Thyroid Cancer Recurrence in Patients Clinically Free of Disease with Undetectable or Very Low Serum Thyroglobulin Values

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Design: This was a retrospective clinical study.

Setting: The study was conducted at a university-based tertiary cancer hospital.

Patients: One hundred seven patients had initial thyroid cancer surgery and subsequent remnant radioiodine ablation. Patients underwent recombinant human TSH (rhTSH)-mediated diagnostic whole-body scan and rhTSH-stimulated thyroglobulin (Tg) measurement before April 2001 if they had no antithyroglobulin antibodies, were clinically free of disease, and had one or more undetectable ($\leq 0.5$ ng/ml) or low (0.6–1 ng/ml) basal Tg measurements on levothyroxine. Patients were stratified according to their rhTSH-Tg responses: group 1, Tg 0.5 ng/ml or less (68 patients); group 2, Tg from 0.6 to 2.0 ng/ml (19 patients); and group 3, Tg greater than 2 ng/ml (20 patients).

Main Outcome Measures: Tumor recurrence was measured.

Results: In group 1, two of 62 patients (3%) with follow-up recurred. In group 2, 63% converted to group 1, whereas two of 19 (11%) converted to group 3 and then recurred. Sixteen of the initial 20 group 3 patients (80%) recurred, including recurrence rates of 69 and 100% for those with an initial rhTSH-Tg greater than 2.0 ng/ml but 5.0 ng/ml or less, and 4.6 ng/ml or greater, respectively. One group 3 patient died of distant metastases. rhTSH-Tg more accurately predicted tumor recurrence than basal Tg. An rhTSH-Tg threshold of 2.5 ng/ml or greater optimally predicted future recurrence with sensitivity, specificity, and negative and positive predictive values of 80, 97, 95, and 84%, respectively.

Conclusions: The prevalence of postablation thyroid cancer recurrence is predicted by the rhTSH-Tg response with an optimal Tg threshold of 2.5 ng/ml. Still, recurrent disease occurs in some patients with an initial rhTSH-Tg of 0.5 ng/ml or less. (J Clin Endocrinol Metab 95: 5241–5248, 2010)
1 ng/ml, is so high that future stim-Tg testing is of limited value (4–6). Indeed, the American Thyroid Association guidelines state that the timing or necessity of further stim-Tg testing is uncertain, and recommend follow-up based primarily on yearly clinical examination and Tg measurements on thyroid hormone replacement (Tg-on) [recommendation 45b (3)].

In 2002 we reported a cohort of 107 differentiated thyroid carcinoma patients thought to be free of disease and studied them with recombinant human TSH (rhTSH; Genzyme Corp., Cambridge, MA.) mediated diagnostic whole-body scan (DxWBS) and stim-Tg (rhTSH-Tg) (7). Patients were stratified into three groups according to their rhTSH-Tg responses: group 1, Tg less than 0.5 ng/ml (68 patients); group 2, Tg from 0.6 to 2.0 ng/ml (19 patients); and group 3, Tg greater than 2 ng/ml (20 patients).

In the initial study, none of group 1 had evidence of tumor on physical examination, chest x-ray, DxWBS, and neck US. By 2005 (6), five were lost to follow-up with no evidence of disease (NED), and one of the remaining 63 patients (1.6%) demonstrated recurrent disease. In group 2, none had evidence of tumor in the initial study. By 2005 (6), one patient was lost to follow-up with NED, and one of the remaining 18 patients (5.6%) demonstrated recurrent disease. In group 3, nine patients (45%) were found to have persistent tumor identified by fine-needle aspiration cytology, surgical pathology, anatomic imaging, or post-131I treatment whole-body scan (RxWBS) in the first study (7). By 2005 (6), tumor was found in seven additional patients. Thus, tumor was identified in a total of 16 of the original 20 (80%) group 3 patients by the second report.

Currently more than half of the original cohort has been followed up over 7 yr since their initial stratification. Here we update this cohort and demonstrate an additional patient with recurrent disease from both group 1 and group 2, 5 and 3 yr after their first rhTSH testing, respectively, report for the first time the prevalence of recurrent cancer when the stratification rhTSH-Tg was greater than 2 ng/ml but 5 ng/ml or less, report the prevalence of recurrent cancer in those accrued during their first stim-Tg test, apply receiver-operator characteristic (ROC) analysis to determine the optimal rhTSH-Tg threshold to predict future recurrence, and report a cancer-related death from group 3.

**Patients and Methods**

**Patients and initial study methodology**

The Ohio State University and The Arthur G. James Cancer Hospital Institutional Review Boards approved ongoing follow-up studies of thyroid cancer patients (protocols 2006C0047 and 2005C0032), including this follow-up study of 107 consecutively evaluated patients with papillary, follicular, or Hurthle cell carcinoma initially reported in 2002 (7) after they underwent evaluation for persistent tumor using rhTSH, shortly after its approval for clinical use.

Eighty-eight patients (82%) were female and 19 (18%) were male, who at the time of initial surgery ranged in age from 10.9 to 85.3 yr (median 36.3 yr). They had undergone ostensibly successful initial therapy including total or near-total thyroidectomy and RRA in all patients as previously reported (6, 7). Three patients were found to have residual tumor that was thought to have been successfully treated before inclusion in the first rhTSH cohort study (6). Patients were tested between January 1999 and March 2001 if they had no anti-Tg antibodies and had been free of disease on the basis of clinical examination and had one or more undetectable (≤0.5 ng/ml) or low (0.6–1 ng/ml) serum Tg-on measurements. All had undergone a 4 mCi 131I DxWBS and RxWBS after initial RRA or after treatment of recurrences, chest x-ray, and in some cases neck US, computed tomography (CT), magnetic resonance imaging, or 18F-fluorodeoxyglucose-positron emission tomography (18FDG-PET) imaging before the initial rhTSH study.

For the first rhTSH evaluation, patients were given rhTSH, 0.9 mg im on 2 consecutive days followed by 4 mCi 131I 24 h later and serum Tg measurement and DxWBS on the fifth day (72 h after the last rhTSH injection) as previously described (8). Time from initial surgery to the first (enrollment) rhTSH test was 10 months to 35 yr (median 3.3 yr, mean 6.9 ± 0.4 SEM yr). Average patient age at the time of enrollment was 44.0 ± 1.3 yr and ranged from 14.4 to 88.2 (median 43.2) yr.

**Initial therapy**

Total or near-total thyroidectomy was performed on all 107 patients, sometimes (36%) after completion thyroidectomy.

Lymph node surgery was therapeutic, rather than prophylactic, with simple excision in 19 patients (18%), ipsilateral modified neck dissection in seven (7%), and bilateral modified neck dissection in three patients (3%) and no lymph node surgery in 78 (72%). After surgery, all were treated with 131I ranging in amounts from 26 to 228 mCi (median 96 mCi). Cumulative 131I administered by the time of the initial report in 2002 ranged from 26 to 800 mCi (median 105 mCi).

**Tumor characteristics, stage, and tumor discovery after rhTSH testing**

The tumors were mainly classic papillary thyroid carcinomas (71%), but some were follicular variant (9%), tall cell variant (2%) and Hurthle cell variant (1%) papillary thyroid carcinomas, and follicular (11%) or Hurthle cell (6%) carcinomas. More than half of the patients (66 of 107) had tumors that were at higher risk of recurrence (T3, T4, or N1 or M1). [To maintain consistency with the first publication of this cohort, tumors were staged according to the 5th edition of the American Joint Committee Cancer Staging Manual (17).]

**Follow-up studies after the initial rhTSH study**

Follow-up included all available data through February 2010. Since June 2001 routine management for these patients included physical examination; serum TSH, Tg-on, and measurement of anti-Tg antibodies at least annually; periodic neck US; and for those with undetectable Tg-on values, a stim-Tg
determination [rhTSH-Tg or Tg measurements off thyroid hormone replacement (Tg-off) with thyroid hormone withdrawal (THW)] TSH >2.5 mIU/liter (6) a minimum of every 5 yr.

Patients were categorized as NED if neck US was negative and they had one or more stim-Tg levels less than 0.5 ng/ml after the first rhTSH study, and all Tg-on levels were less than 0.5 ng/ml. Persistent tumor was identified by fine-needle aspiration cytology, in surgical specimens, or by \(^{131}I\) WBS showing \(^{131}I\) uptake outside the thyroid bed, or considered to be pathologic uptake in the central neck (patient 84). Chest CT (with or without neck CT or neck magnetic resonance imaging) were performed as indicated (typically when neck US was positive or when the Tg-on or stim-Tg was greater than 2.0 ng/ml). \(^{131}I\) DxWBS and/or RxDWBS, or \(^{18}FDG\)-PET scans were performed as indicated, usually when the stim-Tg was greater than 5–10 ng/ml and disease outside the neck was suspected.

Tg measurement

During the course of this study, three different Tg assays were used. The initial enrollment study (7) used the Nichols chemiluminescence immunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA; catalog no. 60-4240, analytical sensitivity 0.07 ng/ml, functional sensitivity 0.5 ng/ml, minimum reported value 0.5 ng/ml). Starting March 2003, the Nichols Advantage Tg assay was used (Nichols Institute Diagnostics; catalog no. 62-7035, analytical sensitivity ≤0.04 ng/ml, functional sensitivity ≤0.3 ng/ml, minimum reported value 0.9 ng/ml). Starting February 2006, the Immulite Tg assay (Siemens Inc., Deerfield, IL; catalog no. PIL2KTY, analytical sensitivity <0.2 ng/ml, in-house functional sensitivity 0.2 ng/ml minimum reported value 0.2 ng/ml). For this study, all Tg values were considered undetectable if they were below the minimum reported value for the assay or 0.5 ng/ml or less.

Anti-Tg antibody (TgAb) measurement

During the course of this study, three different TgAb assays were used. The initial enrollment study (7) used the Nichols chemiluminescence TgAb kit [catalog no. 60-4185, sensitivity 1.53 IU/ml, assay reportable range <2.0 to 56.0 IU/ml, normal range (negative test) <2.0 IU/ml] read on the Corning-Nichols luminometer. Starting March 2003, the Nichols Advantage chemiluminescence TgAb kit (sensitivity 1.2 IU/ml, assay reportable range <2.0–68.0 IU/ml, normal range (negative test) <2.0 IU/ml] read on Nichols Advantage luminometer was used. Starting February 2006, the DPC Immulite 2000 anti-TgAb kit (L2K; Siemens; sensitivity 2.2 IU/ml, assay reportable range <20 to 3000 IU/ml, normal range <40 IU/ml, negative test <20 IU/ml).

Neck US

Neck US was initially performed using a GE Logiq 200 Alpha with a 7.5-MHz linear probe, which was replaced March 2005 by the Esoate Picus Pro with the LA523 13-4 MHz probe. In June 2007 the Biosound Esoate MyLab 25 with the same probe was added. US examinations routinely inspected the superior mediastinum, the bilateral central, and the bilateral lateral neck compartments.

Statistics

All results are reported as mean ± SD. Percentages in the text are rounded to the nearest integer. The log-rank test was used to compare the timing and frequency of recurrences between the groups. Tg levels clinically reported as less than 0.5 ng/ml, or lower than the minimum reported value, are considered as 0.5 ng/ml for statistical purposes. The optimal rhTSH-Tg threshold to predict tumor recurrence was determined by identifying the rhTSH-Tg level that maximized sensitivity and specificity.

Results

rhTSH-Tg 0.5 ng/ml or less (group1)

Group1 included 68 patients. Six were lost to follow-up immediately after the first rhTSH stratification. The remaining 62 were followed after the first rhTSH a mean of 7.0 yr (range 0.8–10.9 yr). Fifty-six remained within group 1. Three patients (no. 41, 77, 112) converted to Group 2 according to their last stim-Tg, all of which were after THW, and none had evidence of tumor on US, whereas a DxWBS was not performed. No evidence of metastatic disease was seen on chest CT in patients 77 and 112. Two (no. 64, 67) of 62 patients (3%) with follow-up had recurrent tumor that was surgically resected (Fig. 1). Patient 64 (T2NxM0, stage 1) was previously reported (6). She underwent her first rhTSH test 3.1 yr after her first thyroid cancer surgery. She developed anti-Tg antibodies and had tumor recurrence found by neck US and underwent surgical resection of metastatic disease in six of 18 resected lymph nodes via a right lateral modified neck dissection 3 yr after her first rhTSH-Tg (Fig. 2) and 6.1 yr after her first thyroid cancer surgery. Since surgery the antibodies have resolved and she has remained NED for 6.2 yr since her last surgery. Patient 67 (T1NxM0, stage 1)
underwent her first rhTSH test 5.8 yr after her first thyroid cancer surgery. She became group 3, had a positive neck US, and had a central neck dissection with metastatic disease in one of seven lymph nodes 5.3 yr after her first rhTSH (11.1 yr after her first thyroid cancer surgery). She has remained NED for 4.1 yr since her last surgery.

**rhTSH-Tg 0.6–2.0 ng/ml (group 2)**

Group 2 included 19 patients. None were lost to follow-up immediately after the first rhTSH stratification. The 19 were followed up after the first rhTSH a mean of 8.1 yr (range 1.7–10.9 yr). Five (26%) remained group 2 with no anatomic evidence of tumor. Twelve (63%) spontaneously converted to group 1 a mean of 3.8 yr after the enrollment rhTSH (range 1.7–8.4 yr). In eight of the 12 patients, this conversion was demonstrated at the first subsequent stim-Tg measurement, which was performed a mean of 2.7 yr after the initial rhTSH (range 1.7–5.6 yr).

In the remaining four patients, this conversion was demonstrated on the second subsequent stim-Tg measurement and took place a mean of 6.0 yr after the initial rhTSH (range 4.0–8.4 yr). Two (no. 52, 79) of 19 patients (11%) converted to group 3 (by rhTSH and THW, respectively) and then had tumor recurrence (Fig. 1). Patient 52 (T2N1M0, stage 1) had a first rhTSH-Tg of 0.6 ng/ml 1.3 yr after her first thyroid cancer surgery. She maintained an undetectable Tg-on, but 23 months after her first rhTSH test, she converted to group 3 (rhTSH-Tg 3.4 ng/ml), had a positive neck US, and subsequently underwent left central neck dissection 2.2 yr after her first rhTSH with two of two metastatic lymph nodes (3.5 yr after her initial thyroid cancer surgery). She subsequently underwent repeated left central neck dissection with removal of an additional one (of one) metastatic lymph node and was previously reported (6). She remains group 3 and has been followed up 9.0 yr since her first rhTSH. Patient 79 (T2N0M0, stage 1) underwent her first rhTSH-Tg 2.4 yr after her first thyroid cancer surgery. Twenty-nine months after her first rhTSH-Tg of 1.0 ng/ml, she developed a detectable Tg-on value as high as 0.8 ng/ml when her TSH was 0.99 mIU/liter. Concurrently her rhTSH-Tg rose to 1.3 ng/ml. Twenty months later, despite a negative neck US and Tg-on of 0.5 ng/ml or less, she became group 3 with a Tg-off of 10.2 ng/ml 3.0 yr after her first rhTSH-Tg. Her DxWBS demonstrated 0.1% neck uptake and visualization of a linear focus in the midline above the thyroid cartilage thought to represent insignificant thyroglossal duct remnant activity. In response to her Tg-off value, she received 131I therapy with pathological uptake in the submandibular region of the contralateral neck on RxWBS 6.5 yr after her first thyroid cancer surgery and subsequently became group 1 and has been followed up 4.6 yr since therapy without tumor recurrence.

**rhTSH-Tg greater than 2.0 ng/ml (group 3)**

Group 3 included 20 patients. None were lost to follow-up immediately after the first rhTSH stratification. However, patients 80 and 75 were lost to follow-up 9 and 12 months after the first rhTSH in the absence of confirmed tumor recurrence. The remaining 18, including two who died, were followed up after the first rhTSH a mean of 4.1 yr (range 2.5–10.7 yr). Patients 23 and 19 have been followed up 3.8 and 10.0 yr since their first rhTSH-Tg, respectively, without definitive tumor recurrence. Patient 23 underwent her first rhTSH-Tg 26.2 yr after her initial thyroid cancer surgery (but 5.7 yr after her first RRA) and then spontaneously converted to group 1 3.1 yr later. She was lost to follow-up 3.8 yr after her first rhTSH test. Patient 19 received additional 131I therapy 11 months after the first rhTSH-Tg and on RxWBS showed only uptake in the thyroid bed region and became group 2 4.2 yr after the treatment. He is the only group 3 patient still under active follow-up who has not demonstrated tumor recurrence. Sixteen of the initial 20 group 3 patients (80%, Fig. 1) demonstrated tumor recurrence (patients 20, 25, 36, 45, 46, 51, 60, 61, 70, 81, 84, 87, 89, 90, 93, 107); their tumor node metastasis staging status was previously reported (6). Excluding the patients lost to follow-up within the first year after the first rhTSH test due to their incomplete evaluations, 16 of the remaining 18 patients (89%) demonstrated tumor recurrence during follow-up. According to the best evidence of tumor recurrence and listing each patient only once, tumor recurrence was confirmed by surgical histology in 10 patients (no. 25, 36, 51, 60, 70, 81,
Patients whose stratification rhTSH testing was their first stimulation after RRA and the testing was within 2 yr (730 d) of their first thyroid cancer surgery

Group 1

Group 1 included 17 qualifying patients; none were immediately lost to follow-up after the first rhTSH stratification. They were followed up after the first rhTSH a mean of 6.7 yr (range 0.8–10.4 yr). Sixteen patients remained within group 1. One patient (6%) converted to group 2 (no. 41) with no anatomic evidence of tumor. No patient developed recurrent tumor (Fig. 1).

Group 2

Group 2 included five qualifying patients; none were lost to follow-up immediately after the first rhTSH stratification. The five were followed up after the first rhTSH-Tg a mean of 8.9 yr (range 6.1–10.5 yr). One (20%) remained within group 2 with no anatomic evidence of tumor. Three (60%) spontaneously converted to group 1. This was demonstrated a mean of 3.5 yr after the initial rhTSH (range 1.9–4.5 yr). This conversion occurred at the first subsequent stim-Tg measurement in one of the three patients and was performed 1.9 yr after the initial rhTSH. In the remaining two patients, this conversion was demonstrated on the second subsequent stim-Tg measurement and took place a mean of 4.3 yr after the initial rhTSH (range 4.0–4.5 yr). One (no. 52) of the five patients (20%) converted to group 3 and had recurrent tumor as described above (Fig. 1).

Group 3

Group 3 included six qualifying patients (no. 36, 45, 51, 75, 84, 93). None were lost to follow-up immediately after the first rhTSH stratification. They were followed up after the first rhTSH a mean of 7.3 yr (range 1.0–10.5 yr). Aside from patient 75 lost to follow-up after 1 yr, all of the remaining five patients (83%) were found to have tumor recurrence an average of 3.2 yr after the first rhTSH (range 2.5–4.1 yr) (Fig. 1).

Discussion

This report may provide the longest available follow-up on a patient cohort that was clinically free of disease and investigated with rhTSH-stimulated DxWBS and Tg using a sensitive Tg assay (lowest reported value of 0.5 ng/ml) and then followed up for long-term outcome. This is important because in the past the majority of recurrent disease found years after patients were declared free of disease was likely persistent disease below the detection level of less sensitive diagnostic methods of the past but recognizable by today’s standards. Thus, the prevalence of tumor recurrence among patients declared free of disease by current test methods during long-term follow-up is less certain but likely lower than in the past.

Prior publications using Tg assays with functional sensitivities of 1.0–3.0 ng/ml have suggested that tumor recurrence after a patient is declared free of disease occurs in less than 0.5–1.5% (4, 5, 11, 12). Previously we reported an incidence of 1.6% among patients with an rhTSH-Tg of 0.5 ng/ml or less when this cohort was followed up for
3–5 yr (6). Now after being followed up a mean of 7 yr (range 0.8–10.9 yr), 3% of patients who initially demonstrated an rhTSH-Tg of 0.5 ng/ml or less have had recurrent disease. The prevalence of recurrence is 11% when the first rhTSH-Tg was 0.6–2.0 ng/ml. In patients whose first rhTSH-Tg was greater than 2.0 ng/ml, the prevalence of eventual recurrent tumor was 80%. Because 10% of these last patients (group 3) were lost to follow-up within 1 yr, this prevalence of recurrent disease could be even higher. Although the risk of tumor recurrence across rhTSH-Tg values between 0.5 and 5 ng/ml is likely a continuum, we saw distinct differences between our patient groups in which tumor recurrence occurred significantly sooner and more often in group 3 than in groups 1 and 2 (both $P < 0.001$), whereas groups 1 and 2 were not significantly different ($P = 0.25$). The mean time ($\pm \text{SD}$) to recurrence in groups 1–3 was $4.1 \pm 1.6$, $3.1 \pm 1.3$, and $2.0 \pm 1.4$ yr, respectively (Fig. 2).

One of the criticisms of prior publications on this cohort was that they combined patients undergoing their first stim-Tg testing after initial therapy along with patients undergoing stim-Tg testing during long-term follow-up. Here we analyze separately patients whose stratification rhTSH testing was their first stimulation after RRA and performed within 2 yr of their first thyroid cancer surgery and report recurrent disease in 0, 20, and 83% from groups 1–3, respectively (Fig. 1), findings similar to what was seen in the overall cohort.

Recently the short-term rates of disease detection in patients studied using Tg assays with functional sensitivities of 0.3 ng/ml or less have been reported and provide insight into the sensitivity and specificity of these assays during levothyroxine (LT4) therapy and after TSH stimulation (13, 14). These studies show that when the Tg-on was less than 0.1 ng/ml, or 0.1–0.5 ng/ml, that 1–3 and 10–24% of patients, respectively, mount a stimulated Tg greater than 2 ng/ml (13, 14). Assays with progressively lower functional sensitivities demonstrate improved Tg-on sensitivity for disease detection; however, this occurs at the expense of test specificity. Thus, as the functional sensitivity of the Tg assay declines, an increasing percentage of patients with detectable Tg levels do not have thyroid cancer and are false positive. For example, Tg assays with functional sensitivities of 0.2–0.3 ng/ml show Tg-on sensitivity and specificity of 54–63 and 89%, respectively (13). Tg assays with functional sensitivities of 0.02–0.1 ng/ml show improved Tg-on sensitivity and decreased specificity of 78–81 and 42–63%, respectively (13). Optimized Tg thresholds for disease detection during LT4 therapy and after TSH-stimulated were around 0.2–0.3 and 1.0 ng/ml, respectively. Using these optimized Tg thresholds, stim-Tg had improved sensitivity of 68–76% and maintained specificity of 81–91% compared with Tg-on measurements, thus permitting a more reliable assessment (13). This finding suggests a continued role for stim-Tg testing at least once after initial therapy in patients with Tg-on values of 0.5 ng/ml or less, even when a Tg assay with a lower functional sensitivity is used. We found stim-Tg to be valuable in our cohort both at our initial report (7) and now after longer follow-up (Table 1) when using a Tg assay with a functional sensitivity of 0.5 ng/ml. ROC analysis suggested an optimal initial rhTSH-Tg threshold of 2.5 ng/ml or greater to predict future disease recurrence (Fig. 3).

Currently patients are restaged about 6–12 months after RRA (15). Low-risk patients who have had RRA, negative cervical US, and undetectable stim-Tg are considered free of disease and believed to have a very low risk of tumor recurrence. Although not seen in this small patient cohort, neck US is important in all patients because they occasionally demonstrate persistent disease despite a negative stim-Tg (15). In patients who are free of disease, the degree

### Table 1. Performance of basal and stim-Tg cutoffs to predict tumor detection

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>NPV (%)</th>
<th>PPV (%)</th>
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<td>98</td>
<td>85</td>
<td>75</td>
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<td>rhTSH-Tg &gt; 2.0 ng/ml</td>
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<td>80</td>
<td>97</td>
<td>95</td>
<td>84</td>
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NPV, Negative predictive value; PPV, positive predictive value.

a TSH 0.2 mIU/liter or less in all patients with basal Tg greater than 0.5 ng/ml except patient 19 described in the text with TSH 4.54 mIU/liter and Tg 0.6 ng/ml without definitive tumor recurrence, and patient 89 with TSH 2.21 mIU/liter and Tg 1.0 ng/ml with tumor recurrence.
of TSH suppression is typically reduced, and long-term follow-up is subsequently based primarily on yearly clinical examination, Tg-on measurements, and periodic neck US. These conclusions, although probably correct, would need to be reconsidered if long-term follow-up series demonstrated a higher rate of eventual tumor recurrence among group 1 patients. This would be especially important if evidence emerged that very early detection of recurrent/persistent tumor influenced long-term patient outcome. Currently there is not compelling evidence that this is true (16).

The 2009 American Thyroid Association guidelines state that the clinical significance of minimally detectable Tg levels is unclear, especially if detected only after TSH stimulation (15). It is suggested that the Tg trend over time will typically identify patients with clinically significant residual disease. Regarding low-level detectable Tg levels during LT4 therapy, the specificity for eventual tumor recurrence in the current series when the initial Tg-on was 0.6–1.0 ng/ml was 98% with a positive predictive value of 75% (Table 1). This finding is in agreement with Schlumberger et al. (13) whose findings suggest that detectable Tg values above 0.3–0.5 ng/ml indicate the presence residual disease. Regarding low-level detectable stim-Tg levels, 63% of our group 2 patients converted spontaneously to group 1, a finding previously reported by others. In our series, this was demonstrated a mean of 3.8 yr after the initial rhTSH (range 1.7–8.4 yr). This finding supports that group 2 patient typically require only careful neck US to find obvious residual disease in the minority and, in the majority, continued observation because they will likely spontaneously convert to group 1 without further therapy. However, 11% of group 2 patients eventually demonstrated tumor recurrence. Their recurrent disease was preceded by a rise in stim-Tg over time and eventual conversion to group 3 in both patients despite undetectable Tg-on values in both and a negative neck US in one. This suggests that periodic stim-Tg testing in group 2 may help clarify which patients become group 1 and require less intensive therapy and follow-up vs. identifying those patients with rising stim-Tg values who are likely to manifest tumor recurrence. Still, there are no compelling data that identifying such patients earlier when the Tg-on is still undetectable will translate into a better long-term outcome (16).

In addition to the question of which patients should undergo follow-up stim-Tg testing, the interval at which this should be done is equally controversial. Together our four group 1 and group 2 patients who demonstrated recurrent tumor did so almost 7 yr after their initial thyroid cancer surgery (range 3.5–11.1 yr), and a mean of 3.4 yr (range 2.2–5.3 yr) after their first rhTSH demonstrated a peak serum Tg of less than 2.0 ng/ml. Three of these four patients converted to group 3 before their recurrent tumors were found. The rise in stim-Tg among these patients suggests tumor growth that might justify intervention as opposed to continued follow-up of indolent metastatic disease that may never become clinically manifest. Perhaps the same outcome could have been achieved in most of them based on neck US alone; however, patient 79 has a negative neck US and the conversion to group 3 in the other two patients may have prompted a higher degree of suspicion during unblinded neck US and certainly prompted US evaluation that was not otherwise being performed annually.

Conclusions

Repeated stim-Tg testing of group 1 patients for tumor recurrence may not be necessary based on questions of cost-effectiveness for this relatively infrequent event. Still, the 3% rate of tumor recurrence in group 1 likely justifies at least lifelong periodic Tg-on follow-up. Group 2 patients demonstrated tumor recurrence in 11%, and both of these patients converted to group 3 before identification of tumor recurrence. Thus, it may be reasonable to perform follow-up stim-Tg testing in group 2 patients who do not convert to group 1, perhaps initially at 1- to 2-yr intervals and then less frequently for those with stable or declining stim-Tg values, at least throughout the first decade after their initial diagnosis and treatment. If further investigation of these patients demonstrates ongoing episodes of recurrent disease beyond the first decade, then lengthening this duration of follow-up testing may be justified. Conversely, there are no definitive data that prove a better outcome when tumor is found by stim-Tg as opposed to later when the Tg-on value becomes abnormal. This caveat is critical when considering the role of stim-Tg testing.

Acknowledgments

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References

2. Mazzaferri EL, Kloos RT 2001 Current approaches to primary ther-
apy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 86:1447–1463
6. Kloos RT, Mazzaferri EL 2005 A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab 90:5047–5057
7. Mazzaferri EL, Kloos RT 2002 Is diagnostic iodine-131 scanning with recombinant TSH (rhTSH) useful in the follow-up of differentiated thyroid cancer after thyroid ablation? J Clin Endocrinol Metab 87:1490–1498
9. Kloos RT 2008 Approach to the patient with a positive serum thyroglobulin and a negative radioiodine scan after initial therapy for differentiated thyroid cancer. J Clin Endocrinol Metab 93:1519–1525
12. Pacini F, Capezzone M, Elisei R, Ceccearelli C, Taddei D, Pinchera A 2002 Diagnostic 131-I-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. J Clin Endocrinol Metab 87:1499–1501