A comparison of methods for thyroid volume determination in patients with Graves’ disease

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Summary

The measurement of the thyroid volume is one of the cornerstones of the calculation of individualized radioiodine therapy dosages for patients with Graves' hyperthyroidism. Thyroid volume determinations are usually made with ultrasonography or with thyroid scintigraphy, although the accuracy of these techniques is not well known. The aim of this study was to assess the accuracy of three modalities for the determination of the thyroid volume in patients with Graves' disease: ultrasonography (US), planar scintigraphy (PS) and single photon emission computer tomography (SPECT) with attenuation correction and scatter correction.

A comparison was made of these three modalities versus magnetic resonance imaging (MRI) as the gold standard. Thyroid volume measurements were done in 25 patients with Graves' disease. Thyroid segmentation was performed manually in gadolinium enhanced T1-weighted MRI images and a summation-of-areas technique was used for the volume measurements. With US, the volumes were calculated using the ellipsoid volume model for two-dimensional measurements. After filtering and thresholding, a standard volume formula was applied to the PS images. The SPECT data were filtered, and after applying a threshold method, an automatic segmentation algorithm was used for the volume determinations.

The thyroid volumes as they were calculated with MRI were 25.0 ± 13.8 ml (mean ± sd, range: 7.0-56.3 ml). PS correlated poorly with MRI ($R^2 = 0.61$), and showed a relatively large bias ($-4.0 \pm 17.6$ ml, mean ± 2 sd). The correlation with MRI was appreciably better for SPECT ($R^2 = 0.84$) than for planar scintigraphy, with a small bias but a large standard deviation ($1.8 \pm 11.9$ ml). US had an excellent correlation with MRI ($R^2 = 0.96$), but it had the largest bias ($-6.6 \pm 8.8$ ml). Functional imaging (PS or SPECT) remains a requirement for choosing the proper dosage regimen.

Substantial improvement over currently used methods for measuring the thyroid volume may be obtained with one of three options: MRI + PS, SPECT, or US (if a correction factor is applied) + PS. A definitive choice in the clinical environment will be based on clinical, logistic and financial considerations.
8.1 Introduction

Individualized treatment protocols for radioiodine ($^{131}$I) therapy in patients with Graves’ disease are based on measurements of thyroid volume and radioiodine uptake.1-3 This is expressed in the formula:

$$D = V \times \left(\frac{100\%}{U}\right) \times 3.7 \text{ MBq},$$

where $D$ equals the $^{131}$I therapy dosage (MBq), $V$ is the thyroid volume (ml), $U$ is the 24-h thyroidal radioiodine uptake (%) and 3.7 is a constant (MBq/g).4 From this formula it follows that the accuracy of the therapy dosage is directly dependent from the accuracy of thyroid volume measurements and radioiodine uptake measurements. The importance of further standardization of the latter has recently been described.5 Validation of the most frequently applied modalities for thyroid volume measurements – ultrasonography and scintigraphy – is lacking.

Worldwide, ultrasonography (US) is probably the most frequently used modality for thyroid measurements in the routine clinical setting. It is a relatively inexpensive and easily accessible technique. In the past, validation studies for volume measurements have been conducted with static B-scanners, using a summation-of-areas technique.6,7 For real-time US scanners operated with hand-held transducers, volume estimations are generally made from measurements of the largest dimensions along the three principal axes, using an ellipsoid model.8

Scintigraphy is the second most frequently applied modality for thyroid volume measurements, as thyroid scintigraphy is also used for a functional diagnosis in the work up for radioiodine therapy. Different mathematical models (ellipsoid, cylinder and surface models) coexist for the calculation of the thyroid volume from two-dimensional scintigraphic data.9,10 Validation studies have been conducted with rectilinear scanners,9 but rarely with gamma cameras.11

Single photon emission computer tomography (SPECT) has been advocated for thyroid volume measurements. Although reportedly SPECT is more precise than planar imaging for such measurements,12-16 most of the described methods are not applicable with ‘off-the-shelf’ hardware and software, which hinders their clinical implementation. Substantial improvement of standard SPECT results has been reported with attenuation correction and scatter correction.17 Currently such corrections can be applied with commercially available equipment.

$^{124}$I PET has great research potential,18-21 but this modality has far too limited accessibility and is too expensive to be considered for clinical use.

Native CT is not suitable for thyroid volume measurements in patients with
Graves' disease. Radiographic contrast media are no option in this patient group, as they may block the thyroid's radioiodine uptake for weeks or even months.

Magnetic resonance imaging (MRI) has a documented place in thyroid imaging. MRI provides excellent delineation of the thyroid from the surrounding tissues, either with or without gadolinium contrast enhancement. The summation-of-areas technique has been well standardized and validated, and its reproducibility (with an error of about 1-2%) is very good.

Ultrasonography and thyroid scintigraphy have become standard clinical practice for measurements of the thyroid volume. The aim of this study was to assess the accuracy of these modalities.

8.2 Patients and methods

Patients
Twenty-five consecutive patients with Graves' hyperthyroidism who had been referred for radioiodine therapy were accrued. The study was approved by the hospital's ethics committee. Written informed consent was obtained from all patients. One patient suspended her participation with only the SPECT study lacking. In one patient, the MRI scan was incomplete at the caudal end, and consequently MRI volume measurements could not be done in this patient. Due to computer failures one SPECT study and one US study were lost after acquisition.

MRI
In all patients, the volume of the thyroid gland was measured on a Philips Gyroscan™ ACS-NT 1.5 T Powertrak 6000 (Philips Medical Systems, Best, The Netherlands). T1-weighted scans were acquired before and after intravenous administration of dimeglumine gadopentetate, 469.01 mg/ml (Magnevist®, Schering AG, Germany) (TR/TE: 552/20 msec; FOV 25 cm; 16 transverse slices, thickness 6 mm/inter slice gap 0.6 mm; NSA 2; total scanning time 3.47 min). A typical example of an MRI study is given in figure 8.1.

The images were processed on a Gyroview™ workstation (Philips Medical Systems, Best, The Netherlands). The circumferences of the thyroid gland were depicted and segmented manually with a mouse, and the area was calculated on each slice. The thyroid volume was then calculated with a summation-of-areas technique, using a multiplication factor of 1.1 to correct for the interslice gaps.
Figure 8.1  T1-weighted gadolinium enhanced thyroid MR study in patient #6 (only 6 cross-sections shown).
Planar scintigraphy

On the day before therapy, 2-13 days after the MRI scan, thyroid scintigraphy was done in all patients 20 min after intravenous administration of 120 MBq $^{99m}$Tc-pertechnetate. The acquisition was done with a rectangular field-of-view gamma camera (ADAC Argus™, ADAC Laboratories, Milpitas, CA) with LEHR collimation and with the patient in a supine position. Acquisition parameters: anterior view, $128 \times 128 \times 16$ matrix, zoom factor $\times 1$, pixel size 4.2 mm, acquisition time 300 s.

A 5×5-point median filter was applied to reduce image noise. A rectangular region of interest (ROI 1) was drawn including the entire thyroid gland and leaving out all nonthyroidal radioactivity concentrations, most notably the salivary glands. Within ROI 1, an area of 5×8 pixels with maximum count density was computed automatically. Using a lower threshold of 30% of this maximum value, an isocontour was created automatically around the thyroid (ROI 2). The 30% threshold level had been derived from phantom studies with volumes ranging from 10 to 40 ml. The thyroid surface was the number of pixels in ROI 2.
multiplied by the pixel size (4.2×4.2 mm). The thyroid volume was calculated with the empirical formula:

\[ V = 0.33 \times A^{3/2}, \]

where \( V \) equals the thyroid volume (in cm\(^3\)), and \( A \) the thyroid surface projection area (in cm\(^2\)).\(^9\) In figure 8.2, the PS images are displayed for the same patient as in figure 8.1.

**SPECT**

One intravenous administration of 120 MBq \(^{99m}\)Tc-pertechnetate was used for both the planar scintigraphy and the SPECT acquisition. Zoom factor (× 1) and matrix size (128×128×16) for SPECT were the same as for planar scintigraphy.

An ADAC Vertex\(^{\text{TM}}\) dual-detector rectangular FOV SPECT camera with Vantage\(^{\text{TM}}\) transmission hardware and software was used, with the two detectors (with Vantage\(^{\text{TM}}\) extra high-resolution collimators) in a perpendicular position. With the patient in the supine position, a 180° anterior rotation, starting from the 270° position, was completed with 32 azimuths at 25 s/azimuth. A matrix size of 128×128 was chosen for both SPECT and planar scintigraphy as a compromise between partial volume effect and acquisition time. Using a \(^{153}\)Gd transmission line source (containing approximately 175 MBq), transmission scanning was done during 24 s/azimuth simultaneously with the emission scan. Total scanning time was 26 min. A scatter window (111-125 keV) was set between the \(^{153}\)Gd transmission source peak (100 keV) and the \(^{99m}\)Tc photopeak (140 keV).

The reconstruction of the transmission scan was done with filtered back-projection, attenuation correction and correction for down-scatter of \(^{99m}\)Tc into the \(^{153}\)Gd window. For the emission scan an iterative maximum likelihood reconstruction algorithm with attenuation correction and scatter correction and resolution recovery was used (ADAC EXSPECT\(^{\text{TM}}\)). Post-processing measurements were done on a Silicon Graphics\(^{\text{TM}}\) workstation (MIPS 10000 processor) (Silicon Graphics, Mountain View, CA), using standard software. For noise reduction, an edge-preserving filter was applied.\(^{33}\) Within the largest transaxial cross-section of the thyroid a ROI of 4×4 pixels was placed in the center of the largest thyroid lobe. If both lobes appeared equally large, the right lobe was chosen. Within this ROI the average maximum pixel value was calculated. A threshold of 45% of this value was applied for the segmentation of the thyroid gland. This threshold value had been established with a least-squares method in experiments using different thresholds with 5% increments. In figure 8.3, the SPECT reconstructions are displayed for the same patient as in figure 8.1.
Ultrasonography

A real-time ultrasound scanner (Pie Medical Scanner 350, Pie Medical, Maastricht, The Netherlands) was used with a 7.5 MHz linear array transducer (width 3.8 cm). With the patient in a supine position and the neck slightly overextended, the thyroid lobes were scanned separately, and measurements were done in the three largest dimensions along the principal axes. In figure 8.4, transaxial US cross-sections are displayed for the same patient as in figure 8.1.
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Figure 8.4  Thyroid US in patient #6: transaxial cross-sections with approximately 1.5 cm interslice gaps.
The volume of each lobe was calculated with the formula for ellipsoid volumes:

\[ V = \frac{\pi}{6} L \times W \times D, \]

where \( L \) is the maximum length, \( W \) the maximum width and \( D \) the maximum depth, measured along the three principal axes of the thyroid lobes. The thyroid volume was the sum of the volumes of the two lobes.

**Statistical analysis**

All quantitative results from the PS, SPECT and US studies were compared with MRI as the gold standard. The statistical analysis was done with linear regression.

Table 8.1  Results of thyroid volume measurements with all four modalities.

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<th>PS (ml)</th>
<th>US (ml)</th>
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Figure 8.5  Linear regression analysis. Scatter plots for thyroid volumes measured with MRI versus (a) planar scintigraphy, (b) SPECT, and (c) ultrasound.
Figure 8.6  Difference versus mean. Bland and Altman plots for thyroid volumes measured with MRI versus (a) planar scintigraphy, (b) SPECT, and (c) ultrasound. Reference lines indicate +2 sd and −2 sd.
Figure 8.7   Thyroid volumes measured with MRI versus (a) planar scintigraphy, (b) SPECT, and (c) ultrasound. Y-axis: difference with MRI, expressed as a percentage of the MRI volume. Reference lines indicate deviations of +20% and −20%, respectively, from MRI measurements.
analysis, and with a method for the comparison of measurements as proposed by Bland and Altman, describing the accuracy of measurements in terms of bias and precision.

8.3 Results

Either with or without gadolinium contrast enhancement, MRI images showed excellent contrast between the thyroid and the surrounding soft tissues in all 25 patients. Both readers found it easier to do the segmentation on the gadolinium images, but no difficulties were experienced in the native images. The mean ± sd for the thyroid volumes measured with MRI was 25.0 ± 13.8 ml (range 7.0-56.3 ml). The results of the volume measurements with the four modalities are presented in table 8.1.

Comparisons of PS and MRI were available in 24 cases. The scintigraphic measurements had a low precision and a considerable bias, as illustrated in table 8.2 and figure 8.5a. The differences between planar scintigraphy and MRI were essentially independent of the thyroid size (figure 8.6a). The percentual difference (mean ± sd) between PS and MRI was -33.2 ± 57.6 (figure 8.7a).

SPECT and MRI data were compared in 22 cases. The differences between the volume estimations with these modalities were essentially independent of the thyroid size. The precision and bias were substantially better than for planar scintigraphy (see table 8.2 and figures 8.5b and 8.6b). The percentual difference (mean ± sd) between SPECT and MRI was -2.3 ± 30.5 (figure 8.7b).

A comparison between US and MRI could be made in 23 cases. Although the bias was large, the precision was good, and there was an excellent correlation with MRI (see table 8.2 and figure 8.5c). Larger differences were found in patients with larger thyroid volumes (figure 8.6c). The percentual difference (mean ± sd) between US and MRI was 27.8 ± 12.3 (figure 8.7c).

Table 8.2 Correlation, bias and precision for planar scintigraphy, SPECT and US versus MRI.

<table>
<thead>
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<th>linear regression</th>
<th>$R^2$</th>
<th>bias</th>
<th>precision</th>
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<td>planar scintigraphy (PS)</td>
<td>$PS = 0.73 \times MRI + 10.87$</td>
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<td>-4.00</td>
<td>17.64</td>
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<td>SPECT</td>
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<td>1.83</td>
<td>11.86</td>
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<td>$US = 0.77 \times MRI - 1.12$</td>
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<td>7.46</td>
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8.4 Discussion

MRI is recognized as a gold standard for volume measurements in general. Gadolinium enhanced MR imaging does not interfere with radiiodine therapy, as gadolinium chelates do not influence the iodide uptake or organification by the thyroid gland. In spite of the excellent imaging capabilities of MRI in several thyroid disorders, the limited availability and capacity as well as the relatively high cost have restrained its clinical application for thyroid volume measurements in patients with Graves’ disease. Even research in this field is scarce. In an adjacent clinical area – volume measurements of large multinodular goiters – excellent inter- and intraobserver agreement were found.

The correlation of PS measurements with MRI was poor. Another indicator of the disappointing performance of scintigraphy is the percentual difference from MRI measurements, as displayed in figure 8.7a. At an acceptance level of 20% difference from the MRI results, untoward volume estimations were obtained in two-thirds of all planar scintigraphic studies. The mean error was 33%; large overestimations and large underestimations were encountered. Similar problems were reported in other studies on Graves’ disease. Igl et al. found that thyroid volumes measured with scintigraphy were 33% larger than measured with US. Veen et al. demonstrated a moderate correlation ($R^2 = 0.72$) in a direct comparison of presurgical scintigraphic measurements and surgical thyroid specimens in 13 patients with Graves’ disease. Especially larger thyroid volumes were severely underestimated with scintigraphy.

Somewhat better results have been reported in patients with thyroid disorders other than Graves’ disease. Using a rectilinear scanner for their scintigraphic measurements in patients with large nodular goiters, Huysmans et al. found observer variations of 17% in comparison with MRI. Wesche et al. compared scintigraphic volume measurements with US (using a static B-scanner), also in patients with large nodular goiters. With a 20% threshold, they found smaller differences with a surface model than with an ellipsoid model, but in small diffuse goiters the discrepancies appeared to be larger with the surface model.

The relative imprecision of the surface model (with an average error of about 20%, maximum about 40%) was already stipulated by Himanka et al. at the introduction in 1955. This model was originally tested with a rectilinear scanner; it has never been properly validated for use with a gamma camera. Nevertheless, Himanka’s formula has enjoyed great popularity for over forty years. It should be noted that other mathematical approaches (including ellipsoid models) thus far have not yielded better results.
The point spread function for collimated gamma camera systems of about 1-1.5 cm and the need for background subtraction result in less favorable spatial resolution and in less accurate measurements of small objects. The accuracy of scintigraphic thyroid volume measurements is too low to justify their use for therapy dosage calculations in patients with Graves' disease. On the other hand, thyroid scintigraphy is still considered by most physicians as essential for a functional diagnosis in the work up for radioiodine therapy.

In the present investigation, SPECT with attenuation correction and scatter correction yielded a sizeable improvement over PS. In comparison with the gold standard, both the mean difference and the range were smaller than those of PS, and so were the percentual differences with MRI. However, at an acceptance level of 20% deviation from the MRI measurements, untoward volume estimations were still observed in one-third of all cases. The largest errors occurred in the lower volume range (<10 ml). The semi-automatic SPECT segmentation procedure that we propose is fast, easy to perform, and not liable to observer variations. It can be performed with standard commercial hardware and software. Others have indicated that more accurate volume determinations with SPECT are feasible with customized hardware and dedicated algorithms. It has been shown that the optimal threshold value depends on object size and contrast. The small size of the thyroid gland in combination with the limited system resolution makes this a challenging research area.

Thyroid SPECT may be a more cost-effective tool for thyroid volume measurements if it is substituted for, rather than added to, planar scintigraphy. This is a realistic option, as the differentiation of diffuse goiter from uni- or multinodular goiter is easily made with SPECT.

The large percentual differences between MRI and US are presented in figure 7c. At an acceptance level of 20% deviation from the MRI measurements, all US studies resulted in untoward volume estimations. This was caused by a substantial bias, viz. a large underestimation by US. The discrepancies were most pronounced for larger thyroid glands. The correlation of US with MRI, however, was near perfect ($R^2 = 0.96$) and from figure 7c it is apparent that a large percentage of US results could be quite acceptable if a correction factor were applied.

More accurate results had been obtained with static B-scanners. This type of US equipment provides a set of spatially well-defined cross-sections that can be accurately computed to a three-dimensional volume, with a summation-of-areas technique similar to those used in CT and MRI. The manufacturing of static B-scanners, however, has ceased a number of years ago. The ellipsoid models that are generally used for volume estimations with modern real-time scanners...
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are principally different; these models do not account for irregular organ shapes such as present in the thyroid.

The cost of US (which has to be added to that of scintigraphy) is moderate. This is one of the reasons for its widespread availability in clinics all over the world. 3D-US scanners are now being developed in which the transducer's position signal and the 2D-image signal are integrated into a 3D-volume set. When this modality becomes commercially available, a controlled study of its accuracy in measuring thyroid volumes is warranted.

At present scintigraphy is frequently used for thyroid volume measurements. In view of the large errors, this practice may be responsible for a substantial number of inadequate radioiodine therapy dosages. Thyroid scintigraphy is still considered as indispensable for a functional diagnosis. For this purpose, SPECT may be a good alternative. US is precise, but the accuracy may vary for specific scanners. Calibration of real-time US scanners is highly recommended before their implementation for volume measurements. We conclude that one of three options may be pursued for thyroid volume measurements: MRI + scintigraphy, ultrasound + scintigraphy, or SPECT. In a clinical environment the accuracy, the availability, the capacity and the cost of the various imaging modalities ultimately determine the physician's choice.

8.5 Acknowledgements

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