

Value of technetium scintigraphy and iodine uptake measurement during follow-up of differentiated thyroid cancer

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Measurement of serum thyroglobulin (Tg) levels and I-131 whole body scintigraphy (WBS) are used in the follow-up of patients with differentiated thyroid cancer (DTC). This study was designed to evaluate the significance of persistent I-131 uptake in the thyroid bed in patients with DTC following surgery and/or radioactive iodine ablation. Tc-99m thyroid scintigraphy (TS) and I-131 thyroid uptake (IU) were also performed to determine their clinical impact on patient management. **Patients and Methods:** Sixty-two non-metastatic patients (14 men, 48 women) with a mean age of 44 years (range: 16–75) who had undergone surgical thyroidectomy for DTC were evaluated prospectively. All patients had undergone technetium and iodine scintigraphy (IS). Although serum Tg levels were measured in all patients, IU was available in 36. **Results:** Tg values were in the range of 0.2–24 ng/ml (median: 0.2 ng/ml) when patients were in the hypothyroid state. I-131 WBS detected residual tissue in the neck in 30 patients (48%); however TS was positive in only 12 (19%). I-131 uptake in the thyroid bed ranged from 0 to 14% (median: 0.1%). Twelve of 13 patients with positive IS and negative TS had uptake values $\leq 0.3\%$ ($p < 0.00001$). When IU values were $\leq 0.3\%$, 54% of our patients did not have any uptake in the thyroid bed on TS or IS, whereas when IU was $> 0.3\%$, 80% of patients had neck uptake on both TS and IS ($p < 0.00001$). **Conclusion:** The results of this study demonstrate that the concordance of IS and TS depends on the IU level after suspension of replacement therapy. Measurements of IU and TS are of considerable value in evaluating patient response to therapy and will substantially reduce the need for repetitive radioiodine scans and unnecessary treatment doses in patients with undetectable Tg values.

Key words: differentiated thyroid cancer, thyroid scintigraphy, I-131 whole body scintigraphy, thyroglobulin

INTRODUCTION

BLOOD Tg level determination and WBS are frequently used for patients with DTC as surveillance for cancer recurrence. After complete surgical and/or radioiodine ablation of the thyroid, serum Tg should be undetectable (generally < 2 ng/ml) and I-131 uptake would be essentially background.¹ Although increased serum Tg and positive radioiodine scan are indicators of the presence of

thyroid cancer, we have been struck by the number of patients with undetectable serum Tg levels despite the presence of persistent I-131 uptake in the thyroid bed. Although identification of iodine avid tissue allows for more aggressive follow-up and/or therapy, the clinical significance of persistent radioiodine uptake in the thyroid bed in patients with undetectable serum Tg levels is not clear. Szilagyi et al. found that more than 50% of patients with total thyroidectomy have evidence of functioning thyroid tissue on I-131 scintigraphy.² It is important to know the size and amount of uptake in the thyroid tissue, which may or may not lead to administration of I-131. A 'tumor specific' scintigraphic evaluation would improve the diagnostic assessment; however, available radiopharmaceuticals are far from being ideal.³

The aim of our work was to determine the significance

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of persistent radioiodine uptake in the thyroid bed. For this purpose, I-131 thyroid uptake was measured and correlated with TS and IS. This study presumes that IU measurements and TS will provide useful information regarding functional activity of the residual thyroid tissue and substantially reduce the need for repetitive radioiodine scans. The main objective was not to compare IS with Tg values, but to define the IU values which allowed visualization of the thyroid remnant on IS and TS.

MATERIALS AND METHODS

Patients

We prospectively investigated 62 patients with DTC. There were 14 male and 48 female patients with a mean age of 44 years (range: 16–75). Forty-seven, 9 and 6 patients had papillary, follicular and mixed thyroid carcinoma respectively. No evidence of distant metastases was present at the time of the initial diagnosis. The median time between surgery and inclusion in this study was 11 months (range: 3–48 months).

Imaging/uptake procedures

All patients underwent Tc-99m pertechnetate and I-131 scintigraphy. I-131 uptake measurements were available for 36 cases. Patients were studied in a hypothyroid state with serum TSH levels greater than 30 $\mu\text{U}/\text{ml}$ and were kept on a low iodine diet.

TS was performed after administration of 111 MBq of Tc-99m pertechnetate. Neck images were acquired at 20 minutes for 200,000 counts using a gamma camera equipped with a pinhole collimator (Toshiba 601, Japan).

The uptake study consisted of oral administration of 0.4–0.7 MBq of I-131. At 24 hours, the neck activity was counted at 25 cm, using a standard NaI thyroid uptake detector (ATOMLAB 950, Biodex Medical, NY, USA). I-131 thyroid uptake was corrected for decay and background and expressed as the percentage of the administered dose by the following formula:

$$\% \text{ uptake} = \frac{\text{pt. neck counts} - \text{background}}{\text{administered activity counts}} \times 100$$

Patients then had diagnostic WBS with I-131 using a tracer dose of 185 MBq. Images of the neck and whole body were acquired 48–72 hours later with a whole body gamma camera (ADAC, Geneseys, CA) equipped with a high energy collimator.

Thyroglobulin (Tg)

The protocol consisted of measurement of serum Tg/TSH levels prior to imaging studies. Thyroglobulin levels were determined by chemoluminescence (Immulate 2000 DPC, LA, USA) with an assay sensitivity of 0.2 ng/ml taking possible TG autoantibodies into account. The upper limit of detection was 300 ng/ml. Patients with anti-TG antibodies were excluded from the study. For statistical

analysis, those who had Tg values above 2 ng/ml were classified as having residual tissue or tumor.

Criteria for positivity and follow-up

An experienced nuclear medicine physician and a resident in training reviewed all scans independently. Abnormal uptake in the neck was considered positive for functioning thyroid tissue without differentiating between thyroid remnant and functioning thyroid cancer. A pair of IS and TS was defined as discordant if an area of uptake was reported in one but not the other (Fig. 1). The agreement between two examiners was 100%.

Patients were imaged with I-131 scintigraphy and/or Tg levels were measured at yearly visits. Those who had Tg values greater than 2 ng/ml (while TSH >30 $\mu\text{U}/\text{ml}$) were classified as having residual thyroid tissue/tumor.

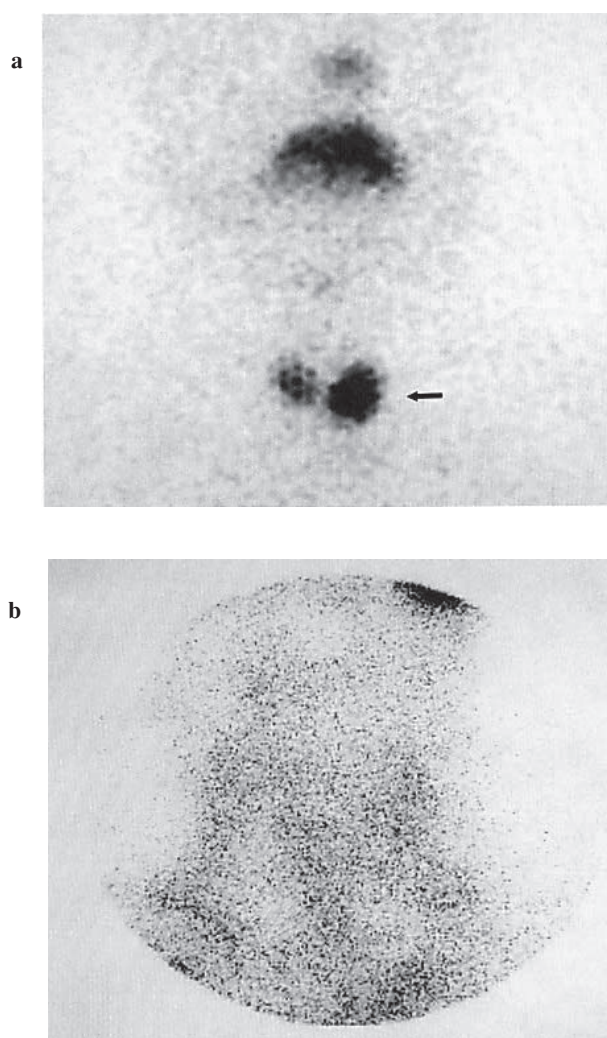


Fig. 1 a: Visualization of the remnant thyroid tissue (arrow) on IS in a patient following total thyroidectomy and 3.7 GBq RAI. b: Tc-99m pertechnetate scintigraphy of the same patient. No uptake is seen on spot neck view. This patient's IU was 0.1% with the serum Tg value undetectable (<0.2 ng/ml).

Statistical analysis

Differences between categorical variables were assessed with chi square tests (Pearson chi square test, Mc Nemar Chi Square test, Fisher's exact, likelihood ratio) and those between continuous variables with Mann Whitney-U test. Probabilities of less than 0.05 were accepted as significant. Spearman's rank-order correlation coefficient was used to evaluate the degree of relationship between two variables. In order to determine the cut-off values for IU and Tg levels, Receiver Operating Characteristic (ROC) analysis was used. IS (+)/TS (+) and IS (-)/TS (-) groups were used for this analysis. The cut-off value for IU was 0.3% and 2 ng/ml for serum Tg. The area under the curve, which indicates the discriminating power, was 0.992 ± 0.014 and 0.901 ± 0.06 for IU and TG respectively. The statistical analyses were done using the SPSS 10 for Windows (Chicago, Illinois).

RESULTS

Clinical details of patients

Initial treatment included total thyroidectomy in all patients. 41 patients were treated with a cumulative I-131 dose of 3.7–14.8 GBq (median: 5.55 GBq) following surgery whereas 21 patients were not given any RAI. Decision to administer RAI and the activity administered was based on the risk-group assignment following surgery including age at the time of initial assessment, tumor size, presence of extrathyroidal invasion and distant metastases.⁴ Second and third doses were given to 3 and 4 patients respectively who had presented with residual tissue in the neck and persistent elevated serum Tg levels.

Laboratory values

In 62 patients, TSH values varied from 30 to 146 μ IU/ml (median: 100). Tg levels were in the range of 0.2–24 ng/ml (median: 0.2). Serum Tg levels were lower in patients who received RAI after total thyroidectomy (mean values; 1.03 vs. 3.08, $p = 0.027$).

I-131 uptake studies

IU measurements, which were available for 36 patients ranged from 0 to 14 (median: 0.1%). IU values were significantly lower in patients who received RAI (mean values; 0.07 vs. 2.34, $p = 0.001$).

Scintigraphic results

I-131 WBS detected residual tissue in 30 (48%) whereas TS was positive in only 12 patients (19%). In 18 technetium studies, areas of radionuclide uptake seen on iodine scintigraphy were not present. 13 out of these 18 patients had IU studies performed which revealed I-131 uptake values smaller than 0.3% in 12 ($p < 0.00001$). The comparison of scintigraphic studies and their relation to IU and Tg values are given in Tables 1–3.

Table 1 Correlation between iodine scintigraphy (IS) and technetium scintigraphy (TS)

	TS (+)	TS (-)	Total (n)
IS (+)	12	18	30
IS (-)	0	32	32
Total (n)	12	50	62

$p < 0.000$, $\chi^2 = 16.055$ (Mc Nemar Chi-Square test)

Table 2 Association between scintigraphic findings and iodine uptake (IU) (n = 36)

	IU > 0.3	IU \leq 0.3	Total (n)
IS (+) TS (+)*	8	0	8
IS (+) TS (-)	1	12	13
IS (-) TS (-)	1	14	15
Total (n)	10	26	36

*IS: Iodine scintigraphy, TS: Technetium scintigraphy
Likelihood ratio: 28.142, $p = 0.000$

Table 3 Association between scintigraphic findings and serum thyroglobulin (TG) (n = 62)

	Tg > 2	Tg \leq 2	Total (n)
IS (+) TS (+)*	10	2	12
IS (+) TS (-)	5	13	18
IS (-) TS (-)	4	28	32
Total (n)	19	43	62

*IS: Iodine scintigraphy, TS: Technetium scintigraphy
 χ^2 : 20.7, $p = 0.000$

Follow-up

Eighteen patients with discordant scan findings (IS+/TS-) were followed for a median period of 37 months (16–47). Of these 18 cases, only 1 patient with an IU value of 0.1 had significant elevation (from 3.6 ng/ml to 11.6 ng/ml, off T4) in serum Tg value and had persistent thyroid uptake on the follow-up visit. This patient was given RAI. Control I-131 WBSs of these 18 patients revealed persistent uptake located in the thyroid bed in 5, whereas in 13 cases uptake was no longer visible after a median time of 8 months.

DISCUSSION

In this study, we tried to evaluate the significance of persistent thyroid bed activity on IS and address the relationship between IS, IU and TS in non-metastatic DTC patients. The relation between IU and scintigraphic visualization of the residual tissue/tumor has been suggested, but no quantitative analysis is available. Our results show that despite total thyroidectomy and/or radioiodine ablation, complete eradication of functioning thyroid tissue was achieved in only 28 patients (45%) with negative IS/TS and low serum Tg levels. Fifteen patients

had low serum Tg levels despite thyroid bed uptake on IS of which 13 were negative on TS.

There was a close correlation between IU and TS, as appreciated by visualization of the remnant tissue on TS in 80% of the patients when IU values were greater than 0.3%. When uptake was $\leq 0.3\%$, visualization was not possible with Tc-99m pertechnetate. The negative predictive value of a negative TS was 93% for having an IU value of $\leq 0.3\%$.

The discrepancy between IS and TS can probably be explained by the mass of the thyroid remnant. It is known that accumulation of Tc, which depends on anion trapping metabolism with sodium iodide symporter (NIS)^{5,6} is correlated with the number of thyroid cells. We assume that thyroid cells had a high potential for iodine uptake, but the residual tissue was too small to be detected with technetium. On the basis of IS, these patients might have been referred for radioiodine ablation; however, their very low I-131 uptake and/or negative TS let us withhold the therapeutic dose of I-131.

Our study has led to the observation that 72% of areas of I-131 uptake in patients with negative TS disappear on subsequent IS, especially in patients with high dose suppression therapy. One patient with aggressive tumor histology and extracapsular invasion was an exception to this trend. This patient (TS-/IS+) had higher baseline serum Tg level (3.6 ng/ml), indicating a more extended disease with significant elevation in serum Tg value (11.6 ng/ml) during follow-up in whom persistent low intensity radioiodine accumulation in the thyroid bed was seen. Although Tg production and iodine uptake are independent processes, low uptake on IS may not be the only source of serum Tg. Nevertheless, some authors have reported that serum Tg concentration can indicate the presence of metastases even if it is measured in the presence of residual thyroid tissue.⁷⁻¹⁰ Moreover, serum Tg levels have been reported to be weakly influenced by Tg production by the remnant tissue at all stages of follow-up.¹¹

In our opinion, it is of great importance to correctly assess the presence and extent of the residual thyroid tissue soon after surgery. The first Tg value should always be confirmed by whole body scintigraphy, which may be used to select patients who have metastatic disease and should be followed aggressively. Among patients with undetectable serum Tg level, negative TS status suggests that residual thyroid tissue is small and routine WBS is not necessary since absence of activity on TS has a high negative predictive value. The decision criteria used by an observer should depend both on his estimates of a prior probability and his judgments regarding the consequences of wrong decisions.

The proposed protocol has the benefit of avoiding any stunning since very small doses of I-131 are administered for IU. Studies with technetium require only a few minutes of the patients' and technologists' time and do not

necessitate a 48–72 hour visit. Although there have been few reports which used Tc-99m pertechnetate for the detection of post-operative recurrent cancer or thyroid tissue,^{12,13} its clinical value for the detection of residual tissue is limited because of the poor sensitivity of the gamma cameras for detection of micrometastases.

In conclusion this study shows that Tc scintigraphy and/or radioiodine uptake can provide useful information regarding functioning residual thyroid tissue. I-131 uptake in the neck should not be considered as treatment failure and TS/IU measurements may serve as an important tool for the selection of patients who do not need I-131 ablation if serum Tg levels are low.

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