group B: recombinant human thyrotropin treatment group.

## Discussion

In the present study we investigated the potential effects of rhTSH preparation on pre-ablation RAIU measurements. According to our results, thyroid bed RAIU may be underestimated in rhTSH-prepared patients. Mean RAIU values were 2.41+/-2.63% and 1.53+/-1.30% for group A and group B, respectively. This finding may be associated with the faster RAI clearance under euthyroid state [18]. Notably, the observed variations did not seem to affect negatively the management of patients enrolled in the study. Follow-up results after 12-18 months revealed high ablation rates both in group A (86.9%) and group B patients (90.9%). Moreover, serum TSH and Tg values on the day of RAIU measurements could be an estimate of TR size.<sup>5</sup> However, no significant differences regarding these variables were observed between group A and group B patients, implying no significant differences in TR size among the two groups.

Although neck ultrasonography and <sup>99m</sup>TcO<sub>4</sub> - thyroid scintigraphy are routinely used for the therapeutic decision making in DTC patients, these modalities may provide minimal information with respect to TR estimation. Neither neck ultrasonography nor <sup>99m</sup>TcO<sub>4</sub> - thyroid scintigraphy should be used for thyroid remnant estimation [19]. On the other hand, TR RAIU can serve as a valuable tool for the evaluation of the completeness of resection and the prediction of individual recurrence risk [20]. Moreover, pre-treatment measurement of thyroid bed RAIU contributes not only to the therapeutic management regarding the decision to either perform TR ablation or not, but also to the selection of RAI activity when tailoring dose according to RAIU values. This test may clearly maximise the degree of individualisation in therapeutic decision-making after TT, an advantage especially important in paediatric patients.<sup>6</sup> Consequently, it is a useful tool, particularly in cases of suboptimal TR extent evaluation based on the surgical report or neck ultrasonography [21].

Traditionally, the decision regarding the administered activity for TR ablation could be made based on three different approaches:

- a. Empirical fixed doses.
- b. Upper bound limits according to blood and whole-body dosimetry.
- c. Quantitative tumour dosimetry [8].

TR ablation can be performed successfully with RAI doses based on TxWBS neck uptake, although there are published data supporting a fixed-dose protocol.<sup>9,21</sup> Nevertheless, RAIU-guided strategy has undoubtedly two important advantages over fixed-dose protocols; unnecessary radiation exposure can be avoided and the occurrence of local side effects due to RAI administration is lower [22-24]. In our department, if RAIU is over 9.0% and there is no evidence of RAI-avid tissue outside the thyroid bed, we opt

for lower activities of 30-40 mCi, instead of doses ranging between 80-120 mCi. In the present study eight group A patients had RAIU values >9 %, indicating a higher risk of side-effects in the post-ablation period. RAI therapy is generally safe; however, there is a risk for potential side-effects [25,26].

In general, TSH levels  $\geq 30$  mUI/L are required for successful TR ablation [17]. Thyrocytes up-regulate the expression, transcription and activity of sodium/iodine symporter in response to endogenous TSH stimulation. For this reason, THW is commonly used to optimize RAI retention, and TSH stimulation is believed to increase RAI uptake in a dose-dependent and a time-dependent manner. Nevertheless, THW is also associated with the hypothyroidism morbidity and impaired quality of life during the preparatory phase of RAI therapy. The availability of rhTSH provides a different approach in enhancing serum TSH concentration, without inducing hypothyroidism. rhTSH preparation is considered as an alternative method to THW based on both ATA and EANM guidelines.<sup>5,6</sup> Similarly, according to a 2015 position statement of the Italian Society of Endocrinology, DTC patients referred for TR ablation should be prepared by rhTSH administration; THW may be considered in certain cases where rhTSH is not available or not affordable [27].

The efficacy of rhTSH-aided RAI therapy for TR ablation has been evaluated in several studies. It was reported to be equally effective to THW in recent meta-analyses [28,29]. In our study, ablation rates were optimal, both in rhTSH-prepared patients and in patients treated under hypothyroid state. Important advantages of rhTSH preparation have been reported in terms of quality of life and adverse effects during and after ablation, including fatigue, headache, sialadenitis, neck pain, taste loss, nausea, radiation gastritis, and bone pain.<sup>12</sup> [30-32], Notably, rhTSH-aided TR ablation was linked to decreased irradiation to the patients. In particular, the specific absorbed dose to the blood was significantly lower in patients undergoing rhTSH preparation compared to those randomized to the THW group [33]. Lower red marrow absorbed dose was also reported [34]. Although rhTSH preparation significantly increases the overall cost of the treatment, the balance may be in favour of its use when the cost to the society due to hypothyroidism – associated loss of productivity (days off work) is taken into account [35,36]. Moreover, rhTSH may allow a shorter hospitalization length because of the faster RAI excretion, partially compensating its high cost [35-37]. Thus, based on a cost-effectiveness analysis, rhTSH preparation should be considered “good value-for-money” with the benefits to both patients and the society obtained at modest net cost [38]. Similar findings were reported for a non-western patient population [39].

## Conclusion

RAI ablation continues to have an important role in the management of DTC patients since TT remains the primary therapeutic option for patients suffering from DTC in many

countries, particularly in those where specialized thyroid cancer services are rare. We suggest that the pre-ablation TR estimation is helpful whenever RAI therapy is performed in non-specialized clinics. RAIU measurement represents a valuable tool for the assessment of the need for ablation, including the appropriate RAI activity. Based on our protocol, RAIU test is applicable even after rhTSH preparation which permits the performance of RAI therapy without the THW-related adverse effects. Although we showed that RAIU may be underestimated in rhTSH-prepared patients, compared to patients who underwent THW, the observed variations did not affect negatively the patient management; therefore, these variations were not found to influence the outcome of ablation therapy. Finally, our findings were in accordance to the previously published studies confirming the efficacy of RAI therapy after rhTSH preparation.

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