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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Utility of Early Postoperative Unstimulated Thyroglobulin in Influencing Decision Making in Patients with Papillary Thyroid Carcinoma

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ABSTRACT

Background. Serum thyroglobulin is used to screen for disease persistence or recurrence of papillary thyroid carcinoma (PTC). We sought to assess the utility of early postoperative unstimulated thyroglobulin levels (uTg) as a decision-making tool to guide the use of radioactive iodine (RAI) in PTC patients.

Methods. We performed a retrospective analysis of a prospectively maintained database of patients surgically treated for PTC from 2015 to 2017. We analyzed uTg approximately 6 weeks postoperatively. Patients undergoing total thyroidectomy or completion thyroidectomy were included in the study, and patients were analyzed according to postoperative uTg and receipt of RAI.

Results. A total of 255 patients were analyzed, with 134 patients meeting the inclusion criteria. The median postoperative uTg was 0.3 ng/mL. Overall, 49.3% (66/134) of patients achieved the target uTg of $\leq$ 0.2 ng/mL at a mean time of 7.9 $\pm$ 0.3 weeks postoperatively; 60% (40/66) of patients who achieved uTg $\leq$ 0.2 ng/mL postoperatively did not receive RAI. A uTg $\leq$ 0.2 ng/mL was maintained at 6 months in 98.1% of patients, including 100% of patients who received RAI and 96.7% of patients who did not receive RAI (p = 0.8). Of those who did not receive RAI, none demonstrated structural disease recurrence on 6-month ultrasound. Patients with early postoperative uTg > 0.2–2.0 ng/mL showed benefit from RAI, while patients with uTg > 2.0 ng/mL did not achieve the targeted uTg level regardless of receipt of RAI.

Conclusions. Postoperative uTg may be used to guide the use of RAI. Achieving near-undetectable uTg within 6 weeks postoperatively could aid providers in assessing disease burden and minimize RAI use for patients with a low-risk of disease recurrence. Continued follow-up is necessary to accurately determine long-term outcomes.

The management of well-differentiated thyroid carcinoma is evolving. Historically, the overwhelming majority of patients with thyroid cancer were treated with three modalities—surgery, radioactive iodine (RAI), and thyroid hormone suppression therapy.[1] As the overall survival of thyroid carcinoma is > 98%, treatment strategies are now more individualized and are based on multiple factors, including risk of recurrence.[2] A three-tiered risk stratification system for differentiated thyroid carcinoma was initially developed, and later revised, as a part of the 2009 and 2015 American Thyroid Association (ATA) guidelines, respectively, in which the risk of recurrence is based on pathologic features and postoperative serum thyroglobulin levels.[3,4]

Serum thyroglobulin measurements coupled with cervical ultrasonography are the mainstay for long-term screening for disease persistence or recurrence in patients with papillary thyroid carcinoma (PTC) following total thyroidectomy. Thyroglobulin is a protein precursor of thyroid hormone produced by both normal thyroid cells and thyroid cancer cells.[5,6] The most recent ATA guidelines suggest thyroglobulin levels may be used as a determining factor to guide clinical management and use of RAI.[4]

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A majority of prior studies assessed the response to therapy following initial total thyroidectomy and RAI.[4,7] Most frequently, the response to therapy is assessed using thyroid-stimulating hormone (TSH)-stimulated thyroglobulin values obtained 6–18 months after initial therapy.[4,8,9] Few studies have examined response to therapy using unstimulated thyroglobulin (uTg).[4,10] The majority of those who have evaluated uTg first assess levels at 3 months or more after initial therapy.[4,10] Postoperative thyroglobulin levels reach a nadir by 3–4 weeks. Earlier classification of response to surgery may aid in treatment strategy and help determine the need for RAI. In this study, we aimed to assess the utility of early postoperative uTg levels as a decision-making tool to guide the use of RAI in patients with PTC.

METHODS

Following Institutional Review Board approval from the University of Wisconsin, we performed a retrospective analysis of a prospectively maintained database of patients surgically treated for PTC from 2015 to 2017. All patients underwent total thyroidectomy or completion thyroidectomy between 2015 and 2017. Central or lateral neck dissection was performed selectively for patients with evidence of clinically positive lymphadenopathy identified based on clinical examination, imaging, pathologic biopsy confirmation, or intraoperative assessment. Inclusion criteria included patients who underwent surgical management for PTC, while exclusion criteria included patients with follicular thyroid carcinoma, poorly differentiated thyroid carcinoma (defined as poorly differentiated thyroid carcinoma, medullary thyroid carcinoma, or anaplastic thyroid carcinoma on surgical pathology), patients undergoing thyroid lobectomy only, and/or patients with incomplete preoperative or postoperative data. Patients were also excluded if TSH suppression was not achieved or if the patient had evidence of thyroglobulin antibodies as this has been shown to interfere with the thyroglobulin assay.[11]

uTg levels were evaluated approximately 6 weeks postoperatively. Thyroglobulin assays were performed using the appropriate degree of TSH suppression recommended by the most recent ATA management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer.[4] These guidelines recommend the status of thyroid carcinoma patients post total thyroidectomy be treated with initial TSH suppression to 0.1–0.5 mU/L for intermediate risk, 0.5–2.0 mU/L for low risk with undetectable thyroglobulin levels, and 0.1–0.5 mU/L for low risk with low thyroglobulin levels. A uTg level $\leq$ 0.2 ng/mL was used to define excellent response postoperatively following total thyroidectomy as an excellent response to therapy is considered the absence of structural or functional disease on imaging and either TSH-stimulated thyroglobulin $<$ 1 ng/mL or suppressed (unstimulated) thyroglobulin $<$ 0.2 ng/mL.[4] Ultrasounds at 6 months and 1 year postoperatively were also evaluated for structural evidence of persistent or recurrent disease. As previously described by Bates and colleagues, persistent disease is defined as a uTg $>$ 0.2 ng/mL, abnormal cervical ultrasonography, or persistent elevation of thyroglobulin antibodies at 6 months after initial therapy.[12] Recurrent disease is defined as evidence of disease after previously achieving an undetectable thyroglobulin level (uTg $\leq$ 0.2 ng/mL or stimulated thyroglobulin $<$ 1.0 ng/mL), negative thyroglobulin antibodies, and negative cervical ultrasonography.[12] For analysis, patients were subdivided into groups based on whether they received or did not receive RAI postoperatively, and on 6-week postoperative uTg levels. Postoperative uTg levels were classified into three groups, including uTg $\leq$ 0.2 ng/mL (which suggests no evidence of disease), uTg $>$ 0.2–2.0 ng/mL (suggestive of either microscopic benign remnant thyroid tissue or microscopic persistent disease), and uTg $>$ 2.0 ng/mL (suggestive of macroscopic benign remnant thyroid tissue or macroscopic persistent disease). Patients were then analyzed for evidence of persistent or recurrent disease at 6 months, based on uTg level and structural disease on ultrasound. Statistical analysis was performed using Student's *t* test or the Mann–Whitney U test, as appropriate. A p value $\leq$ 0.05 was determined to be significant. Data are expressed as number (%) or mean $\pm$ standard error of the mean, unless otherwise stated.

RESULTS

Between 2015 and 2017, 255 patients with PTC were treated surgically at the University of Wisconsin, of whom 134 patients met the inclusion criteria. Mean patient age was 45 $\pm$ 1.2 years. Female patients comprised 74.6% of the study population and 92.5% were Caucasian. The mean thyroid nodule size on pathologic specimen was 2.0 $\pm$ 0.14 cm. Thirty-one patients (23.1%) were found to have a papillary thyroid microcarcinoma on final pathologic specimen evaluation. Seventy-two patients (53.7%) received RAI postoperatively (Table 1). RAI administration and dosing was provider-dependent and was determined by the endocrinologist and nuclear medicine provider based on final pathology and after the initial uptake scan had been performed.

The median postoperative uTg level across all patients was 0.3 ng/mL. The targeted goal uTg level of $\leq$ 0.2 ng/mL was achieved in 49.3% (66/134) of patients at a mean

TABLE 1 Patient demographics

Characteristics	
Mean age, years[a]	45.2 ± 1.2
Female sex	100 (74.6%)
Caucasian	124 (92.5%)
Mean nodule size, cm[a]	2.0 ± 0.14
Papillary thyroid microcarcinoma	31 (23.1%)
Received RAI	72 (53.7%)
Median postoperative uTG, ng/mL	0.3
Postoperative uTG range, ng/mL	119.3

RAI radioactive iodine, *uTG* unstimulated thyroglobulin

[a]Reported as the standard error of the mean

time of 7.9 ± 0.3 weeks postoperatively. Sixty percent (40/66) of patients who achieved the intended uTg level postoperatively did not receive RAI (no RAI). A uTg level ≤ 0.2 ng/mL was maintained at 6 months in 98.1% of those patients, including 100% of patients who received RAI and 96.7% of patients who did not receive RAI ($p = 0.8$) (Fig. 1). At 1 year postoperatively, 94.1% of patients in the no RAI group and 100% of patients who received RAI had no biochemical evidence of disease (based on maintenance of uTg ≤ 0.2 ng/mL; $p = 0.1$), and had no structural evidence of disease on comprehensive cervical ultrasonographic examination.

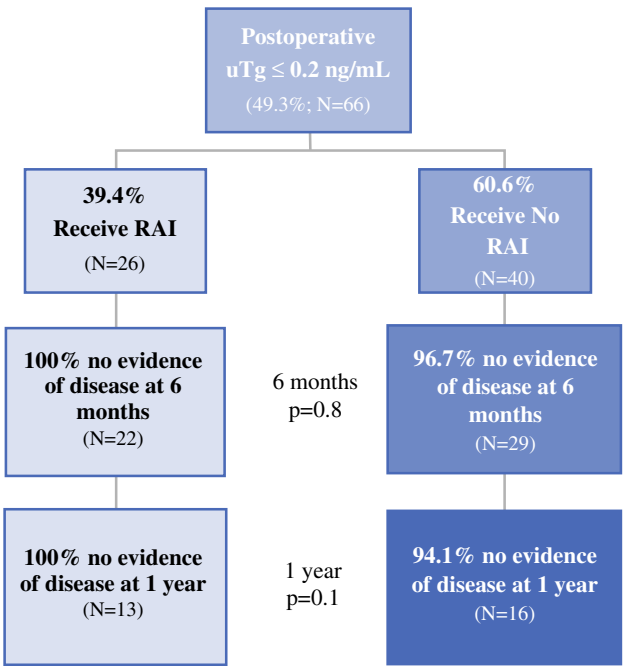

FIG. 1 Longitudinal follow-up of patients achieving goal uTg. *RAI* radioactive iodine, *uTG* unstimulated thyroglobulin

To further evaluate the significance of early postoperative uTg levels, patients were categorized into three groups according to the uTg level at 6 weeks postoperatively. The groups were classified as no evidence of disease (uTg ≤ 0.2 ng/mL), suggestive of either microscopic benign remnant thyroid tissue or microscopic persistent disease (uTg > 0.2–2.0 ng/mL), and suggestive of macroscopic benign remnant thyroid tissue or macroscopic persistent disease (uTg > 2.0 ng/mL). Patients were then subdivided based on whether or not they received RAI. Thirty-five percent (47/134) of patients from the original cohort had a postoperative uTg > 0.2–2.0 ng/mL, and 15.7% (21/134) of patients had a postoperative uTg > 2.0 ng/mL. Sixty-nine percent of patients with a postoperative uTg > 0.2–2.0 ng/mL achieved the goal uTg ≤ 0.2 ng/mL at 6 months postoperatively after receiving RAI, while only 15.4% of patients with postoperative uTg > 0.2–2.0 ng/mL achieved the goal uTg at 6 months without RAI ($p = 0.002$). Of those patients with an initial postoperative uTg > 2.0 ng/mL, only 30.8% of patients who received RAI and 25.0% who did not receive RAI achieved a uTg ≤ 0.2 ng/mL at 6 months postoperatively ($p = 0.4$) (Fig. 2).

DISCUSSION

Among all patients in this cohort with well-differentiated papillary thyroid cancer, 50% achieved a uTg ≤ 0.2 ng/mL by 8 weeks postoperatively, suggesting appropriate initial surgical treatment. There was no increase in recurrence in patients achieving uTg ≤ 0.2 ng/mL in the early postoperative course who did not receive RAI compared with those who received RAI, based on both biochemical data and ultrasonography at 6 months and 1 year postoperatively. On the other hand, patients with a postoperative uTg of > 0.2–2.0 ng/mL who underwent RAI achieved uTg ≤ 0.2 ng/mL by 6 months significantly more often than those who did not undergo RAI. This suggests that in a group of patients with potential microscopic remnant disease, RAI administration effectively ablates remnant thyroid tissue. Patients with postoperative uTg > 2.0 ng/mL rarely achieved goal uTg at 6 months regardless of RAI administration. Persistent elevation in uTg levels support the likelihood that this group had evidence of macroscopic benign thyroid tissue or macroscopic persistent disease remaining, and argues for further investigation prior to consideration of any RAI treatment.

Previously, risk stratification to predict the likelihood of PTC recurrence was assessed after a decision regarding RAI had already been made.[13] Measuring uTg in the early postoperative course may aid in clinical decision making and can minimize the use of RAI administration, thus

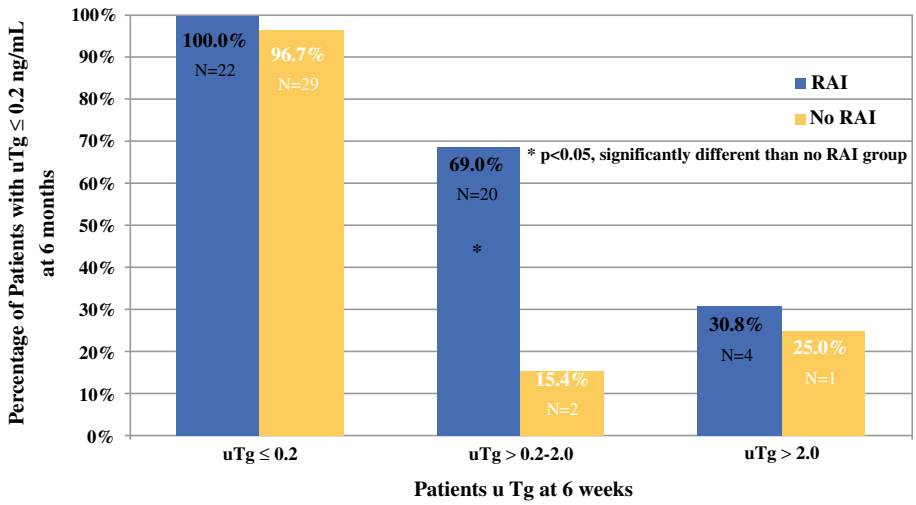

FIG. 2 Percentage of patients maintaining goal uTg at 6 months. *RAI* radioactive iodine, *uTG* unstimulated thyroglobulin

avoiding overtreatment for patients with low risk of disease recurrence. Likewise, recognizing the possibility of macroscopic thyroid remnant or persistent disease allows for further investigation of the source of the persistent uTg level. If further imaging identifies persistent disease in the neck, patients should undergo surgical treatment before any RAI. Alternatively, uTg > 2.0 ng/mL may represent distant metastases. We propose that early postoperative uTg may be used as a decision-making tool to guide the use of RAI in patients with PTC. Based on our results, we propose the following protocol to aid in postoperative decision making (see Fig. 3). Patients with postoperative uTg ≤ 0.2 ng/mL are considered to have an excellent response to therapy and should continue routine follow-up with clinical examination, cervical ultrasonography, and uTg levels.[4] Postoperative uTg > 0.2–2.0 ng/mL represents continued benign remnant thyroid tissue or microscopic persistent disease and likely benefit from RAI administration. uTg > 2.0 ng/mL signifies residual macroscopic thyroid remnant tissue or macroscopic persistent disease, and patients seem to show no significant decrease in uTg level from RAI and therefore warrant re-evaluation of disease burden. If imaging suggests persistent disease in the neck rather than distant metastases, we propose consideration for further surgical intervention prior to RAI administration. This proposal is not meant to be used in isolation as uTg levels should not be the sole determinate of RAI administration. Pathologic characteristics, including extrathyroidal extension, positive margins, vascular invasion, and nodal involvement, should also be taken into account.

Prior studies have also suggested that RAI is not necessary in low-risk papillary thyroid cancer.[5,13] Ibrahimpasic et al.[5] examined uTg levels among patients with low- and intermediate-risk disease. In thir study, postoperative uTg was used as a measure of completeness of resection[5]. Patients with undetectable postoperative uTg levels (uTg < 1 ng/mL) had no significant difference in recurrence-free survival whether they were managed with RAI or not. Now, with a more sensitive assay, the differences in uTg can be assessed at an even more precise level.

Orlov et al.[13] assessed low- and intermediate-risk papillary thyroid cancer patients using stimulated thyroglobulin, at 3 months postoperatively. Patients were then categorized, based on stimulated thyroglobulin level, to receive or not receive RAI.[13] Orlov et al.[13] proposed that patients with a stimulated thyroglobulin level < 1 μg/L should not receive RAI. Patients with stimulated thyroglobulin > 5 μg/L should receive RAI routinely, and those with stimulated thyroglobulin 1–5 μg/L should be further evaluated based on repeat stimulated thyroglobulin level, pathologic features, and patient's comorbidities and attitude toward RAI. Our study similarly proposes a strategy to use thyroglobulin levels for clinical decision making, but using uTg rather than stimulated thyroglobulin levels. Our results suggest that patients with early postoperative uTg ≤ 0.2 ng/mL already achieve an excellent response from surgery and RAI adds no benefit. Patients with early postoperative uTg > 0.2–2.0 ng/mL do benefit from RAI administration as it effectively ablates remnant thyroid tissue, which may allow for easier detection of recurrence in the future.

Our results indicate that if postoperative uTg levels are > 2.0 ng/mL, RAI alone rarely decreases uTg to the target level. In these patients, we propose further evaluation to examine for residual disease burden in the neck or distant metastases. If persistent disease is identified in the neck, we propose the need for further surgical resection (Fig. 3). Many prior studies have evidenced an association between the risk of postoperative complications and surgeon volume.[14,15] What is more, Oltmann et al.[16] demonstrated that the completeness of surgical resection is also associated

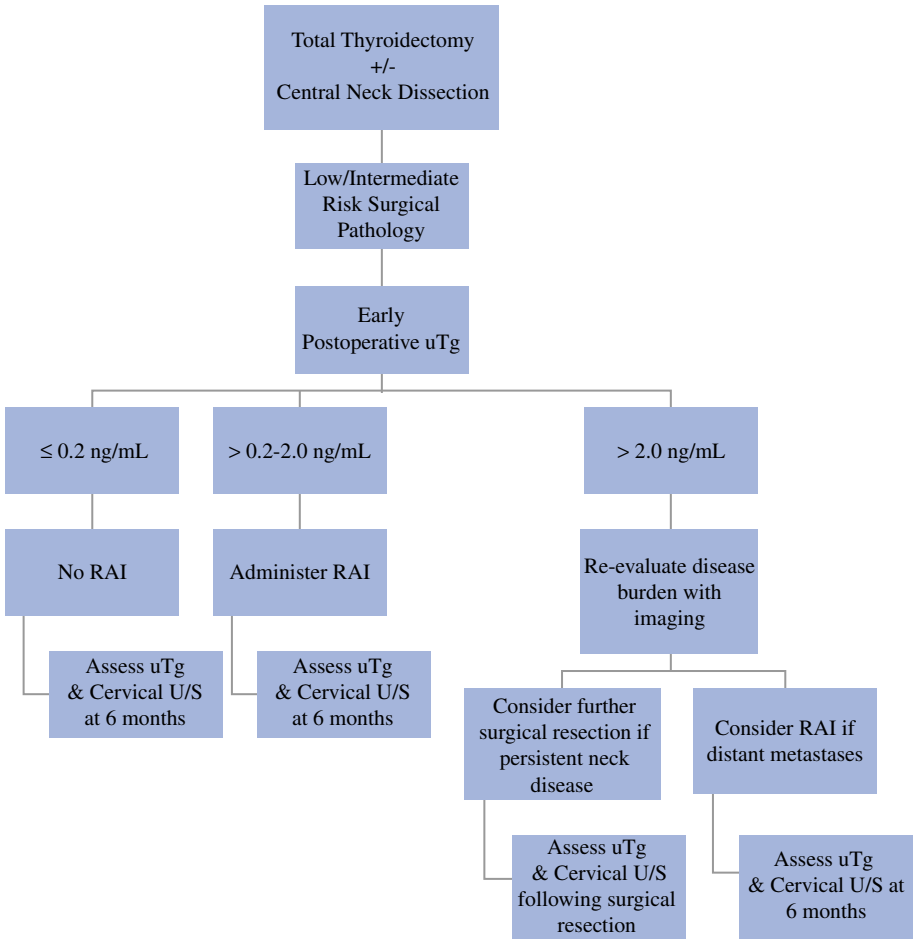

FIG. 3 Proposed post-operative decision-making algorithm based on early postoperative uTg. *RAI* radioactive iodine, *U/S* ultrasonography, *uTG* unstimulated thyroglobulin

with surgeon volume. Therefore, it is prudent to involve a high-volume endocrine surgeon early in the care of these patients. Initial surgical quality is of utmost importance to ensure complete surgical resection of disease as macroscopic disease cannot always be treated with adjuvant RAI administration.

Our analysis does have limitations inherent in its study design. While the data were prospectively collected, they were retrospectively queried. Additionally, longer follow-up is required to make definitive conclusions regarding the proposed strategy's impact on recurrence-free and overall survival. Additionally, some PTCs produce less thyroglobulin.[5] These are often less-differentiated cancer, and, in these cases, thyroglobulin levels are less reliable. Likewise, patients with evidence of thyroglobulin antibodies present cannot be assessed with this method and will require reliance on imaging alone. Patients with thyroglobulin antibodies were excluded from this study. This study was performed in a tertiary referral center with high-volume endocrine surgeons. Patients were often referred from quite a distance away. Therefore, some uTg measurements were not performed at our institution, or using the same assay, which could contribute to the small degree of variability in the results.

CONCLUSIONS

This study supports the use of early postoperative uTg as a predictor of utility of RAI. Patients with uTg considered to have an excellent response from surgery do not require RAI. RAI administration seems to benefit patients with evidence of microscopic disease. However, importantly, patients with evidence of macroscopic thyroid remnant or macroscopic persistent disease based on early postoperative uTg levels warrant further investigation of the source of the persistent uTg level. If further imaging identifies persistent disease in the neck, patients should undergo surgical treatment before any RAI. The use of uTg in such a manner can also provide ongoing critical feedback to the operating surgeons regarding the completeness of resection, providing ample opportunity for ongoing performance improvement.

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