Limited Value of Repeat Recombinant Human Thyrotropin (rhTSH)-Stimulated Thyroglobulin Testing in Differentiated Thyroid Carcinoma Patients with Previous Negative rhTSH-Stimulated Thyroglobulin and Undetectable Basal Serum Thyroglobulin Levels

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Context: One year after initial treatment, low-risk differentiated thyroid cancer (DTC) patients undergo recombinant human (rh)TSH-stimulated serum thyroglobulin (Tg) (rhTSH-Tg) and neck ultrasound (US).

Objective: The need for more rhTSH-Tg in these patients is controversial. We evaluated the utility of a second rhTSH-Tg in DTC patients 2–3 yr after their first evaluation.

Results: At the first rhTSH-Tg, basal and stimulated serum Tg was undetectable in 68 of 85 patients. Neck US was unremarkable in all but one, who had evidence of lymph node disease. Seventeen of 85 patients had undetectable serum Tg that became positive after rhTSH, with negative imaging in 10 and evidence of disease in seven. Patients with no evidence of disease were reevaluated 2–3 yr later (second rhTSH-Tg). In patients in which the first stimulated Tg was undetectable, all had undetectable basal serum Tg, which remained undetectable after rhTSH in 66 of 67 patients (98.5%) and became detectable in one (1.5%) (positive neck US). In the 10 patients with detectable stimulated Tg in the first test, basal serum Tg and US were negative at the second test, but rhTSH-Tg became detectable in six. Compared with the first rhTSH-Tg, the second stimulated Tg in these six patients decreased in one, increased in three, and stabilized in two patients.

Conclusions: The second rhTSH-Tg was informative in patients who had first stimulated Tg detectable but not in those who had undetectable Tg at the first test, in which the only patient with recurrence was diagnosed by neck US. Thus, rhTSH-Tg should be repeated only in patients who have had a positive first rhTSH-Tg and negative imaging. (J Clin Endocrinol Metab 93: 76–81, 2008)
neck US and an undetectable basal and stimulated serum Tg [with negative serum Tg antibody (TgAb)]. These patients have a very low risk of recurrence and according to some guidelines may be shifted from suppressive to replacement L-T4 therapy, although direct proof of this strategy has not yet been published (15, 16, 19). Uncertainty does persist regarding whether the subsequent follow-up of these patients should be based on the periodic measurement of basal serum Tg (with or without neck US) or whether a second rhTSH-Tg should be obtained some years later. To answer this question, we retrospectively evaluated the clinical utility of a second rhTSH-Tg in DTC patients with undetectable basal serum Tg and who had no evidence of disease at their first rhTSH-Tg, performed within 1 yr after initial treatment.

Patients and Methods

Patients

The study group included 85 DTC patients with an undetectable basal serum Tg (and negative TgAb) at their first rhTSH-Tg, performed within the first year after initial treatment. There were 21 males and 64 females with a mean (± sd) age of 47.3 ± 16.4 yr (range 14–75 yr). Thyroid carcinomas were classified as papillary in 75 patients (88.2%) and follicular in 10 patients (11.8%). Sixty-one patients had stage I (71.8%), 11 had stage II (12.8%), and 13 had stage III (15.3%). According to the results of this first test, those with undetectable or detectable rhTSH-Tg and no evidence of disease at imaging (n = 77) underwent a second rhTSH stimulation test during 2–3 yr of follow-up. The remaining eight patients who had evidence of disease at the time of the first rhTSH-Tg underwent different treatments and were not subjected to the second rhTSH-Tg. The mean (± sd) follow-up after diagnosis was 56 ± 30 months (range 13–228 months, median 48 months).

In all patients, the initial treatment consisted in total thyroidectomy and 131I postsurgical thyroid ablation after L-T4 withdrawal with a mean dose of 2830 ± 1295 MBq of 131I (range 1110–5530). Both the first and the second rhTSH-Tg were performed during suppressive L-T4 therapy as previously described (20). Briefly, patients received one injection of rhTSH (0.9 mg im, Thyrogen; Genzyme Therapeutics, Cambridge, MA) for two consecutive days. Serum samples for TSH, Tg, and TgAb measurement were collected before the first rhTSH injection and 3 d after the last injection of rhTSH. Additional diagnostic tests included neck US and chest x-rays in all patients, and diagnostic 131I WBS in 26 of 85 patients at the first rhTSH-Tg and in one of 77 at the second rhTSH-Tg. Additional imaging procedures, mainly computed tomography (CT) scan of the chest, were performed in a few patients to rule out the presence of distant metastases.

In our institution, patients with undetectable serum Tg (<1.0 ng/ml), negative TgAb, and no evidence of disease (at clinical examination, neck US, chest x-rays, and diagnostic 131I WBS when performed) were defined as free of disease, whereas patients with detectable stimulated serum Tg and/or evidence of disease were classified as having persistent/recurrent disease.

Materials and Methods

Serum Tg, TSH, and TgAb were measured by chemiluminescent assay (Immulite 2000; Diagnostic Products Corp., Los Angeles, CA). Tg assay had a functional sensitivity of 0.9 ng/ml and an analytical sensitivity of 0.2 ng/ml. The interassay variability of Tg assay in our laboratory is 3.95%. TgAb were considered negative when less than 20 UI/ml. All patients underwent neck US performed with a color Doppler apparatus (AU 390 Asynchronous; Esaote Biomedica, Firenze, Italy) and a 7.5-MHz linear transducer. Ultrasoundography was performed by experienced endocrinologists (members of our staff) trained in neck US with a high-resolution US system. Neck US was routinely performed in all patients, independently of the results of the rhTSH-Tg test, and the ultrasonographer was blind to the patients’ Tg status. Fine-needle aspiration cytology (FNAC) was performed whenever ultrasound criteria of malignancy (cystic appearance, hyperechoic punctuations, loss of hilum, and peripheral vascularization) were present.

Statistical analysis

All data are presented as the mean ± sd, with medians when appropriate. The nonparametric Mann-Whitney U test was used to compare quantitative data when it was not normally distributed, and the test was performed for unpaired data. We analyzed 2 × 2 contingency tables using the Fisher exact test or by χ² for the 2 × 3 contingency table to evaluate significant differences in frequencies.

The following variables were studied by univariate analysis: age at diagnosis (<45 or >45 yr old), sex, histology of primary tumor (papillary/follicular), local or distant metastases (yes/no), stage at diagnosis, results of postablative WBS (residues or residues plus metastases), and results of the first rhTSH stimulation test (detectable/undetectable Tg).

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Statistically significant variables found in univariate analysis were entered into a multivariate analysis to identify those with independent prognostic significance and to calculate the odds ratio. We used StatView for Windows version 5.0.1 (SAS Institute, Cary, NC) and MedCalc statistical program for Windows for statistical analyses. We considered P < 0.05 to be statistically significant.

Results

Results of the first rhTSH stimulation test within 1 yr after surgery and radiiodine ablation

As shown in Fig. 1, at the time of the first rhTSH stimulation test, both basal and rhTSH-Tg were undetectable in 68 of 85 patients (80%) (first stimulated Tg undetectable). Neck US in this group was negative in 67 of 68 patients (98.5%) and suspicious for a lymph node metastasis in one (1.5%) (false-negative rhTSH-Tg). The metastatic origin of this lymph node was confirmed by FNAC and by WBS performed after the administration of a large activity of radioiodine. In 17 of 85 patients (20%), basal Tg was undetectable, but it became detectable after rhTSH (first stimulated Tg detectable). The mean (± sd) serum peak Tg after rhTSH was 3.8 ± 3.9 ng/ml with a range of 1.1–14.8 ng/ml and a median of 2.4 ng/ml. Ten of 17 patients (58.8%) had no evidence of disease by clinical examination, neck US and chest x-rays and were left untreated.

The other seven of 17 patients (41.2%) had evidence of disease detected by neck US and FNAC in six and by diagnostic WBS in 1 with lung and bone metastases confirmed at CT scan. Peak serum Tg after rhTSH was significantly higher in patients with documented disease than in patients with no evidence of disease (6.7 ± 4.9 vs. 1.9 ± 0.8 ng/ml; P = 0.01, Mann-Whitney U test).

The seven patients with documented disease were treated with therapeutic doses of 131I (mean ± sd cumulative dose of 9,250 ± 5,402 MBq of 131I, range 3,700–20,350). Two patients with lymph node metastases at neck US had no uptake in the posttherapeutic WBS and underwent lymph node surgery. One patient had 131I uptake in the lung and bone and was scheduled for more 131I therapy. The remaining four patients had uptake in regional lymph nodes and are still receiving therapy with 131I.
Results of the second rhTSH stimulation test

A second rhTSH stimulation test was performed at an average (± SD) of 35.9 ± 16.0 months (range 12–84 months, median 29 months) after the first test in the 67 patients with an undetectable first stimulated Tg and who were free of disease at that time (Fig. 1). In all but one (98.5%), serum Tg (and TgAb) was still undetectable both in basal conditions and after rhTSH stimulation, and the neck US was negative. In one patient, serum Tg converted from undetectable to detectable (1 ng/ml) after rhTSH and neck US showed the presence of one lymph node confirmed by FNAC. This patient was treated with 131I therapy, and the disease was confirmed in the posttherapy WBS.

In patients with detectable first stimulated Tg, a second rhTSH stimulation test was performed at an average (± SD) of 22.3 ± 6.1 months (range 13–30 months, median 24 months) in the 10 patients who had detectable rhTSH-Tg but negative imaging at the time of the first rhTSH stimulation test and were left untreated at that time (Fig. 1).

Basal serum Tg was undetectable in all these patients and remained undetectable in four patients with negative neck US after rhTSH stimulation. In six patients, basal serum Tg was undetectable but rose to more than 1.0 ng/ml after rhTSH, and neck US was unremarkable. Compared with the first test, stimulated serum Tg levels had decreased in one patient (from 2.4 to 1.8 ng/ml), remained unchanged in two patients, and increased in three patients (from 2.6, 1.3, and 2.9 to 3.2, 2.2, and 3.6 ng/ml, respectively). These last three patients were considered at risk in view of the increasing trend of stimulated serum Tg and were submitted to intensive imaging procedures (chest CT and [18F]deoxyglucose positron emission tomography), which resulted negative, and in one case, which also resulted negative, to empiric 131I therapy and posttherapy scan.

Concordance between US findings and FNAC

Cumulating the data at the time of the first and the second rhTSH tests, a total of 13 patients underwent FNAC for suspicious findings at neck US. FNAC confirmed the presence of lymph node metastases in eight of 13 (61.5%). Thus, the possibility of exposing a significant proportion (38.5%) of patients to unnecessary FNAC should be considered when interpreting the US finding.

Prognostic variable: univariate and multivariate analysis

The prognostic impact of demographic, clinical, and pathologic features of the patients (age, gender, tumor stage, histotype, local or distant metastases, results of the postablative WBS, and
result of the first rhTSH-Tg) on final outcome were evaluated by univariate and multivariate analyses. As shown in Table 1, by univariate analysis, only the presence/absence of metastases (odds ratio 4.8; 95% confidence interval, 1.3–17.2; \( P < 0.01 \)) and the results of the first rhTSH-Tg (detectable or undetectable serum Tg) (odds ratio 60; 95% confidence interval, 10.8–338; \( P < 0.0001 \)) were significant predictors of persistent disease. However, in the multivariate analysis, only the results of the first rhTSH-Tg were found to be an independent prognostic indicator.

**Discussion**

Recent evidence has shown that, in low-risk patients, an rhTSH stimulation test associated with neck US within 1 yr after initial treatment is sufficient for identifying the large majority of patients (more than 80%) free of disease (negative neck US and undetectable serum Tg) and the small minority with persistent disease (1–6, 10, 11). This strategy has been incorporated into recent guidelines provided by the American Thyroid Association and the European Thyroid Association (15, 16).

Several large retrospective series (7–9) have documented the strong prognostic significance of an undetectable serum Tg obtained after L-T4 withdrawal 6–12 months after initial treatment. On the contrary, the use of rhTSH is relatively recent; thus, the long-term negative predictive value of this methodology is not yet well defined. A recent prospective study by authoritative authors (21) has indicated that a single rhTSH-Tg of less than 0.5 ng/ml without TgAb has an approximately 98% likelihood of identifying patients completely free of disease who do not require frequent imaging and only a Tg stimulation test in the subsequent follow-up. However, these authors included patients who had had their first rhTSH stimulation test at a median of 3.3 yr (mean ± sd 6.9 ± 0.4 yr, range 10 months to 35 yr) after initial treatment, and not all cases were reevaluated with the second rhTSH test. Our study addressed the same issue but, although it is retrospective, it is more homogeneous because all patients had a first rhTSH stimulation test within 1 yr after initial treatment and a second rhTSH stimulation test an average of 3 yr later. Despite these differences, the results follow the same direction. The only divergence in the conclusion is that Kloos and Mazzaferri (21) envisage the possible need to perform additional imaging (neck US) and an rhTSH test at some point during follow-up, whereas, according to our protocol (including neck US as a routine procedure in any examination of the patient), we do not see the need for additional rhTSH tests as long as basal Tg remains undetectable and neck US is unremarkable.

The execution of a second rhTSH stimulation test was of little clinical utility in patients who had no biochemical (undetectable stimulated serum Tg) or clinical (imaging) evidence of disease at the time of their first rhTSH-Tg. In this group, the second test confirmed complete remission in all but one patient, in whom the rhTSH stimulation test was positive and the neck US was also diagnostic. On the contrary, the second test was clinically informative in all patients who had biochemical evidence of possible persistent disease at their first rhTSH stimulation test. In patients of this group, stimulated Tg was undetectable in 40% of patients, demonstrating spontaneous remission (without any treatment), whereas it remained detectable in 60%, indicating the need for further imaging or treatment (in case of an increasing trend of stimulated serum Tg) or the opportunity to wait and see (in case

**TABLE 1.** Univariate and multivariate analysis of demographic and clinical features affecting final outcome (persistent disease or disease free)

<table>
<thead>
<tr>
<th></th>
<th>Persistent disease</th>
<th>Disease free</th>
<th>Univariate analysis</th>
<th>Odds ratio</th>
<th>Multivariate analysis</th>
</tr>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>&gt;45</td>
<td>4</td>
<td>40</td>
<td>( P = 0.13 )</td>
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<td>NA</td>
</tr>
<tr>
<td>&lt;45</td>
<td>9</td>
<td>32</td>
<td></td>
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<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>15</td>
<td>( P = 0.07 )</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Histotype</td>
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<tr>
<td>Papillary</td>
<td>13</td>
<td>62</td>
<td>( P = 0.34 )</td>
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<tr>
<td>Follicular</td>
<td>0</td>
<td>10</td>
<td></td>
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<tr>
<td>Stage</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11</td>
<td>50</td>
<td>( P = 0.31 )</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>11</td>
<td></td>
<td></td>
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<tr>
<td>Postablative WBS</td>
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<tr>
<td>Residues</td>
<td>9</td>
<td>53</td>
<td>( P = 0.47 )</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Metastases</td>
<td>4</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastases Yes</td>
<td>9</td>
<td>23</td>
<td>( P = 0.01 )</td>
<td>4.8 (95% CI 1.3–17.2) ( P = 0.01 )</td>
<td>P = 0.10</td>
</tr>
<tr>
<td>Metastases No</td>
<td>4</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First rhTSH-Tg (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable (&lt;1)</td>
<td>2</td>
<td>66</td>
<td>( P &lt; 0.0001 )</td>
<td>60 (95% CI 10.8–338) ( P &lt; 0.0001 )</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Detectable (&gt;1)</td>
<td>11</td>
<td>6</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

NA, Not applicable.
of decreasing or unchanged stimulated serum Tg) and no evidence of disease at imaging.

It is important to stress that our approach is appropriate for a center specifically concerned with thyroid cancer, but it probably could not be reproduced in an average hospital setting where the risk of performing unnecessary FNAC may be even higher than that encountered by us.

In conclusion, our results suggest that a second rhTSH stimulation test should be repeated during follow-up only in patients who have positive stimulated serum Tg levels at the time of the first rhTSH test and that have continued to display undetectable basal serum Tg in subsequent years. In the other patients, those defined as free of disease at the time of their first rhTSH-Tg, a second rhTSH test is unnecessary as long as basal serum Tg remains undetectable, neck US is negative, and no other clinical or physical suspicion of recurrence is apparent. Our conclusions and those of Kloos and Mazzaferri (21) are quite similar. They state that patients with undetectable stimulated Tg (<0.5 ng/ml) do not require repeated rhTSH-Tg tests but only annual basal serum Tg measurement on replacement l-T4. We give the same indications for patients with undetectable stimulated rhTSH-Tg levels but with a cutoff of 1.0 ng/ml. We recommend additional testing only if basal serum Tg becomes detectable during follow-up. A limitation of these studies is the short follow-up. However, our speculation is supported by the results of at least two similar studies (7, 8) performed in patients studied by thyroid hormone withdrawal, showing that when stimulated serum Tg is less than the institutional cutoff, the rate of recurrence is very low (<1%) at a 12-yr follow-up. The final answer to the question of the best follow-up protocol will probably emerge after more studies.

Finally, some recent studies have shown that with the use of supersensitive assays for Tg measurement, an undetectable basal serum Tg has the same predictive value of an rhTSH stimulated Tg performed with less sensitive assays and that a higher percentage of patients have detectable serum Tg after rhTSH (22, 23). The question is whether the use of these sensitive assays will lose specificity.

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Disclosure Information: The authors have nothing to disclose.

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2001 Prediction of disease status by re-

2005 Thyroid-hormone therapy and thy-


Erratum

In the article “Role of $^{18}$F-Fluorodeoxyglucose Positron Emission Tomography in Preoperative Assessment of Cytologically Indeterminate Thyroid Nodules” by Fernando M. Sebastianes, Juliano J. Cerci, Patricia H. Zanoni, José Soares, Jr., Lilian K. Chibana, Eduardo K. Tomimori, Rosalinda Y. A. de Camargo, Marisa Izaki, Maria Clementina P. Giorgi, José Eluf-Neto, José Cláudio Meneghetti, and Maria Adelaide A. Pereira (The Journal of Clinical Endocrinology & Metabolism 92:4485-4488), the authors report an error in the labeling of column 4 in Table 2, which should be ‘Specificity (%)’ rather than ‘Percentage of true-negative results.’ The authors apologize for their error.