Comparison of methods for thyroid volume estimation in patients with Graves' disease

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Abstract. Individualised dosage models are frequently applied for radioiodine therapy in patients with Graves' hyperthyroidism, especially in Europe. In these dosage schemes the thyroid volume is an important parameter. Thyroid volume determinations are usually made with ultrasonography or with thyroid scintigraphy, although the accuracy of planar scintigraphy for this purpose is not well established. The aim of this study was to compare the accuracy of three modalities for the determination of the thyroid volume in patients with Graves' disease: planar scintigraphy (PS), single-photon emission tomography (SPET) and ultrasonography (US). These three modalities were compared with magnetic resonance imaging (MRI) as the gold standard. Thyroid volume estimations were performed in 25 patients with Graves' disease. The PS images were subjected to filtering and thresholding, and a standard surface formula was used to calculate the thyroid volume. With SPET the iteratively reconstructed thyroid images were filtered, and after applying a threshold method an automatic segmentation algorithm was used for the volume determinations. Thyroid volumes were estimated from the US images using the ellipsoid volume model for multiple two-dimensional measurements. For MRI, thyroid segmentation was performed manually in gadolinium-enhanced T1-weighted images and a summation-of-areas technique was used for the volume measurements. The thyroid volumes 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 suffered from a considerable bias (–4.0±17.6 ml). The differences between PS and MRI volume estimations had a very large spread (33±58%). For SPET both the correlation with MRI (R^2=0.84) and the bias (1.8±11.9 ml) were better than for PS. US had by far the best correlation with MRI (R^2=0.97) and the best precision, but the bias (6.8±7.5 ml) was not negligible. In conclusion, SPET is preferred over PS for accurate measurements of thyroid volume. US is the most accurate of the three modalities, if a correction is made for bias.

Keywords: Thyroid volume – Imaging modalities – Graves' disease – Radioiodine therapy

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Introduction

Radioiodine therapy is a safe and effective form of treatment for patients with Graves' hyperthyroidism, but dosage strategies remain a matter of debate. The relevance of thyroid volume measurements depends on the appropriateness of current dosage models. Individual dosage protocols are mandatory in several European countries because of radiation safety regulations [1]. Such protocols are based on measurements of thyroid volume and radioiodine uptake. This is expressed in the standardised dosage formula: $D=V\times[100\%/U]\times C$ (MBq), where D equals the radioiodine therapy dosage (MBq), V is the thyroid volume (ml), U is the 24-h thyroidal ^{131}I uptake (%) and C is a constant (usually 3.7 MBq/g) [2]. (This constant implies that the biological half-life of thyroidal radioiodine is invariable, which is an undue oversimplification [3, 4].)

It follows from the formula that the accuracy of dosage calculations is proportional to the accuracy of thyroid volume measurements. Validation of these measurements is therefore important. Scintigraphy is often used for thyroid volume estimations as a "by-product" of its application for functional diagnosis in the work-up for

radioiodine therapy [5, 6]. Validation studies have been conducted with rectilinear scanners [7], but rarely with gamma cameras [8]. Single-photon emission computer tomography (SPET) has also been advocated for thyroid volume measurements. Although SPET is reportedly more precise than planar scintigraphy for such measurements [7, 9, 10, 11], most of the described methods are not applicable with "off-the-shelf" hardware and software, which hinders their clinical implementation. Substantial improvement of thyroid SPET volume estimations can be obtained by applying attenuation correction and scatter correction [12]. Currently such corrections can be performed with commercially available equipment**.** Worldwide, ultrasonography (US) is probably the most frequently used modality for thyroid estimations in the routine clinical setting [13]. It is a relatively inexpensive and readily accessible technique. Volume estimations are generally made with an ellipsoid model using measurements of the largest dimensions along the three principal axes of the thyroid lobes [14]. This model has been validated by comparisons with autopsy specimens and with phantoms [13, 15, 16]. Magnetic resonance imaging (MRI) can serve as a gold standard for thyroid volume measurements. It has a well-documented place in thyroid imaging [17, 18, 19, 20, 21, 22, 23]. MR images provide excellent delineation of the thyroid from the surrounding tissues, either with or without gadolinium contrast enhancement [22, 23, 24, 25]. The summation-of-areas technique has been well standardised and validated, and its reproducibility (with errors of 1–2%) is very good [19, 20]. On the other hand the limited availability and capacity, as well as the relatively high cost, restrain the clinical application of MRI for thyroid volume measurements in patients with Graves' disease.

The aim of this study is to assess the accuracy of thyroid volume measurements with planar scintigraphy, SPET and US based on comparison with MRI in patients with Graves' disease.

Materials and methods

Patients. Twenty-five consecutive patients (22 female and 3 male, mean age 42.2 years, range 20.2–75.9 years) were accrued. All had been referred for radioiodine therapy because of recurrent Graves' hyperthyroidism after medical treatment. This investigation was approved by the hospital's ethics committee. Written informed consent was obtained from all patients. One patient suspended her participation with only the SPET study lacking. In one patient the MRI scan was incomplete at the caudal end, and consequently MRI volume measurements could not be performed. Due to computer operating failures the results of one SPET study and one US study were lost after acquisition.

Planar scintigraphy. On the day before radioiodine treatment and 2–13 days after the MRI scan, planar thyroid scintigraphy (PS) was done in all patients 20 min after intravenous administration of 120 MBq technetium-99m pertechnetate. The acquisition was done on a rectangular field-of-view gamma camera (ADAC Argus, ADAC Laboratories, Milpitas, Calif.) with an LEHR collimator, and with the patient in the supine position. The following acquisition parameters were used: anterior view, 256×256×16 matrix, zoom factor ×1, pixel size 1.1×1.1 mm, acquisition time 300 s. A 5×5-point median filter was applied to reduce image noise [21]. A rectangular region of interest (ROI 1) was drawn by hand. This ROI included the entire thyroid gland while excluding all non-thyroidal radioactivity concentrations, notably those in 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 gland (ROI 2). The optimal threshold level had been established in phantom studies with volumes ranging from 10 to 40 ml. The thyroid surface (A) was the number of pixels in ROI 2 multiplied by the pixel size. The thyroid volume was calculated with the formula $V=0.33\times A^{3/2}$, as described by Himanka and Larsson [5]. In Fig. 1 a typical PS image is displayed together with ROI 2 and the segmented image.

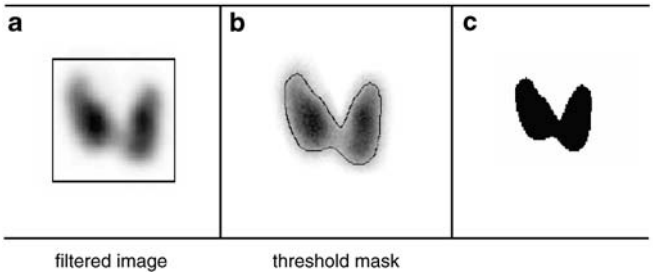

Fig. 1a–c. Planar scintigraphy of the thyroid in patient no. 6. **a** Box ROI around the thyroid; **b** automatic contour detection with a 30% threshold; **c** image after segmentation

SPET. A single intravenous administration of 120 MBq ^{99m}Tc-pertechnetate was used for both the planar scintigraphy and the SPET acquisition. An ADAC Vertex dual-detector rectangular field-of-view SPET camera with Vantage transmission hardware and software was used, with the two detectors with Vantage extra high-resolution (VXHR) collimators under a 90° angle. The zoom factor was ×1, and the matrix size 128×128×16. 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. Using two gadolinium-153 transmission line sources, each 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 peak (100 keV) and the ^{99m}Tc photopeak (140 keV). Transmission scans were reconstructed with filtered back-projection, and were corrected 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 window-based scatter correction as well as resolution recovery (ADAC EXSPECT) was used. Post-processing measurements were done on a Silicon Graphics workstation with MIPS 10000 processor (Silicon Graphics, Mountain View, Calif.). For noise reduction, a 3D edge-preserving 3×3×3-point median filter was applied [26]. Within the largest transaxial cross-section of the thyroid an ROI of 4×4 pixels was placed in the centre of the largest thyroid lobe. If both lobes appeared equally large, the right lobe was chosen. Within this ROI of maximum activity the average pixel value was calculated. A threshold of 45% of this value was used for the segmentation of the thyroid gland. This thresh-

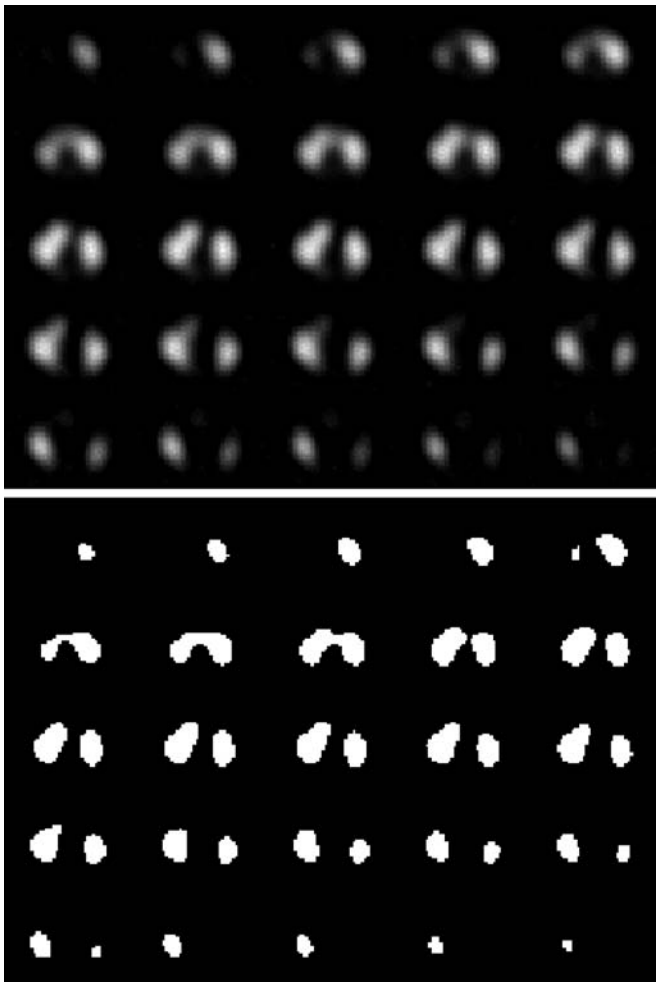

Fig. 2a, b. Thyroid SPET in patient no. 6. **a** Transaxial cross-sections; **b** the same cross-sections segmented with a 45% threshold

old had been established in patient studies, using a minimal mean squared error method. In Fig. 2 the SPET reconstructions and associated segmentations are displayed for the same patient as in Fig. 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. With the patient in the supine position and the neck slightly overextended, the thyroid lobes were scanned separately. In Fig. 3 the transaxial US cross-sections are displayed for the same patient as in Fig. 1. The volume of each lobe was calculated with the standard formula for ellipsoid volumes: $V=(\pi/6)\times L\times W\times D$ [27]. In this formula, L is the maximum length, W is the maximum width and D is the maximum depth, measured along the three principal axes of the thyroid lobes. The calculated thyroid volume was the sum of the volumes of the two lobes.

MRI. In all patients, the thyroid gland was scanned 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).

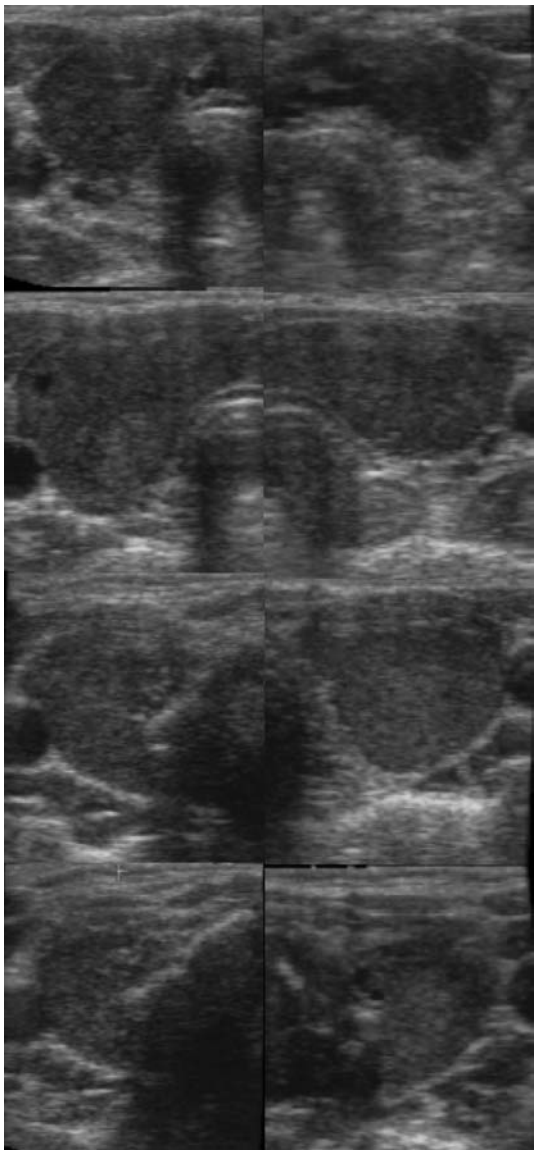

Fig. 3. Thyroid ultrasonography in patient no. 6. Transaxial cross-sections with approximately 1.5-cm interslice gaps

Acquisition parameters were as follows: TR/TE 552/20 ms; 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 MRI study is shown in Fig. 4. The images were processed on a Gyroview workstation (Philips Medical Systems, Best, The Netherlands). First, the circumferences of the thyroid gland were depicted and segmented manually, and the area was automatically calculated on each slice. (At this stage it appeared that in one patient the thyroid gland had not been scanned completely at the caudal end; this patient's MRI study was excluded from the analysis.) The thyroid volume was then calculated with a summation-of-areas technique, using a multiplication factor 1.1 to correct for the inter-slice gaps.

Statistical analysis. Linear regression analysis was performed to assess the correlation between different modalities. The difference-versus-mean method was applied for the comparison of mea-

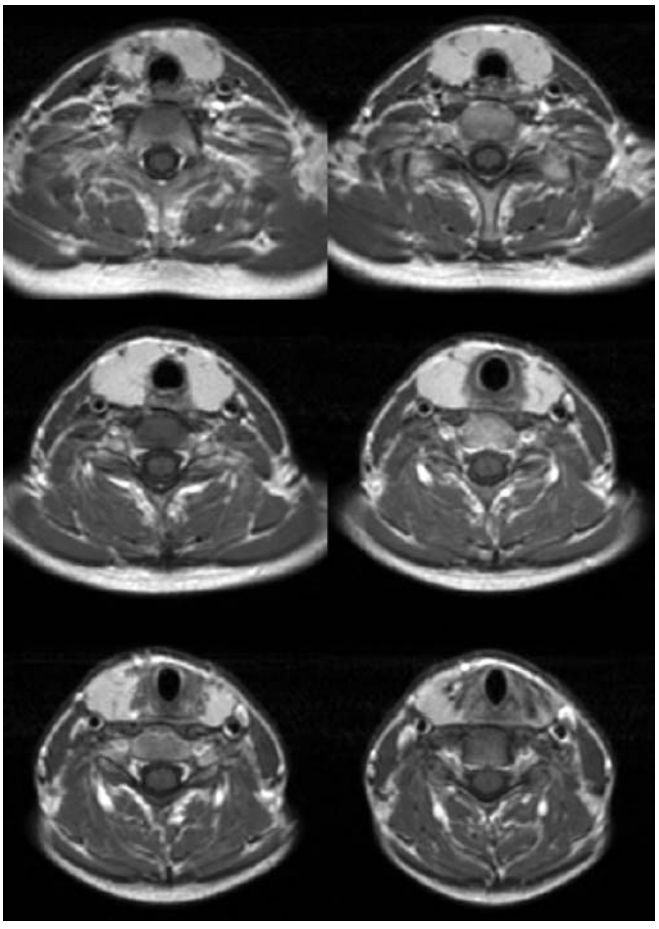

Fig. 4. T1-weighted gadolinium-enhanced thyroid MRI images in patient no. 6 (six cross-sections shown)

Table 1. Results of thyroid volume estimations with all four modalities (all measurements in ml)

	MRI	SPET	PS	US
Mean	33.9	29.6	35.2	26.1
SD	10.9	9.6	12.8	9.9

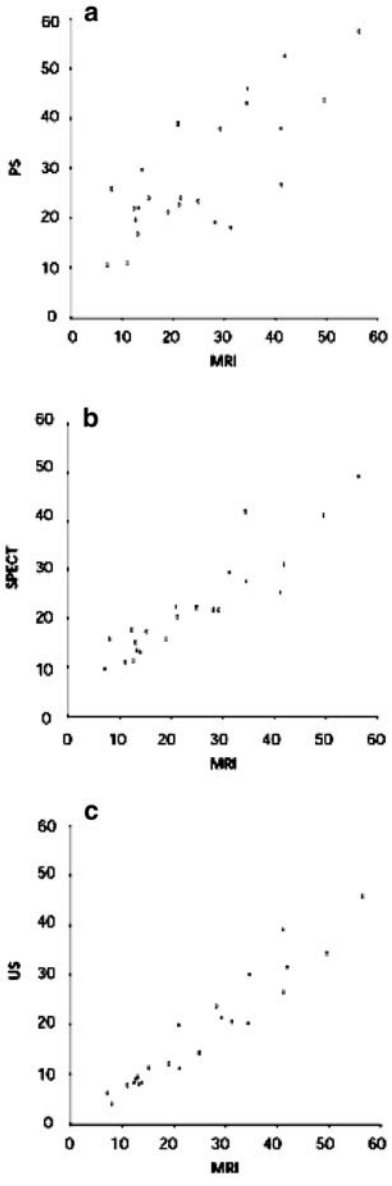

Fig. 5a–c. Linear regression scatter plots for thyroid volumes measured with MRI versus **a** PS, **b** SPET and **c** US

surements [28]. The predictive performance of the various tests was described by the bias and precision [29]. All statistical analyses were performed with SPSS 6.1 for Macintosh.

Results

Either with or without gadolinium contrast enhancement, MRI images provided excellent contrast between the thyroid and the surrounding soft tissues in all patients. Segmentations were performed on the gadolinium-enhanced images. The mean ± standard deviation (SD) for the thyroid volumes was 25.0±13.8 ml (range 7.0–56.3 ml). The results of the volume estimations with all four modalities are presented in Table 1. Figure 5 is the graphic representation of the regression analyses, whereas in Fig. 6 the precision and bias for the different modalities are illustrated by plots of difference versus mean [28, 29]. The numeric results are summarised in Table 2. In Fig. 7 the relative differences of MRI versus PS, SPET and US estimations are displayed.

Comparisons of PS and MRI were available in 24 cases. The PS measurements had the lowest precision of the three methods tested, and suffered from a considerable bias (Table 2, Fig. 6a). The relative difference between PS and MRI volume estimations [(MRI–PS)/(MRI×100%)] amounted to 33.2%±57.6% (mean±SD, see Fig. 7a).

Table 2. Correlation, bias and precision for PS, SPET and US versus MRI

	Linear regression	R^2	Bias	Precision
Planar scintigraphy (PS)	PS=0.73×MRI+10.87	0.61	−4.00	17.64
SPET	SPET=0.70×MRI+5.47	0.84	1.83	11.86
Ultrasonography (US)	US=0.77×MRI−1.12	0.97	6.79	7.46

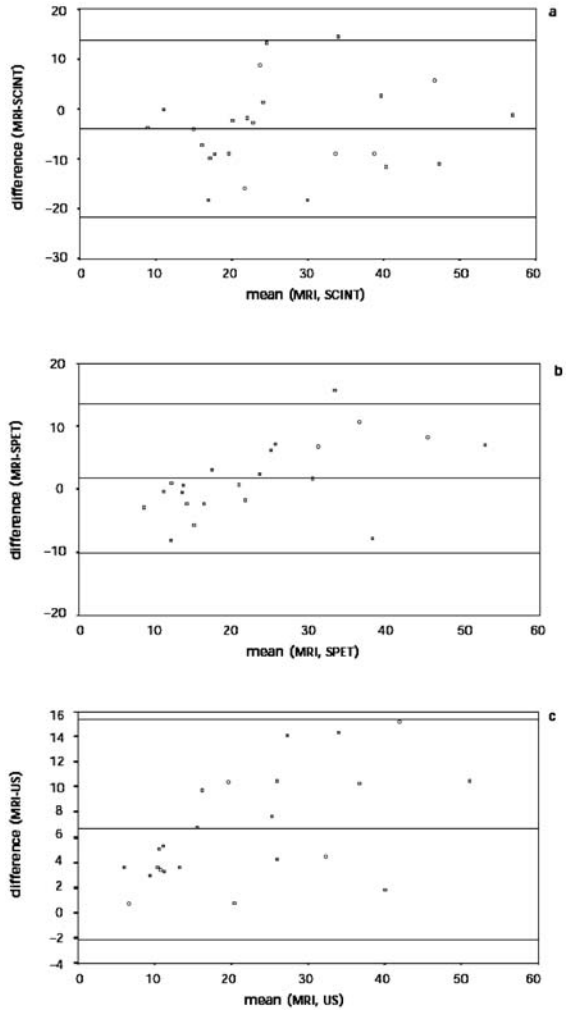

Fig. 6a–c. Plots of difference against mean for thyroid volumes measured with MRI versus **a** PS, **b** SPET and **c** US. Reference lines indicate +2SD and −2SD

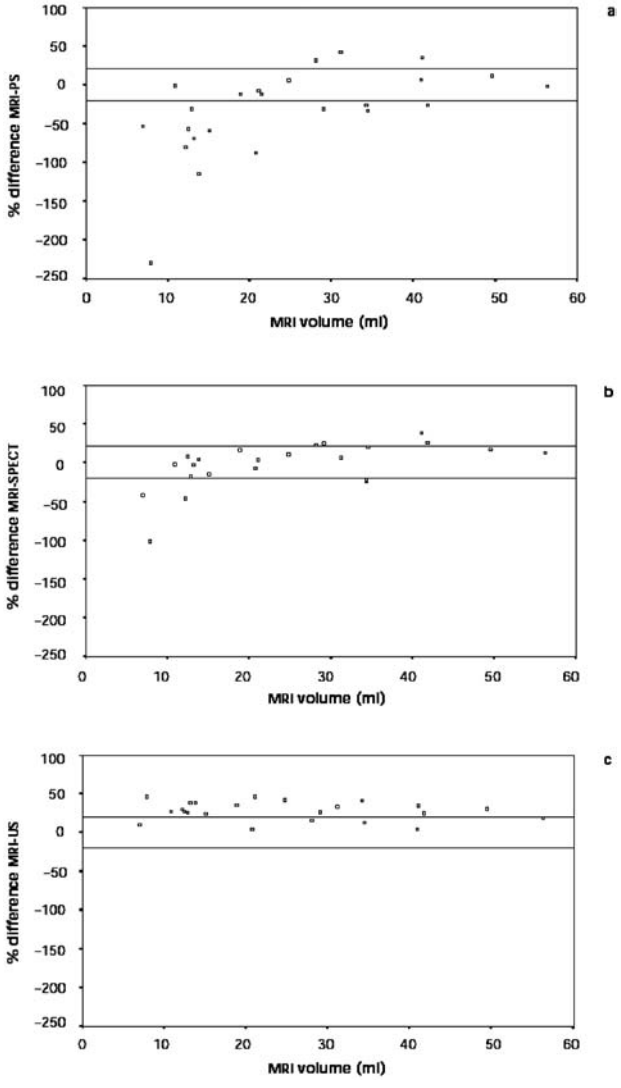

Fig. 7a–c. Thyroid volumes measured with MRI versus **a** PS, **b** SPET and **c** US. X-axis: MRI volume (ml); Y-axis: (MRI minus other modality)/(MRI×100%). Reference lines indicate deviations of +20% and 20% from MRI measurements

SPET and MRI data were compared in 22 cases. The correlation with MRI (R^2=0.84) was better for SPET than for PS, and so were the precision and bias (Table 2, Fig. 6b). The relative difference between SPET and MRI was 2.3%±30.5%; the largest differences were found in patients with thyroid volumes <15 ml (Fig. 7b).

A comparison between US and MRI was made in 23 cases. US had the best correlation with MRI (R^2=0.97). The bias for US was larger than for SPET and for PS, but the precision was better (Table 2, Fig. 6c). The relative differences between US and MRI were about equal over the entire volume range (Fig. 7c).

Discussion

In this investigation we compared planar scintigraphy (PS), SPET and ultrasonography (US) with a gold stan-

dard (MRI). Specific disadvantages were encountered with each of these three methods. We noted large over-estimations as well as under-estimations of thyroid volumes with PS (33±58%). PS volume estimates reported by others were 33% larger than with US [30]. Untoward volume estimations were obtained with PS in two-thirds of all patient studies, when 20% difference from MRI was accepted (Fig. 7). The correlation of PS and MRI estimates was relatively poor (R^2=0.61). Other researchers reported a somewhat better correlation (R^2=0.72) in a direct comparison of pre-surgical PS measurements and post-surgical thyroid specimens [8]. Several models (surface, cylinder, ellipsoid) exist for thyroid volume estimations with PS. The limited precision of the surface model (with an average error of about 20%) was stipulated by the authors at its introduction in 1955 [5]. Originally tested with a rectilinear scanner, this model has never been properly validated for use with a gamma camera. Nevertheless, it has enjoyed great popularity for over 40 years. It should be stressed that other approaches (including ellipsoid and cylinder models) do not yield better results [6]. In thyroid conditions other than Graves' disease, volume estimations seem to be equally dependent on the imaging modality. A very poor correlation between MRI and rectilinear scanner measurements (R^2=0.44) was reported in a study of large nodular goitres [20].

The point spread function of about 1–1.5 cm for collimated gamma camera systems and the need for background subtraction result in less favourable spatial resolution and in less accurate measurements of small objects [31, 32]. PS provides two-dimensional imaging; the lack of the third dimension (depth) must inevitably lead to inaccurate volume estimates. In our view the poor accuracy of PS precludes its use for therapeutic dosage calculations in patients with Graves' disease. It may even be argued that PS volume estimations are one of the major factors contributing to inadequate radioiodine therapy dosages. The qualitative role of thyroid PS for functional diagnosis in thyrotoxic patients is not discussed here.

In the present investigation, SPET with attenuation correction and scatter correction yielded more accurate volume estimations than PS. In comparison with the gold standard, both the mean and the range of the differences were smaller than those of PS. Still, in one-third of all cases volume estimations showed more than 20% difference from MRI. Differences occurred mainly in smaller glands (<15 ml), and are probably caused by resolution effects. In particular, in small objects the limited resolution of SPET may lead to significant overestimation of volumes. Corrections may be feasible by using finer image grids in concert with better modelling of the collimator blurring and scatter during the image reconstruction [33], as well as advanced segmentation methods [12, 34, 35]. The semi-automatic SPET segmentation procedure used in the present work can be performed on most nuclear medicine workstations, is easy and fast to perform, and is not liable to observer variations. A fixed threshold was used, although optimal threshold values depend on object size and contrast [11]. The small size of the thyroid gland in combination with the limited spatial image resolution of SPET makes volume estimation a challenging research area.

The correlation of US with MRI (R^2=0.97) was much better than for PS and SPET, but 74% of the US volume estimations showed more than 20% difference from MRI. This was due to bias (in this case: underestimation). Underestimation of thyroid volumes by US had also been observed in other investigations [13, 15]. Substantial inter-equipment variability has been demonstrated, and therefore calibration of US equipment may be considered [34]. More accurate results have been obtained with the now outdated static B-scanners [37, 38]. This type of US equipment provides a set of spatially well-defined cross-sections that can be accurately computed to a three-dimensional volume using a summation-of-areas technique similar to CT and MRI. With modern real-time scanners, 2D-measurements and ellipsoid models are used for volume estimations [13, 15, 27, 39]. Adaptations to the standard ellipsoid formula may improve the accuracy [40]. Currently 3D scanners are being developed; in these systems the transducer position signal and the 2D image signal are integrated into a 3D volume set [41]. When this modality becomes widely available, a controlled study of its accuracy in measuring thyroid volumes is warranted.

In a clinical environment not only the accuracy but also the availability, capacity and cost of the various imaging modalities ultimately determine the physician's choice.

In conclusion, comparisons with MRI indicate that thyroid volume estimations with planar scintigraphy are inaccurate, and that SPET can offer an acceptable alternative. However, ultrasonography is superior for this purpose if a correction is made for bias.

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