APPLICATION OF POST-SURGICAL STIMULATED THYROGLOBULIN FOR RADIOIODINE REMNANT ABLEATION SELECTION IN LOW-RISK PAPILLARY THYROID CARCINOMA

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Abstract: Background. We present our ongoing experience in the use of postsurgical stimulated serum thyroglobulin (Stim-Tg) to assist in radioiodine remnant ablation (RRA) decision-making.

Methods. Patients with low-risk well-differentiated thyroid carcinoma (WDTC) with undetectable anti-Tg antibodies were prospectively followed after total thyroidectomy and therapeutic central compartment neck dissection, when indicated. Stim-Tg was performed 3 months postoperatively and used to base RRA selection.

Results. Of 104 patients, 59 patients (56.7%) had an undetectable Stim-Tg after thyroidectomy, 35 (33.7%) had Stim-Tg values of 1–5 μg/L, and 10 (9.6%) had Stim-Tg values >5 μg/L. RRA was administered to 1 patient (1.7%) with undetectable Stim-Tg, 6 patients (17.1%) with Stim-Tg 1–5 μg/L, and 9 patients (90%) with Stim-Tg >5 μg/L, for a total of 16 patients (15.4%) receiving RRA. When compared to current RRA selection guidelines, the proposed protocol achieved a significantly lower RRA administration rate.

Conclusion. Stim-Tg measurement performed several months after total thyroidectomy is a useful objective parameter in assisting RRA decision-making for patients with low-risk WDTC.

Keywords: radiology-radiation treatment; thyroid cancer—clinical; thyroglobulin; clinical research; TSH

Well-differentiated papillary carcinoma accounts for approximately 88% of detected thyroid carcinomas. The combination of current clinical practice guidelines and physician-held beliefs regarding the utility of radioiodine treatment for this patient population is being reassessed following a number of reports suggesting that radioiodine remnant ablation (RRA) may not be necessary in all patients.
remnant ablation (RRA) results in vast majority of these patients receiving RRA.2 Despite the nearly ubiquitous use of RRA, there remains great controversy over the efficacy of such treatment, especially for low-risk patients.3–5 Although several studies suggest that the impact of RRA on disease recurrence in low-risk patients remains unclear,3,4,6,7 others continue to advocate for its widespread use.8 In light of such controversy, and given the potential risks imposed by radioiodine treatments,9 there has recently been a need for a selective approach to RRA decision-making.3,5

Current recommendations on the use of RRA are based on cutoffs for clinicopathologic variables validated from large cohort studies (Table 1). The American Thyroid Association (ATA),10 European Thyroid Association (ETA),11 and British Thyroid Association (BTA)12 RRA selection guidelines are based primarily on patient age, tumor size, nodal invasion, and metastases, with the majority of low-risk patients receiving RRA based on the aforementioned parameters.3,8,12 The Mayo Clinic utilizes a comparatively more conservative approach to RRA decision-making3 which is based on a metastases, patient age, completeness of resection, local invasion, and tumor size (MACIS) score13 greater than 6. However, the limitations of the MACIS scoring system and all other existing RRA guidelines stems from the extrapolation of cohort data on validated clinicopathologic variables to predict risk for mortality rather than predicting an individual’s risk for recurrence. Furthermore, our center has recently shown that patient age and tumor size do not reliably predict whether low-risk patients develop residual/recurrent disease after total thyroidectomy as determined by follow-up stimulated thyroglobulin.14 Such observations thereby challenge the view that arbitrary cutoffs for such variables are sufficient in guiding RRA decision-making for individual low-risk patients with well-differentiated thyroid carcinoma (WDTC). Accordingly, we have advocated for an individualized and objective approach to RRA decision-making.

To this end, we have undertaken a novel objective approach to RRA selection in low-risk patients with WDTC using postsurgical stimulated thyroglobulin (Stim-Tg). Although the

| Table 1. Comparison of current thyroid association guidelines for RRA administration in well-differentiated thyroid carcinoma. |
|-------------------------------------------------|--------------------------------|--------------------------------|
| Guideline                                        | No indication for RRA (low-risk of recurrence or cancer-specific mortality) | Probable indication |
| ATA10                                           | TNM stage I disease without any of the following: Multifocal tumor | All stage II disease ≥45 y with any: Multifocal tumor |
|                                                | Nodal metastases Exrathyroidal extension Vascular invasion Aggressive histology | Nodal metastases Exrathyroidal extension Vascular invasion Aggressive histology |
| ETA11                                           | Complete surgery Favorable histology Unifocal tumor, ≤1 cm N1M0 No extrathyroidal extension | Less than total thyroidectomy No lymph node dissection Age <18 y |
| BTA12                                           | Complete surgery Favorable histology Unifocal tumor, ≤1 cm N1M0 | Less than total thyroidectomy Lymph nodes status not assessed at surgery |
|                                                | | Tumor size between 1 cm & 4 cm in diameter |
|                                                | Minimally invasive FTC, <2 cm, no vascular invasion | Tumors <1 cm with aggressive histology (tall-cell, columnar cell, poorly differentiated) |
|                                                | No extrathyroidal extension | Multifocal tumors <1 cm |
| Mayo Clinic13                                   | MACIS score <6 | MACIS score ≥6 |

Abbreviations: RRA, radioiodine remnant ablation; ATA, American Thyroid Association; ETA, European Thyroid Association; BTA, British Thyroid Association; FTC, follicular thyroid carcinoma; MACIS, Metastasis, patient Age, Completeness of resection, local Invasion, and tumor Size.
utility of serum Tg after thyroidectomy and RRA administration has been well established as a valuable technique in the detection of residual/recurrent WDTC,\(^{15–17}\) no studies have prospectively evaluated the utility of a Stim-Tg measurement after total thyroidectomy as selection criteria for RRA administration. However, our center and others have recognized the utility of a stimulated postsurgical (pre-RRA) serum Tg. Numerous studies have shown that postoperative/pre-RRA Stim-Tg can predict disease-free remission, metastases, and mortality in WDTC.\(^{18–22}\) Other studies have shown this parameter to be useful in predicting future risk status\(^{23}\) and \(^{131}\)I uptake.\(^{24,25}\) Given these advantages, researchers have suggested that postoperative/preablative Tg can be used for treatment planning, including adjuvant RRA therapy.\(^{23,24}\)

Based upon previous studies from our center on the clinical significance of pre-RRA Stim-Tg,\(^{22,26}\) the primary objective of the current study was to prospectively determine whether a postsurgical Stim-Tg performed approximately 3 months after total thyroidectomy could be effectively used in RRA decision-making among low-risk patients with WDTC. By applying such a biochemical parameter, unnecessary RRA administration could be avoided for those patients already unlikely to have residual/recurrent WDTC, while recommending treatment for those at higher risk for residual/recurrent WDTC (significantly elevated Stim-Tg values). We also compared the results of this novel approach to existing guidelines for RRA selection recommended by the aforementioned organizations/centers.

PATIENTS AND METHODS

Surgical Management. All patients had an initial total or subsequent completion thyroidectomy, performed at Mount Sinai Hospital, Toronto, Canada. A total/completion thyroidectomy was the routine goal for all surgeries performed on patients in this study. Central or lateral dissections were not routinely performed by our surgeons. The central compartment was grossly examined (inspection and palpation) for evident pathology and when suspicious nodes were detected, a therapeutic level VI dissection was performed on the ipsilateral paratracheal nodes for the involved side. No patient in the study received a lateral neck dissection at the time of total thyroidectomy.

Patient Selection Criteria. Only patients with low-risk papillary thyroid cancer (including follicular variants) were included in this study. Low-risk was defined as patients with WDTC with pathology primarily limited to the thyroid gland, with no metastatic lymph nodes outside the central compartment, and without evidence of extrathyroidal extension or distant metastases. Extrathyroidal extension was determined by gross inspection at surgery or by microscopic examination by pathology. This included any extracapsular or surgical margin extension as seen by the pathologist. Patients with detectable anti-thyroglobulin antibodies (TgAb), measured by 2 independent methods, were excluded from this study, because TgAb may interfere with the accuracy of the Stim-Tg measurement.\(^{27}\) Among approximately 850 patients followed postsurgically by 1 endocrinologist (P.G.W.) at our institution between January 1, 2000, and December 31, 2008, a total of 104 patients were selected for the study. This discrepancy was due to many referred patients not having total thyroidectomies and approximately 15% to 20% of eligible patients having anti-Tg antibody interference, which thereby excluded them from our study. As well, some patients had already received RRA before their referral, and thus could not be entered into the study protocol. Additionally, all patients having extrathyroidal extension and metastases were not included.

It should also be noted that the patients available for selection to this study represent a portion of patients undergoing thyroidectomy at our institution. Of the more than 150 cases performed at our institution each year, only some are referred to the practice of the investigator (P.G.W.), whereas others are cared for by other physicians. This too explains why a small proportion of patients, relative to the high volume of patients at our institution, were selected for this study.

Protocol. Selection for RRA was based on the following strategy, herein titled the Stim-Tg Protocol, and will be referred to as such from herein. After thyroidectomy, all patients were placed on thyroid hormone suppression and underwent a TSH Stim-Tg tests 3 months postoperatively. A stimulated thyroglobulin test was defined as a Tg value observed when a TSH greater than 25 mIU/L was achieved. Stimulation was achieved by 1 of 3 protocols: 9-
day withdrawal from triiodothyronine, 22-day withdrawal from L-thyroxine, or stimulation by recombinant human (rh) TSH (Thyrogen, Cambridge, MA) injection. The protocol for rhTSH stimulation was a 0.9-mg intramuscular (IM) injection on days 1 and 2, and a serum thyroglobulin measurement on day 5. A detectable Stim-Tg was defined by a value of 1 μg/L or greater.

The cohort was subsequently divided according to initial Stim-Tg levels into 3 subgroups: undetectable (<1 μg/L), 1–5 μg/L, and >5 μg/L. Patients with undetectable Stim-Tg measurements were informed that there was no indication for immediate RRA and that there was a possibility that the surgical procedure was curative. They were followed with long-term surveillance (regular neck ultrasound scans and repeat Stim-Tg tests). Based upon our previous knowledge of pre-RRA Stim-Tg and risk for continuing residual/recurrent disease after surgery, all patients with a Stim-Tg value >5 μg/L were strongly advised to proceed with RRA. Patients with Stim-Tg measurements of ≥1 μg/L but <5 μg/L were given the option of deferring immediate RRA therapy in favor of long-term surveillance. A schematic of this protocol is outlined in Figure 1.

All patients were given the option of undergoing immediate RRA regardless of their Stim-Tg values. All patients who did not receive RRA were followed on long-term thyroid hormone suppression therapy (THST) and examined at regular intervals for possible disease recurrence with repeat Stim-Tg, neck ultrasound scan studies, and other imaging and biopsy studies when indicated. All patients who underwent RRA received 131I whole body scans (WBS) 7 days after RRA treatment.

This study was approved by the Research Ethics Board of Mount Sinai Hospital, Toronto, Canada (No. 08-0120-C).

**Biochemical Measurements.** All assays were performed in the Department of Pathology and Laboratory Medicine at Mount Sinai Hospital (Toronto, Ontario, Canada). All thyroglobulin measurements were performed in conjunction with thyrotropin and thyroglobulin antibody measurements. The serum thyroglobulin was measured by a chemiluminescent immunometric assay (Immulite 2000, Diagnostic Products, Los Angeles, CA) with a lower detection limit of 0.9 μg/L. The serum thyrotropin was measured using a third-generation thyrotropin immunometric assay (Immulite 2000) with a lower detection limit of 0.01 mIU/L. The anti-thyroglobulin antibody status was ascertained by 2 separate methods (Immulite 2000 assay, detection limit 20 kIU/L (normal values <20 kIU/L) and the Pharmacia thyroglobulin antibody EIA kit using a Personal Lab Analyzer (BioChem ImmunoSystems, Montreal, Canada), detection limit

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**FIGURE 1.** Radioiodine remnant ablation selection protocol using postsurgical stimulated thyroglobulin for low-risk WDTC. TSH, thyroid stimulating hormone; RRA, radioiodine remnant ablation; THST, thyroid hormone suppression therapy; U/S, ultrasound; Stim-Tg, stimulated serum thyroglobulin.
60 IU/L (normal values <60 IU/L). Individuals with undetectable antibody levels (<20 kIU/L by Immulite and <60 IU/L by EIA kit) were considered to have no interfering anti-thyroglobulin antibodies.

Analysis. Using the aforementioned Stim-Tg subgroups, the total number of RRA treatments were subdivided and calculated as percentages of their respective groups.

As a control for our analysis, we calculated the percentage of patients in our cohort who would have been selected to receive RRA on the basis of existing RRA guidelines (ATA, BTA, ETA, and the Mayo Clinic; Table 1). The recommendation in favor of RRA was considered positive for any patient who did not meet the low-risk criteria of a given RRA guideline. Statistical comparisons between the Stim-Tg Protocol and existing RRA guidelines were performed using chi-square tests. Statistical analyses were performed using SPSS for Windows 15.0 (SPSS, Chicago, IL).

RESULTS

Cohort Characteristics. Demographic and histopathologic data for the 104 selected patients is outlined in Table 2. As commonly observed in most centers, the low-risk WDTC cohort consisted primarily of women over the age of 45, with a mean age of 51.2 years. All patients had papillary carcinoma; of these, 40 patients (38.5%) had classic papillary, 56 patients (53.9%) had follicular variants, and 8 patients (7.7%) had Hürthle cell variants. More than half of the patients had multifocal thyroid tumors. Eight patients (7.7%) had positive lymph nodes for thyroid carcinoma—a maximum of 4 positive nodes per patient, all of which were contained in the central compartment (level VI) and had a central compartment dissection performed.

Tumor sizes ranged from 0.2 cm to 6.8 cm, with a mean diameter of 1.8 cm. Thirty-seven patients (35.6%) had tumors smaller than 1 cm, of which 21 (56.8%) were multifocal. The mean duration of follow-up was 2.9 years (range, 0.35–10.3 years). Of the 104 patients, 20 had a follow-up time of less than 1 year, whereas 21 had a follow-up time between 1–2 years.

Initial Stimulated Thyroglobulin Measurements. The results of postsurgical Stim-Tg tests performed after thyroidectomy are summarized in Table 3, according to the Stim-Tg Protocol. TSH stimulation was achieved by triiodothyronine hormone withdrawal in 59 patients (56.7%), by L-thyroxine withdrawal in 15 patients (14.4%), and by recombinant human TSH injection (Thyrogen) in 30 patients (28.9%; data not shown). After thyroidectomy, 59 patients (56.7%) had undetectable Stim-Tg

<table>
<thead>
<tr>
<th>Table 2. Patient cohort characteristics.</th>
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<tr>
<td>Clinical variable</td>
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<td>------------------------------------------</td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td>Age at surgery</td>
</tr>
<tr>
<td>Duration of follow-up</td>
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<tr>
<td>Pathology</td>
</tr>
<tr>
<td>Tumor foci</td>
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<tr>
<td>Nodal involvement</td>
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<tr>
<td>Tumor size</td>
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<td>Mean 1.8 cm</td>
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*Values represent number (%) except as otherwise stated.
†Positive nodal involvement was defined as any lymph node positive for metastatic papillary carcinoma. In these patients, all nodes were contained in the central compartment (level VI).

<table>
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<th>Table 3. Breakdown of postsurgical Stim-Tg measurements and corresponding RRA administration rates.</th>
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<td>Stim-Tg subgroup</td>
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<td>-----------------</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>&lt;1 µg/L</td>
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<tr>
<td>1–5 µg/L</td>
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<tr>
<td>&gt;5 µg/L</td>
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<tr>
<td>Total</td>
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Abbreviations: Stim-Tg, stimulated thyroglobulin; RRA, radioiodine remnant ablation.
levels, 35 patients (33.7%) had Tg levels of 1–5 lµg/L, and 10 patients (9.6%) had Stim-Tg levels >5 lµg/L.

Radioiodine Remnant Ablation Administration Rates. The details of RRA administered to the 3 Stim-Tg subgroups are summarized in Table 3. The average dose of RRA given was 86.7 mCi, with a range of 60 to 100 mCi. RRA was administered to 1 of 59 patients (1.7%) with an undetectable Stim-Tg, a decision based on patient preference. Nine of 10 patients (90%) with Stim-Tg >5 lµg/L received RRA, as recommended by the treating physician. The single patient in this group not receiving RRA had renal failure requiring hemodialysis, and, therefore, RRA was deferred, especially considering her neck ultrasound scan was negative. Among the patients with Stim-Tg 1–5 lµg/L, 6 of 35 patients (17.1%) received RRA based on both patient preferences and review of clinical risk factors (ie, increasing Stim-Tg values and presence of lymph node positivity). Based upon these considerations, the total number of patients receiving RRA in our cohort of 104 patients after the Stim-Tg Protocol was 16 (15.4%). Post-RRA WBSs showed 131I uptake in the region of the thyroid bed for all patients, with the exception of the single patient who had no uptake in association with an undetectable Stim-Tg (data not shown).

Comparison of Stimulated Thyroglobulin Protocol with Existing Radioiodine Remnant Ablation Guidelines. Theoretically, applying the RRA guidelines proposed by the ETA, BTA, and ATA to the study cohort would result in RRA administration rates seen in Table 4. Chi-square analysis showed that the rates of RRA administration according to ETA, BTA, and ATA guidelines were significantly higher than the Stim-Tg Protocol, chi-square (1, n = 103) = 99.7 (ETA); 79.2 (BTA); 57.8 (ATA); p < .0001. Applying the Mayo Clinic selection criteria to our cohort would yield a slightly higher rate of RRA administration (17.3% vs 15.4%); however, this difference was not statistically significant chi-square (1, n = 103) = 0.14, p > .5.

Follow-Up on Patients Not Receiving Radioiodine Remnant Ablation. To date, all patients in the study with initial undetectable serum Stim-Tg have had no evidence of residual/recurrent disease based on repeat serial follow-up Stim-Tg tests and neck ultrasound studies at 6–12 month intervals (mean, 3.3 years). Furthermore, of the patients in the 1–5 lµg/L subgroup not initially given RRA (followed serially for an average of 3.0 years), only 1 of 29 (3.5%) subsequently received RRA on the basis of suspected clinical risk for residual disease.

Follow-Up on Patients Receiving Radioiodine Remnant Ablation. The 16 patients receiving initial RRA treatment after surgery have been followed for an average of 2.6 years after RRA administration (data not shown). Of these patients, 14 (87.5%) have subsequently had negative Stim-Tg tests and neck ultrasound studies. The remaining 2 patients have required further treatment by either additional RRA administration or surgery due to persistently high Stim-Tg values and are continuing to be monitored closely.

DISCUSSION

Our study has demonstrated that RRA administration rates can be dramatically reduced with the use of Stim-Tg 3 months postsurgery. Much of this reduction is possible by performing a total thyroidectomy and selective central compartment neck dissection (ie, level VI) when indicated, that leaves minimal residual thyroid tissue and allows for Stim-Tg to be a more helpful measure of recurrent disease (as opposed to normal residual tissue) in follow-up.

Table 4. Comparison of RRA administration rates: Stim-Tg protocol versus current guidelines.

<table>
<thead>
<tr>
<th>RRA administration</th>
<th>S-Tg Protocol</th>
<th>ETA (10)</th>
<th>BTA (11)</th>
<th>ATA (12)</th>
<th>Mayo Clinic (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablated, n (%)</td>
<td>16 (15.4)</td>
<td>88 (84.6)</td>
<td>80 (76.9)</td>
<td>70 (67.3)</td>
<td>18 (17.3)</td>
</tr>
<tr>
<td>Not ablated, n (%)</td>
<td>88 (84.6)</td>
<td>16 (15.4)</td>
<td>24 (23.1)</td>
<td>34 (32.7)</td>
<td>86 (82.7)</td>
</tr>
</tbody>
</table>

Abbreviations: RRA, radioiodine remnant ablation; S-Tg, stimulated thyroglobulin; ETA, European Thyroid Association; BTA, British Thyroid Association; ATA, American Thyroid Association.
The debate over the efficacy of RRA stems from the lack of definitive evidence in its ability to benefit low-risk patients. Despite assertions that RRA benefits low-risk patients by reducing recurrence and mortality, others have shown that RRA impact on recurrence or mortality is questionable. Additionally, recent meta-analyses have continued to show that RRA administration may not lead to decreased recurrence or mortality in low-risk patients. Furthermore, there has yet to be any long-term randomized controlled trials that prove the efficacy of RRA on thyroid cancer-related outcomes. To resolve these controversies, there is a need for a more selective approach to RRA decision-making based upon a useful postoperative parameter. In the current study, we evaluated the use of postsurgical TSH-Stim-Tg as a useful parameter for RRA selection in low-risk WDTC. This study is an extension of previous studies from our center that demonstrated the utility of postsurgical Stim-Tg measurements in predicting long-term Stim-Tg status and thereby offers a novel application of this parameter for RRA selection in low-risk patients with WDTC.

Using the proposed Stim-Tg Protocol, the majority of low-risk patients with WDTC (56.7%) had an undetectable Stim-Tg (<1 μg/L) after the required surgery. These patients were considered virtually free of any significant thyroid cancer, and thereby did not receive immediate RRA therapy. Moreover, a mean follow-up of 3.3 years on such low-risk patients has failed to detect residual disease by repeat Stim-Tg measurements and ultrasound scans. This demonstrates that a well-performed total thyroidectomy and selective therapeutic central neck dissection (performed on 8 patients [7.7%]) can prevent the need for future radioiodine, as evidenced by a negative Stim-Tg 3 months after thyroidectomy. Although there have been reports of positive WBSs and detectable residual thyroid cancer despite a stimulated Tg measurement <2 μg/L, (references 35, 36 therein), no patient in our cohort has shown evidence of undifferentiated thyroid carcinoma or anti-thyroglobulin antibody positivity (measured by 2 assays), both of which could have contributed to a false-negative Stim-Tg result. Furthermore, because all selected patients in the current study cohort were at low-risk for aggressive disease, they were also at a decreased risk for developing unsuspected metastatic disease. We therefore believe that the clinical risk of a falsely negative Stim-Tg is low and that the vast majority of patients with initially undetectable Stim-Tg have been rendered disease-free by initial surgery. In our view, this very low chance of a false-negative Stim-Tg does not justify routine RRA administration to patients with an undetectable Stim-Tg.

We have also identified a subgroup of patients with a Stim-Tg value >5 μg/L, all of whom were selected for RRA therapy. Notably, the prevalence of such a finding in our cohort was only 10 of 104 patients (9.6%). The lower cutoff value of 5 μg/L was chosen on the basis of previous studies from our center in which we found that patients with Stim-Tg values greater than 12.5 μg/L before RRA administration had an increased risk for residual/recurrent disease, as documented by subsequent long-term follow-up Stim-Tg values and/or imaging procedures. Thus, in the present study, setting a conservative and therefore lower cutoff value of 5 μg/L was arbitrarily used as a protective measure against a potential risk for residual/recurrent thyroid cancer.

Among the remaining low-risk patients with WDTC, 35 (33.7%) had a Stim-Tg value of 1–5 μg/L. Patients in this intermediate Stim-Tg subgroup were carefully evaluated for residual disease risk on the basis of several parameters, such as aggressive variants of papillary carcinomas, presence of detectable metastatic lymph nodes at surgery, or patient preference to undertake RRA. In this intermediate subgroup, only 6 patients (17.1%) received RRA for these reasons, whereas the remaining 29 patients (82.9%) did not receive immediate RRA. The latter patients had regular follow-ups with Stim-Tg studies in combination with neck ultrasounds at 6- to 12-month intervals to monitor for disease recurrence. To date, follow-up in this nonablated subgroup has failed to show any rise in the Stim-Tg above 5 μg/L and failed to detect any significant changes on ultrasound scan or other imaging procedures. We therefore conclude that RRA therapy is as yet unjustified for the remaining 29 patients in this subgroup. However, given that the mean follow-up to date for patients in this subgroup is 3.0 years, it must be acknowledged that a longer follow-up interval will be required to ultimately confirm the safety of deferring RRA therapy in this subgroup.

Applying Mayo Clinic guidelines to our cohort revealed similar absolute values of RRA administration rates to the Stim-Tg Protocol (17.3% by the Mayo Clinic vs 15.4% by the Stim-
Tg Protocol). However, only 5 patients in common would receive RRA by both guidelines, indicating that selection criteria based on the Stim-Tg Protocol did not precisely agree with RRA selection by using Mayo Clinic guidelines. These disparities, coupled with the overall marked decrease in RRA administration by the Stim-Tg Protocol, strongly suggest that the clinicopathologic criteria, which receive primary importance in the ETA, BTA, ATA, and Mayo Clinic RRA selection guidelines, do not generally correlate with Stim-Tg levels. These observations further substantiate previous reports from our center indicating that age and tumor size do not reliably predict postsurgical Stim-Tg values.

The significant decrease in RRA administration has practical relevance to recent developments in the care for patients with WDTC. A recent study by Bonnet et al. achieved a 30% reduction in RRA therapy (as compared to ETA RRA recommendations) in patients with tumors <2 cm and no lymph node involvement by performing extensive prophylactic central and lateral neck dissections. By comparison, patients in the present study who fit these low-risk criteria (tumors <2 cm, no lymph node involvement, $n=32$) achieved an 87.0% reduction in RRA administration rates using the Stim-Tg Protocol and total thyroidectomies with selective therapeutic central compartment dissections (performed on 8 patients [7.7%]). Furthermore, in the remaining patients in our cohort ($n=58$), the Stim-Tg Protocol achieved significant (82.3%) reduction when compared to ETA RRA guidelines. Moreover, these reductions in RRA administrations were achieved without subjecting patients to extensive prophylactic central and lateral neck dissection with its associated morbidity risks and health care costs.

A significant proportion of patients (84.6%) avoided RRA therapy and were therefore spared potential side effects, which include sialadenitis, lacrimal gland/duct injury, and infertility, and risks for secondary malignancies even 3 decades after treatment. Furthermore, reducing the frequency of postoperative RRA administration achieved a considerable reduction in health care costs. For example, a previous report from our center showed an average cost saving of $4694 Canadian dollars per patient (including materials, administration, and hospital stay) for each 100 mCi (3700 MBq) treatment.

It must be acknowledged that the currently recommended Stim-Tg Protocol for RRA selection is dependent upon a number of important factors that are essential for its successful application. First, thyroidectomies should be performed by an expert surgeon who is capable of removing nearly all thyroid tissue at the initial operation or upon a completion thyroidectomy. An incomplete thyroidectomy would reduce the accuracy of the present RRA selection protocol due to thyroglobulin production from excess residual normal thyroid tissue. Second, all patients included in this protocol did not have detectable interfering serum anti-thyroglobulin antibodies as measured by 2 independent methods. This selection criteria is essential to ensure that misleading Stim-Tg results are avoided because the presence of antibodies in patient samples can interfere with the validity of serum Tg measurement. Third, it should be emphasized that this protocol applies only to patients with low-risk papillary carcinoma, primarily limited to the thyroid gland and possible central compartment (level VI) involvement. Nevertheless, low-risk WDTC occurs in 70% to 88% of a routine endocrinology referral practice, and the potential impact of the currently proposed Stim-Tg Protocol in reducing RRA administration would be substantial. Finally, we acknowledge that a longer follow-up interval for the proposed Stim-Tg Protocol is necessary to ensure the ultimate efficacy of this approach as a method for RRA selection. Nevertheless, results have been quite encouraging and have been further validated by serial Stim-Tg measurements (for nearly 3 years of follow-up) and imaging studies on the subgroup of patients who have not received RRA. To date, there have been no false negatives among this subgroup (who have been followed for more than 3 years) which would justify the administration of RRA.

Furthermore, although we used a stimulated TSH protocol in the current study, it remains to be clearly established whether the use of an ultrasensitive Tg measurement (while on thyroid hormone TSH suppression) may also yield useful guidelines for postsurgery RRA selection.

CONCLUSION

Stim-Tg measurement performed several months after total thyroidectomy is a useful parameter in assisting RRA decision-making in low-risk
The application of this strategy significantly reduced the rate of RRA administration and its associated side effects, health care costs, and patient inconvenience. The proposed Stim-Tg Protocol shows promise as an objective and individualized parameter to assist in RRA selection in low-risk WDTC. Further prospective validation by follow-up long-term surveillance will be required to confirm the efficacy of the proposed Stim-Tg Protocol.

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**COMMENTARY**

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Vaisman and colleagues are to be applauded for further advancing the concept of customizing the treatment of patients with well-differentiated thyroid cancer (WDTC). These authors have built upon previous work that predicated the decision to administer adjuvant radioactive iodine ablation on measurable biochemical findings rather than clinicopathologic criteria (for example, age, size, or other co-dependent factors). This premise is logical, since sometimes the initial surgical procedure is very likely to have been curative (as when the postoperative stimulated thyroglobulin is unmeasurable). By
contrast, when managing patients with upper aerodigestive tract squamous cell carcinoma, adjuvant treatment is often pursued because a comparable metric for determining the completeness of the initial therapy is not available, aside from surgical margin analysis or negative PET findings (neither of which is sufficiently reliable). While the follow-up, is too short to draw definitive conclusions regarding the durability of cure (nearly half of the patients have fewer than 2 years of follow-up), the findings reported by the Walfish group are nevertheless impressive and encouraging.

The impact of this data-driven approach is not only a more objective treatment algorithm, but also one that has the potential to spare many patients unnecessary additional treatment for a disease that may have already been rendered cured. This represents one aspect of a broader trend in which dose-reduction strategies have proven effective and beneficial. It has recently been demonstrated that remnant ablation doses as low as 30 mCi are as effective as the traditional 100 mCi in preventing tumor recurrence,3 paving the way for a paradigm shift in the adjuvant treatment of well-differentiated thyroid cancers.

The Vaisman report is particularly timely in the current climate of increasing cost pressures, and because of the recent alert shared by the American Thyroid Association for the community of physicians involved in the care of patients with thyroid diseases: “The global radiisotope shortage is now impacting the supply of I^{131} . . . . . . . . . this shortage has led to prioritizing the use of existing I^{131} products for those patients with thyroid cancer who have urgency of treatment.” Therefore, although the authors focused on the side effects and costs associated with routine administration of remnant ablation, the rational allocation of what has become a limited and precious resource now represents yet another compelling reason to be receptive to ways in which to economize its use.

Finally, the notions proposed by Vaisman et al are entirely consistent with the emerging trend of personalized medical care. Rather than applying a “one-size-fits-all” approach to patients with diseases that often manifest a heterogeneous biologic behavior, it seems prudent to make every effort to customize the treatment to the patient and their disease (or as Ian Hay has been quoted as saying, “let the punishment fit the crime”).

REFERENCEs