Comparison of Tc-99m Pertechnetate Thyroid Uptake Rates by Gamma Probe and Gamma Camera Methods for Differentiating Graves’ Disease and Thyroiditis

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Abstract

Although technetium-99m (\(^{99m}\)Tc) pertechnetate thyroid uptake rate can be measured by gamma camera with scintigraphy as well as by gamma probe, the normal reference range known as quite different between them. This study was performed to compare their diagnostic accuracy for evaluating patients with hyperthyroidism. We retrospectively reviewed consecutive 371 patients (euthyroid 89, Graves 167, and thyroiditis 115) who had simultaneously measured data of thyroid uptake rates by both gamma probe and camera methods in our hospital from November 2019 to June 2020. The reference ranges in euthyroid patients were 2.0-4.7% and 0.3–1.9% for probe and camera methods, respectively. For differentiating Graves’ disease and thyroiditis, the area under the curve of the camera method was significantly greater than that of the probe method (0.988 vs 0.975, \(p = 0.030\)) on receiver operating characteristic curve analysis. With a cutoff value of 0.7%, the sensitivity and specificity for the camera method were 93.4% and 94.8%, respectively. With a cutoff value of 3.0%, those for the probe method were 92.2% and 91.3%, respectively. In conclusion, \(^{99m}\)Tc pertechnetate thyroid uptake rate measured by the camera method with scintigraphy had higher diagnostic accuracy than the probe method for evaluating patients with hyperthyroidism.

Introduction

Technetium-99m (\(^{99m}\)Tc) pertechnetate has become the most common medical radioisotope used in thyroid scintigraphy because of its short duration for imaging, reduced radiation exposure to the patient, and low cost \(^1\)–\(^3\). Thyroid scintigraphy and uptake rate play important roles in evaluating thyroid gland function and structures, such as functional assessment of thyroid nodules, identifying causes of thyrotoxicosis, and detecting ectopic thyroid tissue \(^2\),\(^4\),\(^5\). For example, thyroid uptake rate helps to differentiate hyperthyroidism from other causes of thyrotoxicosis like thyroiditis. Absent uptake or markedly reduced uptake in a diffuse pattern is associated with subacute thyroiditis or painless thyroiditis, whereas elevated uptake is often associated with Graves’ disease or toxic nodular goiter \(^3\),\(^6\),\(^7\).

Thyroid uptake rate can be measured by using a probe, which is the conventional method, or with a gamma camera-based method \(^8\)–\(^10\). Using the gamma camera, thyroid scintigraphy images can be obtained. Simultaneously, thyroid uptake is calculated semi-quantitatively from the scintigraphy image based on the region of interest (ROI) in the thyroid tissues, background activity, and injector activity values \(^11\). Many previous studies have shown that the camera-based method is fast, efficient, and can be a good substitute for the probe-based method \(^8\)–\(^10\),\(^12\). Furthermore, from scintigraphy images, separate uptake rate about right and left thyroid lobes is available. The national health insurance of the Republic of Korea has been covering the use of gamma camera method for thyroid uptake rate measurement since 2018. However, the probe method is still widely used in many medical centers in Korea. In our hospital, thyroid scintigraphy and uptake rate have been assessed separately using gamma camera and gamma probe after a single injection of \(^{99m}\)Tc pertechnetate. The standard reference range for \(^{99m}\)Tc pertechnetate thyroid uptake rate in euthyroid patients in previous reports was quite different between the
two methods, and there was no comparison study for the diagnostic accuracy of the two methods. These were hurdles for the transit from gamma probe-based method to gamma camera-based method.

Instead of $^{99m}$Tc pertechnetate thyroid uptake rate, laboratory tests such as serum thyrotropin-binding inhibitory immunoglobulin (TBII) level, thyroid-stimulating antibody, and the ratio of free T3/free T4 have been reported as useful for distinguishing thyrotoxicosis etiologies, especially for pregnant or lactating women $^{13-15}$. However, these laboratory test results of thyroid functions are not widely used, and direct comparison studies with thyroid uptake rate are limited.

Therefore, we aimed to determine the normal reference range for thyroid $^{99m}$Tc uptake rate in euthyroid patients for both probe and camera methods and compare the diagnostic testing accuracy for differentiating Graves’ disease and thyroiditis in patients with thyrotoxicosis. We also compared the diagnostic accuracy of thyroid function tests such as free T3/free T4 ratio with thyroid uptake rate for differentiating thyrotoxicosis etiology.

Results

**Baseline characteristics of all patients**

A total of 371 patients (euthyroid 89, Graves 167, and thyroiditis 115) were included in this study. Table 1 presents the baseline characteristics of the patients included in this study. The mean age of the patients was $50.7 \pm 14.4$ years, and 75.2% were female. The median level of Serum thyroid-stimulating hormone (TSH) in patients with euthyroid states was $2.60 \mu U/mL$ (interquartile range [IQR] 1.50–3.50, reference level 0.4–5.0 $\mu U/mL$). The median free T4 level in patients with euthyroid state was 1.20 ng/dL (IQR 1.10–1.30, reference level 0.8–1.9 ng/dL), and the median free T3 level was 3.10 pg/mL (IQR 2.80–3.40, reference level 1.63–3.78). TBII (reference level 0–1.5 IU/L) was positive in 36.7% of total patients and was positive in 87.8% of the patients with Graves’ disease. Of the total patients, anti-thyroid peroxidase antibody (Anti-TPO Ab, reference level 0–60 IU/L) was positive in 36.7% of the patients, and anti-thyroglobulin antibody (Anti-Tg Ab, reference level 0–60 IU/L) was positive in 30.3% of the patients. Among the 167 patients with Graves’ disease, 61 (36.5%) were on anti-thyroid drugs during the thyroid scan.
Table 1
Baseline characteristics of the patients

|                          | Mean ± SD, median (IQR) or percent (number) |
|--------------------------|--------------------------------------------|
|                          | Total patients | Euthyroid state | Graves’ disease | Thyroiditis |
| Proportion (%)           | 100% (371)    | 24.0% (89)      | 45.0% (167)     | 31.0% (115) |
| Age (years, mean ± SD)   | 50.7 ± 14.4   | 53.3 ± 13.0     | 49.4 ± 15.0     | 50.5 ± 14.5 |
| Sex (Female, %)          | 75.2% (279)   | 78.7% (70)      | 74.9% (125)     | 73.0% (84)  |
| TSH (µU/mL), median (IQR)| 0.04          | 2.60            | 0.04            | 0.04        |
|                          | (0.04–0.34)   | (1.50–3.50)     | (0.04–0.04)     | (0.04–0.06) |
| Free T4 (ng/dL), median (IQR) | 1.60         | 1.20            | 2.00            | 1.80        |
|                          | (1.30–2.30)   | (1.10–1.30)     | (1.52–2.75)     | (1.40–2.26) |
| Free T3 (pg/mL), median (IQR) | 4.65         | 3.10            | 8.30            | 5.00        |
|                          | (3.28–9.33)   | (2.80–3.40)     | (4.90–14.40)    | (3.68–7.95) |
| TBII (IU/L), positive (%)| 52.3%         | 0%              | 87.8%           | 3.1%        |
|                          | (148/283)     | (0/22)          | (145/165)       | (3/96)      |
| Anti-TPO Ab (U/mL), positive (%) | 36.7%       | 6.0%            | 59.8%           | 22.2%       |
|                          | (91/248)      | (3/50)          | (70/117)        | (18/81)     |
| Anti-Tg Ab (U/mL), positive (%) | 30.3%       | 24.0%           | 34.2%           | 28.8%       |
|                          | (71/234)      | (12/50)         | (38/111)        | (21/73)     |

Abbreviations: SD, Standard deviation; IQR, Interquartile range; TSH, Thyroid stimulating hormone; TBII, Thyrotropin-binding inhibitory immunoglobulin; Anti-TPO Ab, Anti-Thyroid peroxidase antibody; Anti-Tg Ab, Anti-thyroglobulin antibody. aFree T3 data was available in 340 patients

Reference ranges of the uptake rates by probe and camera methods

We evaluated the uptake rates of patients with euthyroid state, and the distribution of the uptake rates are shown in Fig. 1. Because the $^{99m}$Tc pertechnetate uptake rate in the euthyroid group was not normally distributed irrespective of the method (Fig. 1A and 1B), we set the reference range of uptake rate from 2.5 percentile to 97.5 percentile instead of the mean ± standard deviations (SDs). Consequently, the reference range of uptake rate by the probe method was 2.0–4.7% (median 3.0%) and 0.3–1.9% (median 0.7%) for the camera method.
Correlations of thyroid uptake rates between probe and camera methods

The correlation of probe uptake rate and camera uptake rate is shown in Fig. 2. The uptake rates of the two methods were positively correlated in patients with euthyroid state, Graves’ disease, and thyroiditis and in all patients \((p < 0.001\) in all groups). In contrast, the uptake rate was lower in the camera method than the probe method. The \(r^2\) was 0.98 in total patients.

Comparison of thyroid uptake rates between the euthyroid group and Grave’ disease or thyroiditis

The thyroid uptake rate in patients with Graves’ disease was significantly higher than in those with euthyroid state by both probe and camera methods \((p < 0.001\) and \(p < 0.001\), respectively). Two patients with Graves’ disease showed a lower uptake rate than the normal reference range in both methods. One patient had taken methimazole for one month and was in subclinical hyperthyroidism. Another patient who had stopped taking anti-thyroid drugs 5 years ago was also in subclinical hyperthyroidism with negative conversion of TBII. The thyroid uptake rates in patients with thyroiditis were significantly lower than those in euthyroid patients both by probe and camera methods \((p < 0.001\) and \(p < 0.001\), respectively). No patient with thyroiditis presented a higher uptake than the normal reference range in both methods.

Thyroid uptake rate for differentiating Graves’ disease and thyroiditis

In the receiver operating characteristic (ROC) curve analysis, the area under the curve (AUC) of the camera method \((0.988)\) was significantly greater than that \((0.975)\) of the probe method \((p = 0.030)\). The cutoff value differentiating the two diseases in the probe method was 3.0%, with a sensitivity and specificity of 92.2% and 91.3%, respectively \((p = 0.001)\). The cutoff value in the camera method was 0.7%, with a sensitivity of 93.4% and a specificity of 94.8% \((p = 0.001)\).

Thyroid function test for differentiating Graves’ disease and thyroiditis

Free T3/free T4 and free T3/TSH ratios were available in 253 patients with thyrotoxicosis. The median ratio of free T3/free T4 was 4.2 (IQR 3.1–5.2) and 3.0 (IQR 2.4–3.7) in patients with Graves’ disease and thyroiditis, respectively. The ratio of free T3/free T4 was significantly higher in patients with Graves’ disease than in those with thyroiditis \((p < 0.001)\). The ROC curve analysis showed that the AUC of free T3/free T4 ratio \((0.749)\) was significantly lower than thyroid uptake rates of the probe or camera methods \((p < 0.001,\) and \(p < 0.001,\) respectively). The cutoff ratio of free T3/free T4 differentiating the two diseases was 4.0, with a sensitivity of 55.1% and a specificity of 84.9% \((p = 0.001)\).

Discussion
In this retrospective study, we determined the normal reference ranges for $^{99m}$Tc pertechnetate thyroid uptake rate in euthyroid patients as 2.0–4.7% by the probe method and 0.3–1.9% by camera method, respectively. We also identified that $^{99m}$Tc pertechnetate thyroid uptake rate measured by the camera-based method had higher diagnostic accuracy than the traditional probe method when evaluating patients with thyrotoxicosis. Furthermore, in terms of efficiency and convenience, the camera method is less time-consuming and more convenient for patients and reduces equipment requirements.

The normal reference range for thyroid uptake rate depends on the geographical location and dietary iodine intake of patients. The reference range for thyroid uptake rate in euthyroid patients from this study was similar to that of other studies conducted in recent years. Previous studies have demonstrated that $^{99m}$Tc pertechnetate thyroid uptake rate measured by the probe and camera methods were correlated, consistent with our study results. The thyroid uptake rate was slightly lower in the camera method than in the probe method, and this probably came from several differences in measurement. In the probe method, $^{99m}$Tc thyroid uptake rate might be overestimated by the spill-in effects of extra-thyroidal activities such as salivary glands and saliva in the oral cavity. This overestimation is not encountered in the camera method because the uptake rate is calculated after drawing ROI for the thyroid gland. Therefore, it is somewhat underestimated in the latter due to settings of ROI, especially when the pyramidal lobe or ectopic thyroid tissues are not included in the range of ROI. In addition, the differences in background activity correction methods may also affect the thyroid uptake rate.

$^{99m}$Tc pertechnetate thyroid scintigraphy is one of the most accurate and rapid tests for evaluating patients with thyrotoxicosis, especially when blood tests are insufficient to distinguish Graves’ disease from thyroiditis. Recently, two studies measured thyroid uptake rate using the camera method, elucidating the cutoff value for differentiating Graves’ disease from thyroiditis. One study from Turkey demonstrated that the cutoff value for $^{99m}$Tc pertechnetate uptake of 1.55% was useful to discriminate between Graves’ disease and subacute thyroiditis with a sensitivity of 92%, specificity of 87%, and accuracy of 92.9%. Another study from Japan reported that the optimal cutoff value of $^{99m}$Tc pertechnetate uptake was 1.0% to distinguish Graves’ disease and painless thyroiditis, with a sensitivity of 96.6% and specificity of 97.1%. Their cutoff values were higher than those (0.7%) of the current study. This may be related to the difference in geographical location and iodine intake.

It was recently revealed that quantitative single-photon emission computed tomography/computed tomography (SPECT/CT) is more accurate than the traditional thyroid uptake system. In addition, the quantitative SPECT/CT scan can discriminate patients with destructive thyroiditis from euthyroid patients and is expected to play a critical role in differentiating thyroid disease in the future. Nevertheless, many strengths have been stated with SPECT/CT scan, and traditional planar scintigraphy still plays an important role in the differential diagnosis of thyrotoxicosis patients, including delineations of hot
nODULES. This might be related to the reduced radiation exposure and low cost. Further studies are needed to compare the accuracy and cost-effectiveness between exams.

The strength of our study was direct comparison of $^{99m}$Tc pertechnetate thyroid uptake rate and the ratio of free T3/free T4 for distinguishing thyrotoxicosis etiologies. Although $^{99m}$Tc pertechnetate thyroid scan and uptake rate is a useful method for distinguishing thyrotoxicosis etiologies, it is inappropriate for pregnant and lactating women. In these cases, the ratio of free T3/free T4 is also helpful. The ratio of free T3/freeT4 in Graves’ disease is significantly higher than that in thyroiditis due to the high expression of type 2 iodothyronine deiodinase in Graves’ thyroid tissue that converts T4 to T3. In addition, iodothyronine deiodinase is affected in tissues with thyroiditis, and the total T4 to T3 conversion is reduced. Sriphrapradang et al. reported that the cut-off level of the free T3/free T4 ratio for differentiating Graves’ disease from subacute thyroiditis was 4.4 with a sensitivity of 47.2%, specificity of 92.8%, and AUC of 0.83, which were similar to our results. As shown in our study results of direct comparison analysis of them with $^{99m}$Tc pertechnetate thyroid uptake rate, the ratio of free T3/free T4 may not replace thyroid uptake rate, because thyroid uptake rate showed much better performance. Another strength of the current study is that it suggested the reference range of $^{99m}$Tc pertechnetate thyroid uptake rate in euthyroid patients in iodine sufficient country.

This study had several limitations. First, a retrospectively designed study was conducted in a single center, although a relatively large number of patients were included in our study compared to previously reported retrospective studies. Second, the patients with the euthyroid state could not fully represent the normal population of the country. However, to minimize this limitation, we excluded patients with cold or hot nodules when evaluating reference values for euthyroid state.

In conclusion, we have shown a reference range of 2.0–4.7% using the probe method, and 0.3–1.9% in the camera method for $^{99m}$Tc pertechnetate thyroid uptake rate in euthyroid patients. $^{99m}$Tc pertechnetate thyroid uptake rate by the camera method showed higher diagnostic accuracy than the probe method when evaluating patients with thyrotoxicosis. Furthermore, the camera method is more efficient and convenient for patients. Therefore, thyroid uptake rate by camera method can conveniently substitute the probe method.

**Materials And Methods**

**Patients**

We retrospectively enrolled patients who had undergone $^{99m}$Tc pertechnetate thyroid uptake using gamma probe and thyroid scan simultaneously in our hospital from November 2019 to June 2020. The inclusion criteria were as follows: patients in the euthyroid state without cold or hot nodules in thyroid scan and patients with overt or subclinical hyperthyroidism during thyroid scan, finally diagnosed as Graves’ disease or thyroiditis. Patients with Graves’ disease or thyroiditis without thyrotoxicosis during
the thyroid scan were excluded. We also excluded patients with hot nodules on a thyroid scan. This study was approved by Asan Medical Center Institutional Review Board (IRB No. 2020–1708) and all methods were performed in accordance with the ethical principles of the Declarations of Helsinki. The need for obtaining informed consent from patients was waived by the Asan Medical Center Institutional Review Board (IRB No. 2020–1708) because of the retrospective nature of the study.

**Diagnosis of Graves’ disease and thyroiditis**

The diagnosis of patients with thyrotoxicosis was independently determined by five experienced endocrinologists (MJJ, WGK, TYK, WBK, and YKS) according to thyroid function test, serum TBII level, thyroid scan scintigram pattern, and, finally, the clinical course of the patients. Thyroiditis includes subacute thyroiditis, painless thyroiditis, and immune-related thyroiditis with immune checkpoint inhibitors. The type of thyroiditis was determined based on typical neck pain or a history of immune checkpoint inhibitor use.

**Measurement of serological markers**

TSH levels were measured with an immunoradiometric assay (B·R·A·H·M·S GmbH, Hennigsdorf/Berlin, Germany) with a functional sensitivity of 0.07 mU/L. Serum free T3 and T4 levels were measured by radioimmunoassay (Immunotech, Prague, Czech Republic) with a functional assay sensitivity of 1.0 pmol/L for free T3 and 2.34 pmol/L for free T4.

**Imaging and thyroid uptake rate protocol**

Before injecting approximately 185 MBq (5 mCi) of $^{99m}$Tc pertechnetate, the syringe counts (pre-syringe counts) were measured for 10 sec using the gamma probe (Thyrowiz Plus, NuCare Medical System, Cheongju, Korea) with a high-count filter. It was also measured for 60 sec using a gamma camera (Symbia Evo Exel, Siemens, Erlangen, Germany) equipped with a low-energy high-resolution parallel hole collimator after calibration of the gamma camera and syringe radioactivity. After intravenous injection of $^{99m}$Tc pertechnetate in each patient, the syringe counts (post-syringe counts) were measured again by the uptake probe and gamma camera, respectively. At 20 min after injection, uptake counts of anterior neck and thigh were measured using a gamma probe for 10 sec, with the patient in a sitting position. Then, the thyroid scintigraphy was performed using a single-detector of dual-head gamma camera, with the patient in a sitting position and neck extended, up to a total count of 100,000.

**Calculation of thyroid uptake rate**

Thyroid uptake rate (%) of $^{99m}$Tc using the gamma probe was calculated using the following equation:

$$\text{thyroid uptake rate} (%) = \frac{\text{Neck count-Thigh count}}{\text{Pre syringe count-Post syringe count}} \times 100 \%$$

Thyroid uptake rate (%) of $^{99m}$Tc using the gamma camera was analyzed using Syngo.via software (Siemens, Erlangen, Germany) after drawing the ROI on scintigraphy images of both thyroid lobes and the
background as shown in Fig. 5 and calculated using the following equation:

\[
\text{left lobe uptake rate (\%)} = \frac{\text{background corrected left lobe counts}}{\text{total injected counts}} \times 100\% \\
\text{right lobe uptake rate (\%)} = \frac{\text{background corrected right lobe uptake}}{\text{total injected counts}} \times 100\% \\
\text{thyroid uptake rate (\%)} = \text{left lobe uptake rate} + \text{right lobe uptake rate}
\]

**Statistical analysis**

Statistical analyses were conducted using R (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria; http://www.R.project.org) and GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA; http://www.graphpad.com). Continuous variables are presented as means ± SDs or median with IQR, and categorical variables are presented as numbers (percentages). We used the t-test to compare continuous variables and the chi-squared test to compare categorical variables. Pearson's correlation coefficient (\(r\)) was calculated. Cutoff value was calculated by ROC curve analysis using MedCalc (version 19.6.4; MedCalc Software, bvba, Mariakerke, Belgium). Pairwise comparison of ROC curves was used to compare the diagnostic accuracy of the two methods for differentiating Graves’ disease and thyroiditis in patients with thyrotoxicosis. A \(P\) value of < 0.05 was considered statistically significant.

**Declarations**

**Competing Interests**

The authors declare no competing interests.

**Author contributions**

JR contributed to concept; MJ wrote the main manuscript text; MJ, WGK, and MJJ prepared the tables and figures; JA, SJ, JP, TYK, WBK, and YKS proposals and helped analyzing data; All authors reviewed the manuscript.

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### Figures

**a**

![Figure 1a](image1)

**b**

![Figure 1b](image2)

**Figure 1**

Distribution of uptake rates in patients with the euthyroid state. (a) Distribution of uptake rates by probe method. (b) Distribution of uptake rates by camera method.
Figure 2

Correlation of thyroid uptake rates by camera method and probe method. (a) Correlation of thyroid uptake rates by camera method and probe method in patients with euthyroid state (b) Correlation of thyroid uptake rates by camera method and probe method in patients with Graves' disease (c) Correlation of thyroid uptake rates by camera method and probe method in patients with thyroiditis (d) Correlation of thyroid uptake rates by camera method and probe method in total patients.
Figure 3

Comparison of thyroid uptake rate by camera method and probe method. (a) Comparison of thyroid uptake rate in patients with Graves’ disease and euthyroid state by probe method. (b) Comparison of thyroid uptake rate in patients with Graves’ disease and euthyroid state by camera method. (c) Comparison of thyroid uptake rate in patients with thyroiditis and euthyroid state by probe method. (d) Comparison of thyroid uptake rate in patients with thyroiditis and euthyroid state by camera method.
**Figure 4**

Receiver operating characteristic (ROC) curves for differentiating Graves’ disease and thyroiditis. (a) ROC curve by probe method. (b) ROC curve by camera method. (c) ROC curve by free T3/free T4 ratio.
Figure 5

99mTc pertechnetate thyroid scintigraphy image shows the regions of interest for measuring thyroid uptake rate.