CLINICAL STUDY

Compliance with follow-up and the informative value of diagnostic whole-body scan in patients with differentiated thyroid carcinoma given recombinant human TSH

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Abstract

Objective: Protocols for monitoring patients with differentiated thyroid cancer (DTC) include measurement of serum Tg and, for most patients, whole-body scan (WBS) with low radioiodine activities (‘diagnostic’ WBS). Recently, recombinant human thyroid-stimulating hormone (rhTSH) has become available to provide the TSH stimulation necessary for these procedures, whilst avoiding thyroid hormone withdrawal and hypothyroid complications. In addition, the inclusion of diagnostic WBS in DTC follow-up has recently become controversial. We have assessed the compliance with withdrawal-aided monitoring and the informative value of diagnostic WBS in consecutive tertiary referral center patients.

Design: Forty-eight patients received rhTSH (0.9 mg) in two consecutive daily injections, with radioiodine administration 24 h, diagnostic WBS 48 h, and serum Tg testing prior to and 72 h later.

Methods: Compliance with withdrawal-aided monitoring was assessed with a questionnaire provided by the referring physician, patient record analysis, and patient interview. The informative value of diagnostic WBS was assessed by comparing findings against serum Tg measurements in light of physical and other radiological examinations.

Results: Forty of the forty-eight patients were female, the mean age was 43.9 years and the median follow-up from diagnosis was 4.5 years (range 1 – 19 years). Twenty-seven (56%) patients were compliant and 12 (25%) were non-compliant; compliance was not known in nine. Of 17 patients with clinically suspicious or significant findings on any available modality, four had uptake outside the thyroid bed on WBS but stimulated Tg \(2.5 \text{ ng/ml} \) on immunometric assay, while five had a negative WBS with serum Tg \(2.5 \text{ ng/ml} \).

Conclusions: Thyroid hormone withdrawal substantially impairs, and rhTSH administration substantially promotes, compliance with DTC monitoring. rhTSH-aided WBS is informative and should be included in the follow-up of unselected patients with DTC.

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Introduction

In the follow-up of differentiated thyroid carcinoma (DTC), the use of recombinant human thyroid-stimulating hormone (rhTSH) has emerged as an acceptable alternative to thyroid hormone withdrawal in providing the TSH stimulation needed to increase the sensitivity of serum thyroglobulin (Tg) measurement and/or a whole-body scan (WBS) with low activities of radioiodine (‘diagnostic’ WBS) (1, 2). The demonstrated equivalence of rhTSH with withdrawal in aiding the detection of clinically significant persistent tumors or metastases is surpassed by the ability of rhTSH to avoid the morbidity and decreased quality of life associated with hypothyroidism secondary to withdrawal (3–5). These adverse effects of hypothyroidism might deter patients from complying with recommended follow-up regimens (1, 2, 6). Adherence to these regimens is particularly important in higher risk patients and those with previously documented persistent or metastatic disease, because early detection and treatment are associated with a better prognosis (7).

Although follow-up logarithms vary according to individual clinical circumstances, current regimens all include periodic assessment of TSH-stimulated serum Tg levels. In addition, they have generally incorporated diagnostic \(^{131}\text{I} \) WBS, with the first such scan performed up to 1 year after thyroid remnant ablation (1, 2, 6). If the first diagnostic scan is positive, diagnostic WBS is repeated at up to yearly intervals until two successive scans are negative. The informative value of diagnostic WBS and the utility of this method in the follow-up of
most patients have recently been questioned by some investigators (8–11), but affirmed, at least in certain patient groups, by others (12, 13).

With the introduction of rhTSH into the follow-up of DTC at our tertiary referral center, we sought to test the hypothesis that thyroid hormone withdrawal and its hypothyroid complications deter patients and/or their healthcare providers from follow-up protocol adherence, and that the use of rhTSH might encourage participation in proper thyroid cancer surveillance. We also assessed the informative value of diagnostic WBS in a relatively large series of consecutive patients. We now report the results of these investigations.

Materials and methods

Patients and study overview

The study involved 48 consecutive patients with DTC who were referred to the Chaim Sheba Medical Center from March 2001 through June 2002 for their diagnostic $^{131}$I WBS and serum Tg measurement performed after rhTSH stimulation. All patients had previously received these procedures under thyroid hormone withdrawal. These patients were referred from several endocrine services, all of which adhere in principle to the National Comprehensive Cancer Network protocol (14). To determine compliance with follow-up protocols under withdrawal, we designed a standard questionnaire for the referring physicians, and used completed questionnaires, patient records, and/or patient interviews to obtain comprehensive information regarding the patients’ prior follow-up. To ascertain the informative value of diagnostic WBS in our patients, we compared the findings of this procedure with those of serum Tg measurement in light of subsequent clinical examination and the findings of any other radiological surveillance conducted based on the diagnostic WBS and/or serum Tg findings.

rhTSH-aided diagnostic WBS

rhTSH administration and rhTSH-aided scanning were performed as in the pivotal phase III study of rhTSH (Thyrogen; Genzyme Corp., Cambridge, MA, USA) (3). Patients received two consecutive daily i.m. injections of rhTSH (0.9 mg) with oral administration of 4 mCi $^{131}$I 24 h after the second injection. WBS was performed with a minimum of 140 000 counts on a dual-head helix gamma camera (Elscint, Haifa, Israel) equipped with high-energy collimators, 48 h after the second dose of rhTSH. Patients continued their thyroid replacement dosage while receiving the rhTSH-aided follow-up and were encouraged to follow a low iodine diet.

Serum Tg measurement

Serum Tg concentrations were measured with a chemiluminescent enzyme-labeled immunometric assay (Immulite; DPC, Los Angeles, CA, USA) with a functional sensitivity of 0.8 ng/ml and a lower limit of detection of 0.2 ng/ml. Tg levels were measured at baseline, i.e. immediately before the first rhTSH injection, and at 72 h after the second rhTSH injection, when stimulated Tg levels have been documented to peak (15). Tg antibodies were measured at baseline using an immunometric chemiluminescent assay (Immulite).

Statistical methods

Descriptive statistics were provided for all relevant parameters, and statistical significance was evaluated using the $\chi^2$ test. A $P$ value $<0.05$ was deemed statistically significant.

Results

Patient and tumor characteristics

Table 1 presents clinical and tumor characteristics of the study population. Of the 48 patients, 40 (83%) were female. Mean±s.d. age was 43.9±15.9 years (median 43 years) at referral and 42.1±15.8 years at diagnosis. Median follow-up from diagnosis was 4.5 years (range 1–19 years). Two patients had received radiation to the head/neck for Hodgkin’s lymphoma, and one had occupational radiation exposure.

Tumor histology was papillary in 28 patients, papillary, follicular variant in three, follicular in seven, and oncocyctic (Hürthle cell) or sclerosing type in one each. In eight patients, the histological determination was unavailable.

In 24 patients with sufficient information, staging at diagnosis was: $T1 = 6$, $T2 = 14$, $T3 = 5$, $T4 = 1$ (where $T$ indicates primary tumor; $T1$: tumor is less than 1 cm diameter; $T2$: tumor is more than 1 cm but less than 4 cm; and $T3$: tumor is more than 4 cm); $N0 = 19$, $N1 = 4$, $N2 = 1$ (where $N$ indicates node metastasis; $N0$: absence of lymph node metastasis; $N1$: positive lymph node metastasis); $M0 = 22$, $M1 = 2$ (where $M$ indicates distant metastasis; $M0$: no spread outside the neck region; $M1$: distant metastasis). When considering risk stratification according to pTNM, 22 patients were considered to be low risk (15 stage I, 7 stage II) and two high risk.

Adherence to the follow-up protocol

The mean and median intervals between the latest and the current diagnostic WBS were 25.9 and 22 months respectively (range 5–84 months). We defined adherence to the follow-up protocol as having an initial follow-up diagnostic WBS up to 1 year after remnant ablation, and repeating diagnostic scans at up to yearly intervals until two successive scans were negative. According to these criteria, 27 (56%) of 48 patients were compliant and 12 (25%) were non-compliant.
Table 1 Clinical and tumor characteristics of the study population.

<table>
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<tr>
<th>Patient number</th>
<th>Date of birth</th>
<th>Sex</th>
<th>Age at diagnosis (years)</th>
<th>Histology</th>
<th>Radiation history</th>
<th>Staging at diagnosis</th>
<th>Date of surgery</th>
<th>Thyroidectomy type</th>
<th>Date of additional surgery</th>
<th>Surgery type</th>
<th>First ablative No. of I x</th>
<th>Total I dose (µCi)</th>
<th>No. of WBS since diagnosis</th>
<th>Last WBS date</th>
<th>Time since last WBS (months)</th>
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</table>

N, no; Y, yes; R, right; L, left; follic, follicular; mod, modified.
In the remaining nine (19%) patients, the physician questionnaire or patient interview reported compliance, but previous WBS images or Tg measurements were unavailable. The compliance status of these patients was therefore classified as unknown. Physician questionnaires and/or patient interviews of the 12 non-compliant patients indicated that the reason for non-compliance was unwillingness to undergo hypothyroidism in seven, and was unclear in the remaining five.

**Results of diagnostic WBS**

Twenty (42%) of 48 patients had iodine uptake on the diagnostic scan. In eight of the 20, the uptake was located in the thyroid bed and later determined to be clinically insignificant. Two patients had only physiological uptake in the salivary glands. The other ten patients had uptake outside the neck bed, which was later determined to be clinically significant. Clinically significant uptake was attributed to cervical or mediastinal lymph node involvement in nine patients and bone metastases in one individual.

**Figure 1** Changes in serum Tg concentration in 20 patients with measurable Tg levels on thyroid hormone replacement therapy before and/or after stimulation by rhTSH. Serum Tg concentration was measured by chemiluminescent enzyme-labeled immunometric assay. Twenty-seven patients with Tg levels <0.2 ng/ml at both times and one patient with interference from Tg antibodies were omitted from the Figure. Several patients’ serum Tg concentrations were the same.

**Results of serum Tg measurement**

Two of forty-eight patients had Tg antibodies, one of whom had undetectable serum Tg and who was not possible to evaluate for this parameter. At baseline, 43 (91%) of the 47 patients had undetectable serum Tg (defined as concentrations <1.0 ng/ml, but in all cases <0.9 ng/ml) under thyroid suppression therapy. Serum Tg was >1.0–2.5 ng/ml in one patient and >2.5 ng/ml in three patients.

After rhTSH stimulation, serum Tg was >1.0 ng/ml in 18 patients, 14 of whom had undetectable unstimulated Tg, and >2.5 ng/ml in 11 of these 14. All four patients with serum Tg concentration >1.0 ng/ml at baseline had increased Tg levels after stimulation. The mean ± S.D. increase after rhTSH administration for all 47 patients who could be evaluated was 9.7 ± 31.0 ng/ml. Figure 1 presents Tg levels before and after rhTSH stimulation for 20 patients with detectable serum Tg levels at either time.

**Informative value of diagnostic WBS**

Forty-eight patients could be evaluated for both diagnostic WBS and serum Tg findings. Table 2 shows the concordance between these findings.

Using a combination of all the available diagnostic methods (WBS, Tg, clinical examination, other radiologic modalities), 17 patients had clinically suspicious or significant findings. Of the 17, four had uptake outside the thyroid bed on WBS but serum Tg <2.5 ng/ml; they were found to have cervical or mediastinal tumor, with one patient having bone metastases. Another five patients had negative WBS but serum Tg >2.5 ng/ml. Four of the five were found to have metastatic disease, two of whom were re-operated, and three were treated with radioiodine. The remaining eight patients had cervical or mediastinal uptake on WBS and Tg levels of >1.0 ng/ml; all were found to have cervical or mediastinal tumor.

<table>
<thead>
<tr>
<th>Diagnostic WBS subgroup</th>
<th>Serum Tg findings</th>
<th>Changes in clinical management</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 patients with negative uptake</td>
<td>21 negative</td>
<td>No changes</td>
</tr>
<tr>
<td>2 patients with positive but insignificant uptake (salivary gland)</td>
<td>3 intermediate, 6 positive</td>
<td>2 received additional surgery, 3 received additional radioiodine treatment and 4 received additional radiological surveillance</td>
</tr>
<tr>
<td>8 patients with thyroid bed uptake</td>
<td>6 negative, 2 intermediate</td>
<td>All received additional radiological surveillance, which found the uptake to be clinically insignificant in 6</td>
</tr>
<tr>
<td>10 patients with uptake outside the thyroid bed</td>
<td>3 negative, 1 intermediate, 6 positive</td>
<td>All received additional radiological surveillance, which found the uptake to be clinically significant in all cases. All patients received additional surgery (n = 2) and/or radioiodine (n = 8) treatment</td>
</tr>
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Serum Tg: negative = <1.0 ng/ml, intermediate = ≥1.0 to <2.5 ng/ml, positive = ≥2.5 ng/ml.
In all 17 cases of clinically significant positive rhTSH-aided scans, follow-up or management was changed because of this result (Table 2), as is our standard practice with detection by WBS alone or in combination with methods for persistent or recurrent disease or an excessively large thyroid remnant. The changes included use of additional monitoring modalities, e.g., FDG-PET, ultrasound in 17 patients, additional radioiodine treatment in 13 patients (one for remnant ablation), and additional surgery for metastatic disease in four patients. Patients who had been compliant with the follow-up protocol had a significantly lower incidence of management-altering WBS findings (29.6%) than did non-compliant patients (50%) ($\chi^2 = 3.84$, $P = 0.05$).

Safety
rhTSH administration was very well tolerated. The only complications noted were minor transitory headache in two patients.

Discussion
Our study of 48 consecutive patients receiving initial rhTSH-aided monitoring for persistent or recurrent DTC at a tertiary referral center shows a substantial rate (at least 25%) of non-compliance with prior withdrawal-aided monitoring. Conversely, the use of rhTSH as an adjunct to monitoring ‘recaptured’ a substantial number of patients for proper follow-up. Of note, many of our non-compliant patients avoided a follow-up WBS for more than 1 year after a positive scan. A desire to avoid unpleasant health issues may have contributed to non-compliance, while the ‘publicity buzz’ surrounding a new monitoring adjunct may have fostered renewed compliance in our series. In addition, in some cases, physicians may have encouraged their patients who seemed at greatest risk for persistent or recurrent disease to take advantage of the new approach. It should be noted that our physician questionnaire was non-validicated and that our patient numbers were relatively small for a statistical analysis comparing subgroups. However, our anecdotal impression was that concern over adverse effects of withdrawal-related hypothyroidism was a key factor affecting compliance. This would suggest that these adverse effects can seriously hamper early detection and treatment of persistent or recurrent DTC, which have been shown to improve survival (7).

Our study also sought to assess the informative value of diagnostic WBS in a relatively large series receiving both this modality and serum Tg testing. The informative value and utility of diagnostic WBS relative to stimulated serum Tg testing plus neck ultrasound and other radiological modalities have become controversial, based on apparently inconsistent studies (9–14). For example, Pacini et al. (16) found that only a few of 72 patients had positive withdrawal-stimulated diagnostic WBS and rhTSH-stimulated serum Tg < 1 ng/ml by immunometric assay, and that in 99.4%, WBS uptake represented a clinically insignificant thyroid bed residue. On the other hand, Robbins et al. (13) noted positive scans in 31% of patients whose rhTSH-stimulated Tg did not rise above 2 $\mu$g/l on immunoradiometric assay. Forty percent of these positive scans were consistent with metastatic disease. In a lower risk subgroup, 13% had positive WBS and Tg $\leq 2 \mu$g/l, and more than half of positive scans were consistent with metastatic disease.

In the present study, scanning seemed to be informative, especially in patients non-compliant with previous follow-up. We found that although diagnostic WBS missed a substantial subgroup (6/48 patients) with confirmed ($n = 5$) or suspected ($n = 1$) metastatic disease, it identified an equally large subgroup with metastatic disease and serum Tg < 2.5 ng/ml on immunometric assay. In addition, we found that stimulated serum Tg rose in a subgroup of patients substantial enough to call into question the sensitivity of unstimulated Tg as previously shown. Serum Tg rose above 1 ng/ml in 38% of our patients who could be evaluated and above 2.5 ng/ml in 25%. These observations agree with those of larger studies, in which stimulated Tg rose above 2.5 ng/ml in 19% (11), above 1.0 ng/ml in 43% (10), and above 2 $\mu$g/l in 52.2% (13). Of note, however, all our patients with positive WBS and stimulated serum Tg increased above 2.5 ng/ml were confirmed to have persistent or metastatic disease. These results, and the observation of substantial subgroups missed by each modality, suggest that at least in a population of heterogeneous, tertiary referral center patients, rhTSH-aided diagnostic WBS and serum Tg testing are complementary in the follow-up of DTC.

In conclusion, we have shown that thyroid hormone withdrawal substantially impairs, and rhTSH administration substantially promotes, compliance with follow-up of DTC. In introducing rhTSH stimulation as an adjunct to such monitoring, one might expect to diagnose persistent or metastatic disease in an appreciable percentage of patients. We also demonstrated the informative value of rhTSH-aided diagnostic WBS, especially in previously non-compliant patients. At this stage, we recommend continued complementary use of rhTSH-aided diagnostic WBS and serum Tg measurement in the follow-up of unselected patients with DTC.

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