European Journal of Endocrinology (2003) **148** 19–24 ISSN 0804-4643

CLINICAL STUDY

Serum thyroglobulin and ^{131}I whole body scan after recombinant human TSH stimulation in the follow-up of low-risk patients with differentiated thyroid cancer

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Abstract

Objective: The 'standard' postoperative follow-up of patients with differentiated thyroid cancer (DTC) has been based upon serum thyroglobulin (Tg) measurement and ^{131}I whole body scan (^{131}I-WBS) after thyroid hormone (T_4) treatment withdrawal. However, ^{131}I-WBS sensitivity has been reported to be low. Thyroid hormone withdrawal, often associated with hypothyroidism-related side effects, may now be replaced by recombinant human thyroid stimulating hormone (rhTSH). The aim of our study was to evaluate the diagnostic accuracy of ^{131}I-WBS and serum Tg measurement obtained after rhTSH stimulation and of neck ultrasonography in the first follow-up of DTC patients.
Design: Ninety-nine consecutive patients previously treated with total thyroidectomy and ^{131}I ablation, with no uptake outside the thyroid bed on the post-ablative ^{131}I-WBS (low-risk patients) were enrolled.
Methods: Measurement of serum Tg and ^{131}I-WBS after rhTSH stimulation, and ultrasound examination (US) of the neck.
Results: rhTSH-stimulated Tg was ≤ 1 ng/ml in 78 patients (Tg−) and >1 ng/ml (Tg+) in 21 patients, including 6 patients with Tg levels >5 ng/ml. ^{131}I-WBS was negative for persistent or recurrent disease in all patients (i.e. sensitivity = 0%). US identified lymph-node metastases (confirmed at surgery) in 4/6 (67%) patients with stimulated Tg levels >5 ng/ml, in 2/15 (13%) with Tg $>1<5$ ng/ml, and in 2/78 (3%) who were Tg-negative.
Conclusions: (i) diagnostic ^{131}I-WBS performed after rhTSH stimulation is useless in the first follow-up of DTC patients; (ii) US may identify lymph node metastases even in patients with low or undetectable serum Tg levels.

European Journal of Endocrinology **148** 19–24

Introduction

Total or near-total thyroidectomy is advocated for patients with papillary or follicular thyroid carcinoma, and is often followed by ^{131}I-ablation (1–5). However, recurrence rates as high as 20% have been reported in these patients (1, 6, 7), and close follow-up should permit the early detection of persistent or recurrent disease. For years, the 'standard' follow-up has been based upon clinical examination, measurement of serum thyroglobulin (Tg) levels, and ^{131}I whole body scintigraphy (^{131}I-WBS) (1–4, 8). Until recently, these diagnostic procedures were performed following thyroid hormone treatment withdrawal, in order to increase serum thyroid-stimulating hormone (TSH) levels above 25 μU/ml (2). However, the resulting hypothyroidism was poorly tolerated by many patients (9). Recombinant human TSH (rhTSH) recently became available and produces effective thyroid stimulation; its use eliminates the need for thyroid hormone therapy withdrawal and, consequently, hypothyroidism-related side effects are avoided (10–13).

Recently, the diagnostic significance of ^{131}I-WBS obtained following thyroid hormone (T_4) withdrawal was questioned because of its poor sensitivity (14), and some investigators have suggested that serum Tg determination alone is the most cost-effective first line in the follow-up of differentiated thyroid cancer (DTC)

patients (14, 15). In these studies, most recurrences occurred in neck lymph nodes and were demonstrated by neck ultrasonography.

The aim of our study was to evaluate, following rhTSH stimulation, the sensitivity of ^{131}I-WBS versus serum Tg determination, considered as the 'gold standard', in the first post-ablation follow-up examination of patients with papillary or follicular thyroid cancer who had no evidence of persistent disease (i.e. low risk patients). An additional aim of the study was to assess, in these low risk patients, the usefulness of neck ultrasonography.

Subjects and methods

Subjects

Between July 2000 and March 2002, 126 patients underwent total thyroidectomy, followed by the administration of an ablative dose of ^{131}I, for well-differentiated papillary or follicular thyroid carcinoma at the Scientific Institute 'Casa Sollievo della Sofferenza' in San Giovanni Rotondo, Italy. All cases underwent an apparently complete surgical resection of the tumour and no age criteria of exclusion were adopted in the study. Nine subjects exhibiting positivity for anti-Tg antibodies and/or a low recovery test after surgery were subsequently excluded from the study. A ^{131}I-WBS performed 4–7 days after the ablative dose revealed ^{131}I uptake foci outside the thyroid bed in 18 patients, who were scheduled for additional surgery and/or ^{131}I treatment. The other 99 patients, with no extra-thyroid uptake foci, were enrolled in the study.

The first post-ablation follow-up examination was performed 6–12 months after thyroid ablation. Patient characteristics at the time of enrolment are shown in Tables 1 and 2 .

Study protocol

The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983. All patients gave informed, written consent. The follow-up examination consisted of a ^{131}I-WBS and measurement of serum Tg obtained after rhTSH stimulation, and an ultrasound (US) examination of the neck. Patients were placed on a low-iodine diet and instructed to avoid iodine-containing foods for at least 20 days before the study. T_4 therapy was maintained in all patients. On day 1 (d1), blood samples were drawn for determination of baseline serum TSH and Tg levels. Tg recovery and anti-Tg antibodies were evaluated in the same sample to validate the Tg assay results. Thereafter, each patient received an intra-muscular injection of rhTSH (0.9 mg) (Thyrogen, Genzyme Transgenics Corp., Cambridge, MA, USA). On day 2 (d2), a second injection of rhTSH (0.9 mg) was administered. On day 3 (d3), 185 MBq (5 mCi) ^{131}I were given. On day 5 (d5), ^{131}I-WBS and neck US were performed, and serum TSH and Tg levels were measured.

Based on rhTSH-stimulated Tg levels, patients were classified as Tg-positive (Tg+) (>1 ng/ml) or Tg-negative (Tg $-$) (≤ 1 ng/ml). rhTSH-stimulated Tg levels equal to or above 5 ng/ml were considered indicative of persistent disease, thus warranting further ^{131}I treatment even in the absence of any other evidence of disease. Patients who were negative at the first follow-up were scheduled for yearly clinical examination, serum Tg determination on T_4 therapy, and neck US. Those with negative ^{131}I-WBS and US examinations, with rhTSH-stimulated serum Tg levels >1 ng/ml $<$ 5 ng/ml were followed-up every six months.

In the case of neck lymph node abnormalities at US, an US-guided fine-needle aspiration biopsy (FNAB) was performed, and in the case of positivity at cytological examination further surgery was warranted. Lymph nodes were considered suspicious by at least one of the following criteria: diameter >5 mm and of rounded shape, presence of microcalcifications and/or a cystic component, absence of hyperechoic hilus, hypervascularization at colour-Doppler examination.

Methods

Serum Tg was measured by IRMA (Byk-Sangtec, Dietzenbach, Germany), with a clinical sensitivity of 1 ng/ml (14, 17, 18). Tg recovery was evaluated in the same assay after the addition of 10 μl of the spiking

Table 1 Clinical characteristics of the 99 patients. Values are means±S.D.

	All (n = 99)	Tg− (n = 78)	Tg+ (n = 21)
Age (years)	49±13	48±13	50±16
Males/females	24/75	19/59	5/16
Histology (papillary/follicular)	83/16	64/16	19/2
^{131}I ablative dose (GBq)	3.8±1.2	3.9±1.3	3.8±1.2
Post-ablative dose ^{131}I uptake (</> 5%)	73/26	59/19	14/7
Tg after T_4 withdrawal (ng/ml)	14.8±46.0	5.5±14.7	53.7±93.1*

Tg after T_4 withdrawal: serum Tg level measured at the time of the ablative dose.
*$P < 0.05$ vs Tg $-$. The two groups were not significantly different as far as other parameters were concerned (Student's t test or Mann Whitney U test when appropriate, or chi-square or Fisher's exact test when appropriate).

Table 2 pTNM classification of the 99 patients (16).

	N0	N1	Nx
T1	11	7	1
T2	36	12	—
T3	8	2	—
T4	8	7	—
Tx	2	1	4

solution containing 50 ng/ml (normal recovery values: 70–130%). Serum anti-Tg antibody titres were measured in a two-step immunoenzymometric assay (Eurogenetics, Turin, Italy). TSH levels were measured by electro-chemiluminescence (Elecsys, Roche Diagnostics GmbH, Mannheim, Germany).

^{131}I-WBS was performed using a two-heads gamma-camera (Toshiba GCA 901, Japan) equipped with high energy collimators and thick crystals; scan speed was 5 cm/min, and a total count of at least 140 000 c.p.m. was recorded. Scans were reviewed by a group of 3 nuclear medicine specialists (S M, G V, V F) and 2 endocrinologists (M T, U C), blinded to the Tg results, and an agreement was reached for each ^{131}I-WBS. Neck uptake in the median region could be located to the thyroid bed with the use of anatomical marks, and the location was further confirmed by neck US that did not show any abnormality in lymph node areas.

Neck US was performed using a Toshiba power-Doppler scanner equipped with a high-frequency probe (7.5 MHz).

Statistical analysis

Data are expressed as means±standard deviation or as median and range of values when appropriate. Comparison between groups was performed using Student's *t*-test (either unpaired or paired, as required) or Mann–Whitney U test when appropriate. Differences between proportions were evaluated using chi-square or Fisher's exact test when appropriate.

Results

Baseline blood samples were drawn on day 1. Tg recovery >70% and no anti-Tg antibodies were confirmed in all cases. Mean serum TSH levels were 0.4±1.0 μU/ml. Serum Tg levels were undetectable in 92 patients, and ranged from 1.5 to 25.0 ng/ml in the other 7 patients.

Following rhTSH stimulation (on day 5), the mean serum TSH level was 34±15 μU/ml. Serum Tg levels remained undetectable in 78 patients (Tg− patients) and were above 1 ng/ml (range: 1.3–58 ng/ml) in the other 21 patients (Tg+ patients) (Tables 1 and 3, Fig. 1). Serum Tg became detectable in 14/92 patients with an undetectable baseline Tg level, and increased, being >5 ng/ml, in 6 patients. According to post-ablation thyroid-bed ^{131}I uptake, the rhTSH-stimulated Tg levels of patients with uptake >5% ($n = 26$, median value: 0.6 ng/ml, range 0.2–58) were not significantly different from those of patients with lower uptake ($n = 73$, median value: 0.5 ng/ml, range 0.2–21).

The ^{131}I-WBS was totally negative in 94/99 (95%) patients (75 Tg− and 19 Tg+). In the remaining

Table 3 Clinical features and outcome of the 21 patients with d5-Tg levels >1 ng/ml (Tg+).

Patient	**Age** (years)	**Gender**	**Histology**	**d5-Tg** (ng/ml)	**^{131}I-WBS** (185 MBq)	**Neck US**	**^{131}I-WBS** (3.7 GBq)
1	39	F	Follicular	1.3	Negative	Negative	NP
2	53	F	Papillary	1.4	Positive*	Negative	NP
3	51	F	Papillary	1.6	Negative	Negative	NP
4	45	F	Follicular	1.8	Negative	Negative	NP
5	49	M	Papillary	1.8	Negative	Negative	NP
6	62	F	Papillary	2.0	Positive*	Negative	NP
7	43	F	Papillary	2.1	Negative	Negative	NP
8	47	F	Papillary	2.2	Negative	Negative	NP
9	33	F	Papillary	2.2	Negative	Positive	NP
10	27	M	Papillary	2.3	Negative	Positive	NP
11	46	F	Papillary	2.5	Negative	Negative	NP
12	64	F	Papillary	3.6	Negative	Negative	NP
13	23	F	Papillary	3.9	Negative	Negative	NP
14	57	F	Papillary	4.4	Negative	Negative	NP
15	42	F	Papillary	4.6	Negative	Negative	NP
16	68	F	Papillary	7.2	Negative	Positive	NP
17	76	F	Papillary	14.4	Negative	Negative**	Negative
18	74	M	Papillary	17.4	Negative	Negative	LM
19	58	F	Papillary	21.0	Negative	Negative	Negative
20	62	M	Papillary	27.3	Negative	Positive	NP
21	21	M	Papillary	57.6	Negative	Positive	NP

d5-Tg: serum thyroglobulin levels 3 days after the second injection of rhTSH (day 5). ^{131}I-WBS:* in both cases, there was only a slight uptake in the thyroid bed (<0.5%). Neck US:** in this patient, a further neck US performed 6 months later revealed lymph node metastases. In all cases, lymph node metastases were confirmed by cytology and histology.
NP, not performed; LM, lung metastases.

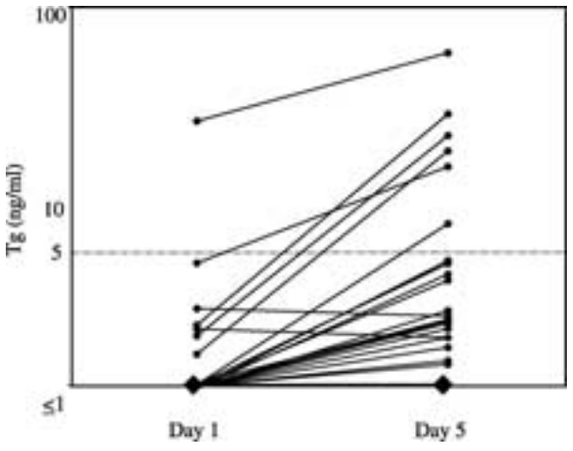

Figure 1 Serum Tg concentrations after rhTSH. Day 1 and day 5: serum thyroglobulin determined, respectively, before and 3 days after rhTSH stimulation. Patients were sub-grouped according to Tg serum levels at day 5: ≤1 ng/ml, Tg − (◆), $n = 78$ patients or >1 ng/ml, Tg+ (●), $n = 21$ patients. Tg values are on a logarithmic scale. The broken line represents the Tg values of 5 ng/ml.

five patients (three Tg− and two Tg+), it disclosed only a slight uptake in the thyroid bed (<0.5% of administered activity), which was considered clinically insignificant. The sensitivity of ^{131}I-WBS was thus equal to 0%.

Neck US revealed suspicious lymph nodes in seven patients, including two Tg− and five Tg+ patients (two with stimulated Tg levels between 1 and 5 ng/ml, three with stimulated levels >5 ng/ml). The diagnosis of lymph node metastases was confirmed by FNAB, and subsequently at surgery, in all seven patients. In the remaining 92 cases, 76 Tg− and 16 Tg+, US did not disclose any abnormality.

rhTSH-stimulated Tg levels were >5 ng/ml in six patients (all with papillary cancer), including the three patients (# 16, 20, and 21 in Table 3) with lymph node involvement at neck US. In the other three patients (# 17, 18, 19), both ^{131}I-WBS and US examinations were negative; a ^{131}I-WBS was performed after a dose of 3.7 GBq (100 mCi) following T_4 withdrawal and revealed lung metastases in one (# 18). In the other two patients, no abnormal uptake was observed; in one (# 17) neck US evidenced lymph node metastases, confirmed at surgery, 6 months later and in the second patient (# 19) bone scintigraphy and computed tomography of the neck and chest were negative; at the time of this report (about one year after the study procedures), no evidence of malignancy is detectable (Table 3).

All Tg+ patients ($n = 15$) in whom persistent or recurrent disease was not demonstrated are currently followed-up every 6 months with clinical examination, serum Tg determination on T_4 therapy, and neck US. The same procedures are performed once a year in the remaining 84 patients. To date, no evidence of recurrent disease has been detected in any of these patients.

Discussion

In the present study, we assessed the diagnostic accuracy of ^{131}I-WBS after rhTSH stimulation in the detection of persistent or recurrent disease in the first follow-up study of a series of 99 consecutive patients who had previously undergone total thyroidectomy and radioiodine ablation for a follicular or papillary thyroid carcinoma. None of these patients had uptake foci outside the thyroid bed on the ^{131}I-WBS performed 4–7 days after the ablative dose, and were thus considered as low risk patients (14).

Serum TSH levels measured on day 5 ranged from 10 to 97 μU/ml. In some patients, serum TSH levels were below 25 μU/ml, the currently accepted cut-off for adequate stimulation after T_4 withdrawal, and this is probably due to the time of sampling which was three days after the second injection of rhTSH, while serum TSH is known to reach peak levels (>100 μU/ml) 24 h after the second injection of rhTSH (day 3) and then declines (12, 13). The only purpose of the measurement of TSH levels on day 5 (in the same blood sample drawn for Tg measurement) was to verify that each patient had received the rhTSH injections. This was not checked on day 3 to avoid additional blood sampling.

Overall, detectable rhTSH-stimulated Tg levels (>1 ng/ml) were observed on day 5 in 21% of the patients, including 14/92 (15%) of those with undetectable baseline Tg levels. These findings are consistent with previous reports on the prevalence of detectable Tg levels following either rhTSH stimulation (13, 17-21) or T_4 withdrawal (13–15).

^{131}I-WBS was totally negative for persistent or recurrent disease in all patients. It only disclosed a low uptake (<0.5% of the administered dose) in the thyroid bed in five patients (three of them Tg−), compatible with the presence of a small amount of normal thyroid tissue. Previously, this has been considered not clinically significant (14–15), provided that surgical resection of the thyroid tumour was complete and that palpation and neck US did not disclose abnormalities in the thyroid bed. In fact, follow-up of such patients has not revealed thyroid disease recurrence (14, 15). Consequently, the ^{131}I-WBS provided no explanation for the elevated Tg levels in any of the Tg+ patients. Similar findings on the low diagnostic accuracy of ^{131}I-WBS following T_4 withdrawal have recently been reported (14, 15). Several recent retrospective studies suggested that rhTSH-stimulated Tg levels alone can identify residual thyroid malignancy in some patients, but in these studies most patients were not studied at the first follow-up after initial treatment and some already had known metastases (13, 19–21). Moreover, some groups have reported positive rhTSH-stimulated ^{131}I-WBS in 60–70% of patients with detectable rhTSH-stimulated Tg (19, 21), and in 74% of patients when performed after T_4 withdrawal (17). Some

patients included in these studies (19, 21) had known metastases; in contrast, patients with ^{131}I uptake foci outside the thyroid bed on the post-ablation ^{131}I-WBS were excluded from our study, because they were directly scheduled for further surgery and/or additional ^{131}I therapy.

Neck US examination appeared to be relevant in these patients. It identified lymph node metastases (subsequently confirmed at surgery) in eight patients with papillary cancer (seven at the first follow-up), 4/6 (67%) with stimulated Tg levels >5 ng/ml, 2/15 (13%) with Tg $>1<5$ ng/ml and 2/78 (3%) who were Tg−. This finding is in accordance with the fact that cervical lymph nodes are the most common site of recurrence in patients with papillary thyroid carcinoma; furthermore, previous studies have shown that a neck recurrence was first demonstrated by routine US in some patients with undetectable serum Tg levels (14), and this strongly suggests a role for US in the routine follow-up of all DTC patients.

As far as the natural history of this disease is concerned, there are data indicating that early detection of recurrent disease will improve the result of subsequent therapy (2). Other data suggest that small neoplastic foci may remain clinically occult for years or even decades (6). It is therefore questionable whether a very early discovery of lymph node metastases will improve prognosis over a somewhat later diagnosis. It should also be considered that in the individual patient, when a lymph node metastasis is discovered, it is not possible to predict whether it will remain stable or increase in size.

When rhTSH-stimulated serum Tg levels are detectable and neck US is negative, ^{131}I treatment has been advocated. Although most authors consider 1 ng/ml as a cut-off for detectable Tg levels (2–5), a cut-off of 10 ng/ml was used following thyroid hormone treatment withdrawal for the administration of 3.7 GBq (100 mCi) because ^{131}I-WBS was negative in almost all patients with serum Tg between 1 and 10 ng/ml (14). When using rhTSH, Tg stimulation is reduced as compared with thyroid hormone withdrawal (17, 19); accordingly, we arbitrarily decided to use a cut-off of 5 ng/ml. This does not mean that Tg levels between 1 and 5 ng/ml are not significant; rather it means that these patients should be controlled some months later.

Finally, in 15 patients with serum Tg levels >1 ng/ml, the source of Tg production was not identified. In all series of papillary and follicular carcinomas there are patients with detectable serum Tg levels but with no other evidence of disease (14, 17). Some of these patients will develop clinical disease months or years later, but in other patients serum Tg levels will decrease or even become undetectable (22).

In conclusion, our findings confirm that diagnostic ^{131}I-WBS has no role in the first-line follow-up of low risk DTC patients; moreover, undetectable rhTSH-stimulated serum Tg levels cannot reliably exclude the presence of lymph-node metastases in the neck and, consequently, neck US is warranted in these patients, even in those with undetectable rhTSH-stimulated Tg levels.

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Received 4 June 2002
Accepted 10 October 2002