Preoperative Serum Thyrotropin to Thyroglobulin Ratio Is Effective for Thyroid Nodule Evaluation in Euthyroid Patients

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. This study was designed to assess the efficiency of the serum thyrotropin to thyroglobulin ratio for thyroid nodule evaluation in euthyroid patients.

Study Design. Cross-sectional study.

Setting. Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China.

Subjects and Methods. Retrospective analysis was performed for 400 previously untreated cases presenting with thyroid nodules. Thyroid function was tested with commercially available radioimmunoassays. The receiver operating characteristic curves were constructed to determine cutoff values. The efficacy of the thyrotropin:thyroglobulin ratio and thyroid-stimulating hormone for thyroid nodule evaluation was evaluated in terms of sensitivity, specificity, positive predictive value, positive likelihood ratio, negative likelihood ratio, and odds ratio.

Results. In receiver operating characteristic curve analysis, the area under the curve was 0.746 for the thyrotropin:thyroglobulin ratio and 0.659 for thyroid-stimulating hormone. With a cutoff point value of 24.97 IU/g for the thyrotropin:thyroglobulin ratio, the sensitivity, specificity, positive predictive value, positive likelihood ratio, and negative likelihood ratio were 78.9%, 60.8%, 75.5%, 2.01, and 0.35, respectively. The odds ratio indicating malignancy for the thyrotropin:thyroglobulin ratio was 5.80. With a cutoff point value of 1.525 μIU/mL for thyroid-stimulating hormone, the sensitivity, specificity, positive predictive value, positive likelihood ratio, and negative likelihood ratio were 78.9%, 60.8%, 75.5%, 2.01, and 0.35, respectively. The odds ratio indicating malignancy for thyroid-stimulating hormone was 3.23.

Conclusion. Increasing preoperative serum thyrotropin:thyroglobulin ratio is a risk factor for thyroid carcinoma, and the correlation of the thyrotropin:thyroglobulin ratio to malignancy is higher than that for serum thyroid-stimulating hormone.

Keywords
thyrdoïd nodule evaluation, thyroid carcinoma, thyroid function test, thyrotropin, thyroglobulin

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The prevalence of palpable thyroid nodules (TNs) is 5% to 10% in people older than 50 years and may be up to 50% to 70% in people older than 60 years on thyroid ultrasonography.¹-³ In patients with TNs, the first course of action is to determine whether the nodule is malignant. Within current diagnostic algorithms, measuring serum thyroid-stimulating hormone (TSH) is the first and essential step.⁴ Previous studies have demonstrated that an elevated level of TSH, even within the normal range, was linked to a greater likelihood of thyroid malignancy in patients with TNs.⁵-⁷

Part of earlier studies demonstrated that the level of thyroglobulin (Tg) could be used for TN evaluation, but most reports in recent decades present opposing conclusions.⁸-¹⁰ The widely accepted view is that preoperative serum Tg is not helpful for TN evaluation but is mainly used as the baseline to guide follow-up.¹¹ Measuring the preoperative serum Tg level is not included in current diagnostic algorithms.

Numerous studies have discussed associations between the risk of malignancy and serum TSH or Tg concentrations in patients with TNs, but no study has explored the association between the TSH:Tg ratio and malignancy risk. The present study was performed to investigate the efficiency of

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serum the TSH:Tg ratio for TN evaluation in euthyroid subjects by comparison to that of serum TSH.

**Patients and Methods**

**Patients**

Retrospective analysis was performed with Sun Yat-sen University Cancer Center’s institutional review board approval. Previously untreated cases presenting with TNs, hospitalized in the Sun Yat-sen University Cancer Center between January 1, 2013, and December 31, 2013, were reviewed. All cases underwent serum TSH measurement following current guidelines. The exclusion criteria were (1) cases without serum Tg measurement, (2) clinical or subclinical hypothyroidism or hyperthyroidism, (3) use of antithyroid drugs or with a history of thyroid hormone replacement therapy, (4) use of any medication that could affect thyroid function, (5) patients who underwent fine-needle aspiration biopsy within 4 weeks before blood sampling, (6) cases with an alanine aminotransferase concentration $>$80 IU/mL, (7) patients with an indeterminate histological diagnosis. Four hundred cases were included in the study. Postoperative histological diagnosis is the gold standard for this study.

**Histological Results**

According to pathological diagnosis, nodules were benign in 158 cases and malignant in 242 cases. In cases with malignancy, 1 case presented with anaplastic thyroid cancer and papillary thyroid cancer (PTC), 1 case presented with PTC and medullary thyroid cancer (MTC), 2 cases presented with MTC, and all of the other cases presented with PTC.

**Laboratory Tests**

Serum TSH, Tg, and thyroglobulin antibody (TgAb) levels were measured in each case with the same blood sample. Levels were quantified by commercially available radioimmunoassay. The reference ranges for TSH, Tg, and TgAb were 0.27 to 4.2 μIU/mL, 1.4 to 78 ng/mL, and 0 to 115 IU/mL, respectively. The TSH:Tg ratio was calculated with its unit transferred to IU/g (Figure 1).

**Statistical Analyses**

The geometric means of serum TSH and Tg concentrations in patients with malignant and benign nodules were compared. The cutoff point values of serum TSH and TSH:Tg ratio were determined by receiver operating characteristic (ROC) curve analysis. A cutoff point value was selected at which the sum of sensitivity and specificity was greatest. With the cutoff point values, we evaluated TNs using TSH:Tg ratios and TSH. These were then compared with the gold standard. The efficacy of the ratios and TSH for TN evaluation was evaluated in terms of sensitivity, specificity, positive predictive value (PPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and odds ratio (OR). A 2-tailed $P$ value $<$0.05 was considered significant.

**Results**

The mean greatest dimension of TNs was $30.12 \pm 15.42$ mm in patients with benign nodules and $17.19 \pm 11.59$ mm in those with malignancy ($P < .001$). The geometric mean of serum TSH concentration was $1.95 \pm 1.70$ μIU/mL in individuals with malignancy and $1.27 \pm 1.63$ μIU/mL in patients with benign nodules ($P < .001$). The geometric means of serum Tg concentrations were $19.54 \pm 1138.90$ ng/mL in patients with malignant nodules and $87.91 \pm 746.38$ ng/mL in patients with benign nodules ($P = .032$).

The median value of the serum TSH:Tg ratio was $86.2$ IU/g, 95% confidence interval (CI; 56.2-129.6) IU/g in patients with malignancy and $19.9$ IU/g, 95% CI (11.8-29.5) IU/g in patients with benign nodules.

The ROC curves were constructed for TSH and TSH:Tg ratios (Figure 2). The area under the curve (AUC) for the TSH:Tg ratio was 0.746, 95% CI (0.697, 0.795). The AUC for TSH was 0.659, 95% CI (0.603, 0.714). When the sum of specificity and sensitivity was maximal, the TSH:Tg ratio

![Figure 1. The equation for the thyroid-stimulating hormone:thyroglobulin ratio construction.](https://oto.sagepub.com)

![Figure 2. Receiver operating characteristic curves for the serum thyroid-stimulating hormone:thyroglobulin ratio and thyroid-stimulating hormone concentration.](https://oto.sagepub.com)
was 24.97 IU/g. Taking 24.97 IU/g as the cutoff point value for the TSH:Tg ratio, we predicted cases with ratios $\geq 24.97$ IU/g to be malignant, whereas cases with ratios $< 24.97$ IU/g were taken to be benign. The TSH was 1.525 mIU/mL when the sum of specificity and sensitivity was the largest. We predicted cases with TSH $\geq 1.525$ mIU/mL to be malignant, whereas cases with less than this level were predicted to be benign. Comparisons of predictive results to histological diagnoses are displayed in Table 1.

The accuracy of the TSH:Tg ratio was 71.8%, with sensitivity = 78.9%, specificity = 60.8%, PPV = 75.5%, PLR = 2.01, and NLR = 0.35. The OR indicating malignancy for the TSH:Tg ratio was 5.80. This indicates that when the ratio is in the higher range, the risk of malignancy is elevated 5.80-fold in comparison to absence of malignancy. When the TSH level is in the higher range, the risk of a malignancy is increased 3.23-fold compared with nonmalignant cases. The OR indicating a malignancy of TSH:Tg ratio is apparently higher than that of TSH. These data reinforce that both high TSH level and high TSH:Tg ratio are risk factors for thyroid carcinoma. Furthermore, the correlation of TSH:Tg ratio to a malignant state is higher than that of serum TSH.

### Table 1. Comparisons of Nodule Evaluations Based on the TSH:Tg Ratio and TSH to Histological Diagnoses.

<table>
<thead>
<tr>
<th>Histological Diagnosis</th>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio-based evaluation</td>
<td>191</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>96</td>
</tr>
<tr>
<td>TSH-based evaluation</td>
<td>179</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>84</td>
</tr>
</tbody>
</table>

Abbreviations: Tg, thyroglobulin; TSH, thyroid-stimulating hormone.

### Table 2. Comparisons of Nodule Evaluations Based on the TSH:Tg Ratio and TSH to Histological Diagnoses in Normal and Elevated TgAb Subgroups.

<table>
<thead>
<tr>
<th>Histological Diagnosis</th>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal TgAb subgroup</td>
<td>142</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>91</td>
</tr>
<tr>
<td>Elevated TgAb subgroup</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: Tg, thyroglobulin; TgAb, thyroglobulin antibody; TSH, thyroid-stimulating hormone.

### Discussion

TSH is a main regulator of thyroid hormone production by thyroid follicular cells and plays a critical role in normal thyroid function and in disorders. Differentiated thyroid cancer expresses the TSH receptor on cell membranes and responds to TSH stimulation by increasing the expression of several thyroid-specific proteins and by elevating cell growth rates. Furthermore, data demonstrate that serum TSH concentration in patients with malignant nodules is higher than that of patients with benign nodules. Taken together, it is believed that TSH plays a role in thyroid cancer development and progression and as a growth factor in thyroid tumors, and it is a link within a complex signaling network that modulates thyroid cell growth and function.

Produced by thyroid follicular cells, the synthesis and secretion of Tg is an active process requiring stimulation by TSH. Without TSH, little or no Tg would be released into the circulation. Although TSH concentration is not the only factor affecting serum Tg level, Tg concentration is supposed to be correlated with serum TSH level. In fact, the Tg level does not vary in accordance with TSH level. In our study, the geometric mean Tg level in patients with malignancy was significantly lower than that in patients with benign nodules. The large standard deviation indicated that Tg levels vary tremendously between cases and can be elevated in patients with benign nodules and in patients with malignancy. Therefore, Tg cannot be independently used as an effective marker for TN status, which accords with previous reports.

To our knowledge, this is the first study designed to evaluate the efficiency of the TSH:Tg ratio for TN evaluation. Our data showed that the median serum TSH:Tg ratio differed significantly between malignant and benign thyroids. The OR of the TSH:Tg ratio was 5.80. This indicates that when the ratio is in the higher range, the risk of malignancy is elevated 5.80-fold in comparison to absence of malignancy. When the TSH level is in the higher range, the risk of a malignancy is increased 3.23-fold compared with nonmalignant cases. The OR indicating a malignancy of TSH:Tg ratio is apparently higher than that of TSH. These data reinforce that both high TSH level and high TSH:Tg ratio are risk factors for thyroid carcinoma. Furthermore, the correlation of TSH:Tg ratio to a malignant state is higher than that of serum TSH.
It is reported that approximately 20% of patients with thyroid cancer have elevated TgAb, which reinforces our data. In our cohort, only 6.3% patients with benign nodules presented with elevated TgAb. As reported, TgAb levels interfere with Tg measurement irrespective of the assay used. However, most reports propose that TgAb should be taken into consideration only in cases with significantly elevated TgAb levels. In this study, the geometric means of serum Tg concentration in patients with normal TgAb were higher than those in patients with elevated TgAb, but the difference was not statistically significant. However, this difference should be further explored because of insufficient cases in the TgAb-elevated subgroup. The OR for the TSH:Tg ratio indicating a malignancy was 24.50 in the TgAb-elevated subgroup and 4.63 in the TgAb-normal subgroup. This result indicates that the efficiency of the TSH:Tg ratio is better in patients with elevated TgAb. The OR of the TSH:Tg ratio in the subgroup with normal TgAb is still higher than the OR for TSH alone. This demonstrates that the TSH:Tg ratio is more effective than TSH alone for TN evaluation regardless of TgAb level. Considering the assays used for Tg measurement, when the ratio is referred to, the cutoff point value of TSH:Tg ratio may differ.

The present data showed that the TSH:Tg ratio is higher in histologically confirmed carcinoma than in benign nodules. Compared with TSH, the sensitivity, specificity, PPV, and PLR of TSH:Tg ratios were higher, while the NLR was smaller. This demonstrates that more patients with a malignancy would be identified. In the meantime, fewer benign nodules would be misdiagnosed as malignant. The OR indicating a malignancy of TSH:Tg ratio was higher than that of TSH alone. Overall, the serum TSH:Tg ratio is more effective than TSH for the evaluation of TN. An elevated TSH:Tg ratio was linked with a greater likelihood of thyroid malignancy in patients with TNs. We speculate that findings in this study could contribute to a TN evaluation algorithm. Serum TSH:Tg ratios could be used for TN evaluation instead of serum TSH. Comprehensively considering clinical factors, TSH:Tg ratios, and ultrasound features, clinicians determine whether fine-needle aspirate (FNA) is indicated or follow-up needs to be conducted.

FNA biopsy is the preoperative gold standard diagnostic method. Most cases can be diagnosed with a combination of FNA, ultrasonography, laboratory findings, and clinical data. Some patients still cannot obtain definitive diagnoses, especially those with micronodules and large (≥4 cm) cystic nodules. Ten percent to 25% of TNs are categorized as indeterminate. A median of 34% (range, 14%-48%) of patients with indeterminate cytology findings who underwent surgery were found to have a malignancy. Furthermore, the false-negative rate for nodules larger than 4 cm is approximately 10% to 15%, and some cystic nodules remain undiagnosed despite repeated biopsies. As the gold standard in the study, a definitive pathological diagnosis of each case was required. For these reasons, we used postoperative histological diagnosis as the gold standard instead of FNA results. We performed this study with data from patients who underwent surgery. The indications of thyroidectomy for malignant and benign TNs were different. As a result, selection bias was caused in this study. Our data showed that the mean greatest dimension of TNs in the benign group was significantly larger than that in the malignant group. This is an evidence of selection bias. As a result of the limitation of a retrospective analysis and selection bias, we cannot accurately evaluate how many patients with benign nodules would be suggested to undergo further confirmatory tests or how many patients with malignancy would be missed. Consequently, the efficiency of the TSH:Tg ratio for nodule evaluation needs to be confirmed with prospective studies.

Conclusion

Increased preoperative serum TSH:Tg ratio is a risk factor for thyroid carcinoma, and the correlation of TSH:Tg ratio to malignancy is higher than that of serum TSH.

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Author Contributions

Lina Wang, drafting, data analysis, interpretation of data, final approval accountability for all aspects of the work; Hao Li, revising, data analysis, interpretation of data, final approval, accountability for all aspects of the work; Zhongyuan Yang, drafting, acquisition of data, final approval, accountability for all aspects of the work; Zhuming Guo, revising, interpretation of data, final approval, accountability for all aspects of the work; Quan Zhang, design, revising, final approval, accountability for all aspects of the work.

Disclosures

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References


