

PROGNOSTIC VALUE OF POSTSURGICAL STIMULATED THYROGLOBULIN LEVELS AFTER INITIAL RADIOACTIVE IODINE THERAPY IN WELL-DIFFERENTIATED THYROID CARCINOMA

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Abstract: *Background.* In well-differentiated thyroid carcinoma, predictors of future positivity of stimulated thyroglobulin (>2 µg/L) after initial radioactive iodine treatment are not known.

Methods. In a retrospective study, we used logistic regression analysis to determine whether postoperative stimulated thyroglobulin measurements and pathologic stage independently predict future stimulated thyroglobulin positivity.

Results. We followed 141 patients with well-differentiated thyroid carcinoma for a median of 35 months; follow-up stimulated thyroglobulin measurements were positive in 20.6% (29/141). The natural logarithm of the postsurgical stimulated thyroglobulin was independently associated with a positive stimulated thyroglobulin at long-term follow-up (odds ratio [OR], 4.44;

95% confidence interval [CI], 2.33–8.45; $p < .001$); there was a trend for a positive association of TNM stage with positive follow-up stimulated thyroglobulin ($p = .054$). Lymph node positivity predicted a positive stimulated thyroglobulin in papillary cancer.

Conclusions. Stimulated thyroglobulin measurements prior to initial radioactive iodine treatment independently predict future stimulated thyroglobulin positivity in well-differentiated thyroid carcinoma. ©2007 Wiley Periodicals, Inc. *Head Neck* 30: 693–700, 2008

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Approximately 26,000 people are diagnosed with thyroid cancer in the United States each year,¹ and the incidence is increasing.² Papillary and follicular carcinoma (well-differentiated thyroid cancer) account for most cases of thyroid cancer.³ The mortality rate for patients with well-differentiated thyroid cancer is low, particularly in individuals seen with early-stage disease.^{2,4} However, life-long monitoring is necessary because recur-

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rence (particularly, local regional disease) is not uncommon, even in patients considered at low risk of thyroid cancer-related death.⁵ Various clinical-pathologic staging systems are known to predict survival in well-differentiated thyroid cancer.⁶ Thyroid cancer classification systems are believed to identify a majority (70% to 85%) of patients who are at low risk of mortality.⁷ The American Joint Committee of Cancer TNM pathologic staging system has been endorsed by the American Thyroid Association for use in well-differentiated thyroid cancer, as it predicts survival, is universally available, is widely accepted for other disease sites, and is a requirement for cancer registries.⁷ However, it is not known whether the TNM classification may predict future disease activity of well-differentiated thyroid cancer, as measured by the surrogate outcome of a positive stimulated thyroglobulin at long-term follow-up after radioactive iodine remnant ablation.

It is well established that measurement of serum thyroglobulin is useful in detecting persistent or recurrent disease in patients with well-differentiated thyroid carcinoma who have undergone total or near-total thyroidectomy and initial radioactive iodine therapy.⁸⁻¹¹ Negative stimulated thyroglobulin measurements after radioactive iodine treatment are considered a surrogate outcome for absence of disease in well-differentiated thyroid carcinoma. Thus, the routine measurement of serum thyroglobulin has been recommended in the follow-up of well-differentiated thyroid carcinoma.^{7,12} Certainly, serum thyroglobulin measurements are meaningful only when interfering antibodies are absent.¹³

Recently, the prognostic value of stimulated thyroglobulin measurements prior to remnant ablation has been explored. Various values of post-surgical thyroglobulin have been found to be significantly associated with the results of posttherapy scans¹⁴ or the presence of disease at long-term follow-up.¹⁵⁻²¹ Our primary objective was to determine whether pathologic disease stage (American Joint Committee of Cancer TNM classification system, 6th edition) and postsurgical thyroglobulin measurements independently predict the presence of a positive stimulated thyroglobulin result in the follow-up of patients with well-differentiated thyroid carcinoma. We also explored whether a simplified staging classification (which distinguishes disease confined to the thyroid compared with more extensive disease), independently predicted a positive stimulated thyroglobulin measurement at follow-up.

PATIENTS AND METHODS

Patients. We reviewed the charts of consecutive patients with well-differentiated thyroid carcinoma followed in a tertiary care thyroidology clinic from 1983 to July 1, 2006, at Mount Sinai Hospital in Toronto, Canada. We included all patients with papillary or follicular thyroid carcinoma (or variants) whose initial surgery was a total or near-total thyroidectomy and who received radioactive iodine remnant ablation. Patients who had at least 1 available stimulated thyroglobulin measurement at the time of ablation (postsurgical thyroglobulin) and at long-term follow-up were included. Patients with a primary solitary papillary carcinoma lesion of less than 1 cm in diameter (uncomplicated microcarcinoma) were excluded, as such patients are typically not treated with radioactive iodine remnant ablation in our clinical practice. Patients with positive anti-thyroglobulin antibodies at the time of the thyroglobulin measurements were excluded. All of the radioactive iodine treatments and biochemical measures procedures were performed at Mount Sinai Hospital. We abstracted demographic, clinical, biochemical, and pathological data. The study was approved by the Ethics Review Board of Mount Sinai Hospital.

Biochemical Measurements. All assays were performed at the Department of Clinical Biochemistry of Mount Sinai Hospital (Toronto, Ontario, Canada). Thyroid-stimulating hormone (TSH) and thyroglobulin antibody measurements were performed concurrently with all measurements of thyroglobulin. The serum thyroglobulin was measured by a chemiluminescent immunometric assay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA). This thyroglobulin assay utilizes the CRM-457 international thyroglobulin standard and has a lower detection limit of 0.9 µg/L. The serum TSH was measured using a third-generation TSH immunometric assay (Immulite 2000, Diagnostic Products Corporation); this assay has a normal range of 0.5 to 5.0 mIU/L and 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 and the Pharmacia thyroglobulin antibody EIA kit using a Personal Lab Analyzer from BioChem Immuno Systems, detection limit 60 IU/L).

Treatment and Follow-Up Protocol and Definitions. All patients underwent a total or near-total thyroidectomy and took tri-iodothyronine postop-

eratively. Patients underwent postoperative radioactive iodine treatment approximately 3 to 4 months after thyroidectomy (after a minimum 2-week period of withdrawal from tri-iodothyronine). The postsurgical thyroglobulin was measured immediately prior to remnant ablation when patients were clinically and biochemically hypothyroid. After radioactive iodine treatment, serum thyroglobulin was routinely measured while patients were taking thyroxine. Patients with undetectable thyroglobulin measurements while on thyroxine therapy ($<1 \mu\text{g/L}$) underwent periodic follow-up measurements of stimulated thyroglobulin (after a 21- or 22-day period of withdrawal from L-thyroxine).²² A positive stimulated thyroglobulin at follow-up was defined by a value $>2 \mu\text{g/L}$ in the absence of anti-thyroglobulin antibodies. For patients who had multiple follow-up stimulated thyroglobulin measurements, the first available measurement was used for the analysis, such that the timing of measurements was relatively comparable among patients. In patients who had detectable thyroglobulin measurements while on thyroxine, the follow-up stimulated thyroglobulin values were obtained when patients were clinically and biochemically hypothyroid, prior to repeat radioactive iodine therapy (a minimum of 2 weeks tri-iodothyronine withdrawal). The American Joint Committee on Cancer (TNM, 6th edition) classification was used²³ to assign pathologic stage. We also examined the predictive ability of a simplified pathologic classification system in which the previously described DeGroot stage²⁴ of I (intrathyroidal disease in absence of lymph node metastases) was compared to more advanced stages of extrathyroidal disease (including DeGroot stage II—lymph node metastases, DeGroot stage III—extrathyroidal invasion, or DeGroot stage IV—distant metastases).

Statistical Analyses. The results of descriptive analyses were summarized using summary measures expressed as mean \pm SD or median (minimum–maximum, or interquartile range [IQR]) for continuous variables and number (percent) for categorical variables. The primary analysis was a logistic regression analysis predicting a positive stimulated thyroglobulin measurement at follow-up ($>2 \mu\text{g/L}$). The clinical pathologic TNM stage and the natural logarithm of postsurgical stimulated thyroglobulin measurement were simultaneously entered into the logistic regression model. The natural logarithm of the postsurgical stimulated thyroglobulin was used for analysis, since

the distribution of postsurgical stimulated thyroglobulin values was wide and not normally distributed. Undetectable postsurgical stimulated thyroglobulin measurements were assumed to have a value of 1 for the purpose of natural logarithm transformations (in order to avoid negative values). The TNM stage was assumed to be ordinal, with respective stages II, III, and IV, compared with stage I. We performed a sensitivity analysis in which we substituted a simplified postoperative stage (disease confined to the thyroid compared to extrathyroidal disease [including extrathyroidal local invasion, lymph node metastases, or distant metastases]) in the model. Sensitivity analyses were also performed in patients with strictly papillary histology. In an additional secondary analysis in patients with papillary thyroid carcinoma who did not have extrathyroidal extension or distant metastases at presentation, we examined whether local regional lymph node status (positive or negative) and postsurgical stimulated thyroglobulin independently predict a positive follow-up stimulated thyroglobulin.

The results of the logistic regression analyses were reported as coefficient, corresponding SEs, and odds ratio (OR) estimates with corresponding 95% confidence intervals (95% CIs) and associated *p* values. The goodness-of-fit of the final models was assessed using the Hosmer–Lemeshow test.^{25,26} We calculated the 95% CI of proportions using Wilson's method using CIA software (London, UK).²⁷ All statistical tests were performed using 2-sided tests at the .05 level of significance. The descriptive analyses and logistic regression analyses were performed using SPSS 12.0 (Chicago, IL). In terms of sample size justification, a minimum of 10 times as many outcome events were required for each parameter examined in a multivariable model (thus a total of at least 20 positive outcomes was required for each logistic regression analysis for the 2 predictor variables explored).^{28,29}

RESULTS

Patient Characteristics. The baseline characteristics of the 141 study patients are shown in Table 1. The study population was largely composed of patients with papillary carcinoma (93.6%, 132/141). The ratio of women to men was approximately 3:1, and the mean age was 43.7 years (SD, 13.6 years). Approximately two thirds of patients had undergone a total thyroidectomy, and the rest

Table 1. Baseline characteristics of study patients.

Characteristic	Percentage (n/N) of patients for categorical variables or mean \pm SD for continuous variables
Female sex	74.5 (105/141)
Histology	
Papillary	93.6 (132/141)
Follicular	2.8 (4/141)
Hürthle cell	3.5 (5/141)
Age,* y	43.7 \pm 13.6 (range, 12.0–78.0)
Primary surgery	
Total thyroidectomy	68.1 (96/141)
Near-total thyroidectomy	38.9 (45/141)
Ablative dose radioactive iodine,* mCi	101.6 \pm 36.1 (range, 53.0–253.0)
American Joint Committee on Cancer (TNM) pathologic stage	
Stage I	68.8 (97/141)
Stage II	10.6 (15/141)
Stage III	11.3 (16/141)
Stage IV	9.2 (13/141)
Undetectable postoperative stimulated thyroglobulin measurement prior to ablation	12.1 (17/141)
Whole body scan result (after radioactive iodine remnant ablation)	
No visible uptake	4.3 (6/138)
Visible uptake thyroid bed alone	68.1 (94/138)
Visible uptake lateral neck or mediastinum	24.6 (34/138)
Visible uptake in distant metastases	2.9 (4/138)

*Indicates that the values are in mean \pm SD (range).

had a near-total thyroidectomy, depending on the personal practice preference of the surgeon performing the procedure. The mean ablative dose of radioactive iodine was 101.6 mCi (SD, 36.1 mCi). Approximately two thirds of patients had TNM stage I disease. Furthermore, most patients had thyroid bed uptake alone on postradioactive iodine therapy whole body scans (Table 1). The median TSH value at the time of initial radioactive iodine treatment was 66.0 mIU/L (IQR 39.0, 100.0 mIU/L). An undetectable postsurgical stimulated thyroglobulin measurement was observed prior to remnant ablation in 12.1% of patients (17/141), all of whom had either TNM stage I (13/17) or II (4/17). The median postsurgical stimulated thyroglobulin value was 7.0 μ g/L (IQR 3.0, 20.0 μ g/L), with a wide variation of measurements ranging from undetectable up to 1000.0 μ g/L. At follow-up after remnant ablation, 115/136 (84.6%) patients had undetectable thyroglobulin measurements (<1 μ g/L) while on thyroxine therapy.

Stimulated Thyroglobulin Measurements at Follow-Up. The median time from primary thyroidectomy to follow-up stimulated thyroglobulin measurement was 35 months (IQR 14, 84 months). The median TSH at the time of measurement of the follow-up stimulated thyroglobulin measurement was 54.7 mIU/L (IQR 39.3, 75.0 IU/L). Approximately 1 in 5 patients (20.6%, 29/141) had a positive follow-up stimulated thyroglobulin measurement (>2 μ g/L). The pathologic TNM stage was III or IV in 27.9% (11/29), and the primary disease extended beyond the thyroid in 79.3% (23/29) of individuals with a positive follow-up stimulated thyroglobulin (see Figure 1). The median postsurgical thyroglobulin value was 30.0 μ g/L (IQR 13.6, 55.0 μ g/L) in the 29 individuals with a positive stimulated thyroglobulin measurement, whereas it was 5.0 μ g/L (IQR 3.0, 9.98 μ g/L) in others. The percentages of individuals with a positive or negative follow-up stimulated thyroglobulin measurement using various hypothetical cutoffs for postsurgical stimulated thyroglobulin are shown in Table 2.

Multivariable Logistic Regression Analyses in Patients with Well-Differentiated Thyroid Carcinoma. In the primary analysis, pathologic TNM stage and the natural logarithm of postsurgical stimulated thyroglobulin were entered in a logistic regression model predicting a positive follow-up stimulated thyroglobulin measurement (>2 μ g/L). The natural logarithm of postsurgical stimulated thyroglobulin independently predicted a positive follow-up stimulated thyroglobulin (OR, 4.44; 95% CI, 2.33–8.45; p < .001; Table 3). Postoperative TNM stage also tended to independently predict a positive follow-up stimulated thyroglobulin (p = .054), particularly for TNM stage IV (OR, 7.42; 95% CI 1.53–35.89; p = .013; Table 3). The model fit was as adequate, as judged by the following: Cox and Snell r^2 = .337, Hosmer and Lemeshow X^2 = 10.59 with 8 degrees of freedom (p = .226; data from 141 patients). We substituted the presence of extrathyroidal disease (defined by the presence of lymph node metastases, or extrathyroidal invasion, or distant metastases [DeGroot stages II, III, or IV]) for TNM pathologic stage in a secondary analysis. In this model, we found that both the natural logarithm of the postsurgical stimulated thyroglobulin (OR, 4.75; 95% CI 3.32–9.73; p < .001) and the presence of extrathyroidal disease (OR, 14.14; 95% CI, 4.13–48.43; p < .001) independently predicted the presence of a positive stimulated thyroglobulin at follow-up. The model

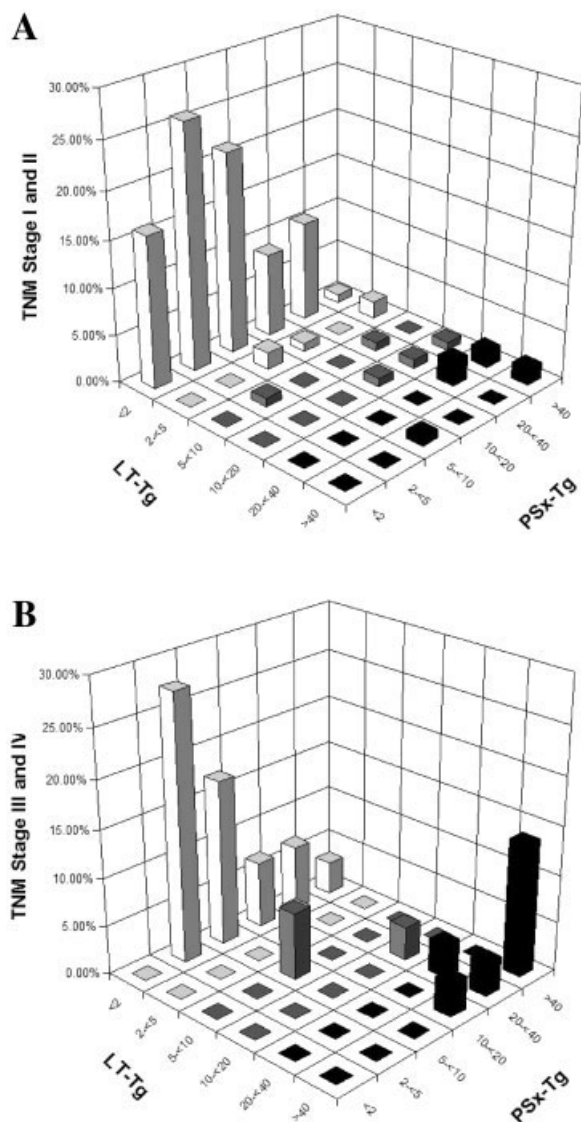


FIGURE 1. The relationship between TNM pathologic stage and observed PSx-Tg and follow-up LT-Tg measurements. PSx-Tg: postoperative stimulated thyroglobulin measurement (measured after thyroid hormone withdrawal, prior to radioactive iodine remnant ablation, $\mu\text{g/L}$). LT-Tg: stimulated thyroglobulin measurement at long-term follow-up (after thyroid hormone withdrawal), value of $>2 \mu\text{g/L}$ considered positive. TNM pathologic stage: American Joint Committee on Cancer TNM classification (6th edition). (A) The percent distribution of PSx-Tg and LT-Tg for patients of TNM stage I and II ($n = 112$). (B) The percent distribution of PSx-Tg and LT-Tg for patients of TNM stage III and IV ($n = 29$).

fit was adequate (Cox and Snell $r^2 = .395$, Hosmer and Lemeshow $X^2 = 2.30$ with 8 degrees of freedom, $p = .971$ [data from 141 patients]).

Secondary Analyses in Patients with Papillary Thyroid Carcinoma. The same multivariable analyses performed in the patients with well-differen-

tiated thyroid carcinoma were tested in sensitivity analyses restricted to patients with papillary thyroid carcinoma. In a multivariable model including data from 132 patients with papillary carcinoma, the natural logarithm of postsurgical stimulated thyroglobulin independently predicted a positive follow-up stimulated thyroglobulin (OR, 4.52; 95% CI, 2.35–8.69; $p < .001$). In this model, there was also a trend for postoperative TNM stage to predict a positive follow-up stimulated thyroglobulin ($p = .127$), with a significant independent association for TNM stage IV (OR, 5.98; 95% CI, 1.17–30.66; $p = .032$). The model fit was as adequate, as judged by the following: Cox and Snell $r^2 = .337$, Hosmer and Lemeshow $X^2 = 11.61$ with 8 degrees of freedom ($p = .170$). In another model including data from 132 patients with papillary carcinoma, both the natural logarithm of the postsurgical stimulated thyroglobulin (OR, 4.65; 95% CI, 2.29–9.42; $p < .001$) and the presence of extrathyroidal disease (OR, 11.01; 95% CI, 3.18–38.16; $p < .001$) independently predicted the presence of a positive stimulated thyroglobulin at follow-up. The model fit was adequate (Cox and Snell $r^2 = .387$, Hosmer and Lemeshow $X^2 = 2.19$ with 8 degrees of freedom, $p = .974$ [data from 132 patients]). In a multivariable analysis restricted to patients with papillary thyroid carcinoma who did not have extrathyroidal invasion or distant metastases, we explored whether the natural logarithm of postsurgical thyroglobulin and the presence of lymph node metastases independently predicted a positive follow-up stimulated thyroglobulin. In these 114 patients, both the natural logarithm of the postsurgical stimulated thyroglobulin (OR, 5.37; 95% CI, 2.17–13.24; $p < .001$) and the presence of lymph node metastases (OR, 11.46; 95% CI, 2.53–51.95; $p < .001$) independently predicted the presence of a positive stimulated thyroglobulin at follow-up. The model fit was adequate (Cox and Snell $r^2 = .299$, Hosmer and Lemeshow $X^2 = 2.20$ with 8 degrees of freedom, $p = .974$).

DISCUSSION

We determined that the natural logarithm of postsurgical stimulated thyroglobulin measurements independently predicts future positivity of stimulated thyroglobulin measurements in patients with well-differentiated thyroid cancer treated with radioactive iodine. Pathologic stage, including TNM stage IV or extension of disease outside the thyroid (lymph node metastases, local

Table 2. The prognostic value of various values of postoperative stimulated thyroglobulin in predicting the positivity of stimulated thyroglobulin measurements at follow-up.

PSx-Tg cutoff* ($\mu\text{g/L}$)	Percentage of individuals with a positive LT-Tg who had a PSx-Tg [†] at or above the listed cutoff (95% confidence interval); (number)	Percentage of individuals with a negative LT-Tg who had a PSx-Tg [†] below the listed cutoff (95% confidence interval); (number)
1.0	100.0 (88.3–100.0); (29/29)	15.2 (9.7–23.0); (17/112)
5.0	96.6 (82.8–99.4); (28/29)	49.1 (40.0–58.2); (55/112)
10.0	79.3 (61.6–90.2); (23/29)	75.0 (66.2–82.1); (84/112)
20.0	65.5 (47.3–80.1); (19/29)	85.7 (78.0–91.0); (96/112)
30.0	51.7 (34.4–68.6); (15/29)	94.6 (88.8–97.5); (106/112)

*PSx-Tg, postoperative stimulated thyroglobulin measurement (measured after thyroid hormone withdrawal, prior to radioactive iodine remnant ablation, $\mu\text{g/L}$).

[†]LT-Tg, stimulated thyroglobulin measurement at long-term follow-up (values $>2 \mu\text{g/L}$ considered positive, with lower values considered negative).

extrathyroidal invasion, or distant metastases [DeGroot stages II, III, or IV]) were also found to be independently associated with a positive stimulated thyroglobulin at follow-up. These findings were robust when examined in a subgroup of patients with papillary thyroid carcinoma. Furthermore, in a subgroup of patients with papillary thyroid cancer who did not have extrathyroidal invasion nor distant metastases, the presence of positive lymph nodes was found to be independently associated with a positive stimulated thyroglobulin at follow-up.

It should be acknowledged that a positive stimulated thyroglobulin at follow-up may represent recurrence or persistence of thyroid carcinoma or could be a reflection of a persisting benign remnant. However, a negative stimulated thyroglobulin at follow-up is generally considered a reasonable surrogate for the absence of thyroid carcinoma at follow-up. Thus, the converse findings of our study is that strictly intrathyroidal early-stage well-differentiated thyroid carcinoma and very low-stimulated thyroglobulin measurements at the time of initial radioactive iodine treatment are independently associated with the absence of biochemically detectable disease at follow-up.

These findings are suggestive that positive stimulated thyroglobulin measurements in long-term follow-up of well-differentiated thyroid carcinoma are likely to represent disease recurrence or persistence rather than simple detection of residual thyroid remnant.

In prior studies of well-differentiated thyroid carcinoma, a variety of minimum cutoff values of postoperative stimulated thyroglobulin in the periablation period have been suggested to predict the presence of disease at follow-up: 2.0 $\mu\text{g/L}$,²⁰ 4.5 $\mu\text{g/L}$,¹⁹ 5.0 $\mu\text{g/L}$,¹⁸ 5.7 $\mu\text{g/L}$,¹⁵ or 13.2 $\mu\text{g/L}$ (20 pmol/L),¹⁶ 27.5 $\mu\text{g/L}$,²¹ and 30.0 $\mu\text{g/L}$.¹⁸ Clearly the sensitivity of a postsurgical stimulated thyroglobulin measurement in predicting positivity of stimulated thyroglobulin measurements at follow-up is highest at low cutoff values for postsurgical thyroglobulin. In contrast, the specificity of postsurgical stimulated thyroglobulin measurements is higher when the cutoff is increased (Table 2). In this study, we have shown that prognostic ability for predicting future disease activity for well-differentiated thyroid carcinoma can be improved by considering postsurgical thyroglobulin measurements in the context of pathologic stage of disease. It is not known at this time

Table 3. Results of a multivariate logistic regression analysis predicting the presence of a positive stimulated thyroglobulin at follow-up in patients with well-differentiated thyroid carcinoma.

Variable	Odds ratio (95% confidence interval)	p value
TNM pathologic stage (overall)	–	.054
TNM stage II compared to I	0.88 (0.15–5.17)	.886
TNM stage III compared to I	0.38 (0.04–3.81)	.413
TNM stage IV compared to I	7.42 (1.53–35.9)	.013
Natural logarithm of the postsurgical stimulated thyroglobulin prior to remnant ablation	4.44 (2.33–8.45)	<.001

Note: The presence of the outcome of interest is defined by a stimulated thyroglobulin measurement at long-term follow-up of $>2 \mu\text{g/L}$. The multivariable model includes data from 141 study patients. The model fit was as follows: Cox and Snell $R^2 = .337$, Hosmer and Lemeshow $\chi^2 = 10.59$ with 8 degrees of freedom ($p = .226$).

whether postsurgical thyroglobulin measurements can be used to guide treatment. However, 12.1% of patients with thyroid carcinoma in our series had undetectable postsurgical stimulated thyroglobulin measurements prior to radioactive iodine remnant ablation, suggesting that perhaps they might have avoided radioactive iodine treatment.

A limitation of our study is the use of the surrogate biochemical outcome of a positive stimulated thyroglobulin at follow-up. Justification for the use of this surrogate outcome is the fact that, in patients with thyroid carcinoma who have undergone total or near total thyroidectomy and initial radioactive iodine treatment, stimulated thyroglobulin measurements are known to be highly sensitive and specific in detection of disease.¹⁰ Furthermore, stimulated thyroglobulin measurements after thyroidectomy and radioactive iodine treatment are associated with persistence or recurrence of well-differentiated thyroid carcinoma at further follow-up.³⁰ Yet, early detectable stimulated thyroglobulin measurements may frequently become undetectable with longer follow-up, in the absence of any therapy.^{31,32} Given that about 80% of the follow-up stimulated thyroglobulin measurements in our study was performed more than 1 year after thyroidectomy, we believe that these measurements were at steady state after remnant ablation.

In conclusion, we suggest that stimulated thyroglobulin measurements be performed routinely in patients with well-differentiated thyroid carcinoma before undergoing initial radioactive iodine treatment, and such measurements should be considered in the context of pathologic stage of disease. Our study confirms the prognostic value of such measurements, as observed in other studies in which alternative clinical outcomes were studied.^{15–21} Moreover, the utility of postoperative stimulated thyroglobulin measurements in guiding selective radioactive iodine remnant ablation in patients with early-stage well-differentiated thyroid carcinoma merits further study.

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