

# Interobserver Variation for Ultrasound Determination of Thyroid Nodule Volumes

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Thyroid ultrasound is used in the routine clinical assessment and the follow-up of thyroid disorders. The follow-up of patients with thyroid nodules is mostly based on thyroid nodule volume determinations performed by different observers. However, for the judgment of treatment effects there is uncertainty about the interobserver variation of thyroid nodule volume measurements by ultrasound because there are no prospective blinded studies available comparing the interobserver variation in thyroid nodule volume measurement. The aim of our study was therefore to determine the variation of thyroid nodule volume determinations for different observers. We conducted a prospective blinded trial. Our study population consisted of 42 probands (8 men, 34 women) with an uniform distribution of thyroid nodule sizes (25 uninodular and 17 multinodular thyroid glands). We compared the results of 3 ultrasonographers with certified experience in thyroid ultrasound. The interobserver variation for the determination of thyroid nodule volume ( $n = 38$ ) was 48.96% for the ellipsoid method and 48.64% for the planimetric method. The interobserver variation for determining thyroid volume ( $n = 40$ ) was 23.69% for the ellipsoid method and 17.82% for the planimetric method. A regression analysis revealed that the probability for the identification of the same nodule in nodular thyroids by all sonographers is 90%, if the nodule is at least 15mm in greatest diameter. Future investigations should not describe changes in nodule volume less than 50% as therapy effects because only volume changes of at least 49% or more can be interpreted as nodule shrinkage or growth. Reporting of nodule volume modification 50% or more and lack of information for ultrasound procedures introduce a bias in studies evaluating the effects of nodule treatments. The clinical interpretation of a shrinking/growing thyroid nodule based on volume determinations by ultrasound is not well established because it is difficult to reproduce a two-dimensional image plane for follow-up studies.

## Introduction

THYROID ULTRASOUND is used in the routine clinical assessment of thyroid disorders as well as in epidemiologic surveys evaluating the prevalence of thyroid disorders (1–5). Thyroid ultrasound is very sensitive for the detection of nonpalpable thyroid nodules. Focal lesions of 2 mm in diameter are detectable by high-resolution ultrasound (6,7). In patients/probands with and without clinically apparent thyroid disorders it detects thyroid nodules in up to 30% of patients/probands (1,2).

Several recent meta-analyses of the effect of thyroid hormone treatment of thyroid nodules reported difficulties in evaluating previous studies and to establish an evidence based therapeutic effect for thyroid hormone treatment (8–10). Among other uncertainties the lack of data concerning interobserver variations for the determination of thyroid

nodule volumes and the arbitrary decisions to regard thyroid nodule volume changes of 50% or more (11–13) or 20%–49% (11,14,15) as relevant is a major obstacle for the assessment of therapeutic effects. The interobserver and intraobserver variability for the ultrasound determination of thyroid volumes have been evaluated by several investigators (16–19). Moreover, interobserver correlations for thyroid volume measurements have been reported (17,20–22). However, there are no prospective blinded studies comparing the results of ultrasonography in thyroid nodule volume measurements neither between different investigators nor for the intraobserver reliability (8,23). Because thyroid nodules are more difficult to measure and to detect than the thyroid gland because of their smaller volume and thus the probability for larger volume measurement errors and because of the necessity to distinguish the nodule from the surrounding thyroid it is unlikely that the data for ultrasound ob-

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server variability of thyroid gland volume measurements can be applied to thyroid nodule volume determinations. We therefore investigated the interobserver variation in the measurement of nodule volume in a blinded prospective clinical trial. The aim of our study was therefore to determine the variation of different observers in ultrasound measurement of the nodule volume because follow up investigations are most often done by different investigators. Because various methods have been used for measuring thyroid volumes (17), we calculated planimetric as well as elliptic volumetry methods.

## Materials and Methods

### Subjects

We conducted a prospective blinded trial in 2003. The study was approved by the local Ethics Committee (no. 014/2003). All probands gave written informed consent. Our study population consisted of 42 probands (8 men, 34 women). We prospectively calculated the number of probands necessary to achieve a greater than 0.90 power or greater than 90% probability of detecting an effect (thyroid nodule volume observer differences). We calculated a minimum sample size of 35 probands to achieve a greater than 0.90 power at the given significance level ( $\alpha = 0.05$ ). We chose a larger sample size to achieve greater ability to detect a significant difference. The probands were randomly selected from patients with asymptomatic thyroid nodules that were identified during consultations of our university outpatient clinic in 2002. In order to guarantee an uniform distribution of the nodule sizes we selected 14 probands with initial nodule sizes less than 1 mL, 14 probands with initial nodule sizes 1–2 mL and 14 probands with initial nodule sizes greater than 2 mL. The study measurements were done by three certified ultrasonographers with 3–4 years experience in thyroid ultrasound and without knowledge about the patient's medical history or the existence of any thyroid disease (goiter or nodules). All probands were living in a borderline iodine sufficient area with a mean urinary iodine excretion of 109  $\mu\text{g}$  of iodine per gram of creatinine (24).

### *Ultrasonography and volumetry of the thyroid gland and of the thyroid nodules*

Prior to the ultrasound measurements all three ultrasonographers performed five calibrating cases (no study probands) to define correct measuring points (see below). The observers used a high-resolution Siemens Adara ultrasound imaging system (Siemens, Mountain View, CA) with a 7.5-MHz linear transducer with an effective length of 85 mm. For each examination the probands were in the supine position with extension of the neck. The observer kept the transducer perpendicular to the skin. The results were documented by a study nurse and each examination was recorded on videotape to be available for later examination.

It is likely, that the accuracy of ultrasound measurements of thyroid nodules between different investigators will be influenced by (1) the different interobserver performances, (2) the echogenicity of the surrounding thyroid tissue or acoustic impedance (difference in tissue characteristics), (3) the size of a nodule, especially if a history of thyroid nod-

ules is not known, (4) the number of thyroid nodules in a lobe, and (5) the different geometric assumptions that thyroid nodules are an ellipse or a sphere.

The volumes of the thyroid gland and of the thyroid nodules were calculated in two different ways. Planimetric volumetry was compared to the elliptical method. Also the echogenicities of the thyroids and of thyroid nodules were assessed. According to the protocol the interobserver variations for calculation of thyroid and nodule volumes were estimated. Moreover, the probability to identify a thyroid nodule in a thyroid lobe and the probability to reliably measure this thyroid structure depending on the nodule size were investigated in uninodular as well as in multinodular thyroid glands. All 84 thyroid lobes of 42 probands were explored and all available nodules were measured. Moreover, in all cases (uninodular and multinodular thyroids or thyroid lobes) and for each investigator the thyroid nodule identified as the largest, was documented. We documented cases of nonagreement.

Volumes calculated by the ellipsoid formula are based on the assumption that each lobe or nodule is an ellipsoid (17,18,25). The ellipsoid method calculates volumes on two-dimensional images by measuring glandular size in longitudinal, anteroposterior and transverse dimensions. The planimetric method is based on the circumferences of the thyroid lobe or nodule in two orthogonal planes. Furthermore, the nodule sizes were estimated by defining the largest diameter. Before starting the statistical analyses the video tapes were reanalysed by a trained medical student to investigate if all observers measured the same thyroid nodule and to avoid introducing a bias through nonagreement in detecting the same thyroid structure. All cases of agreement and nonagreement between the observers were documented.

As mentioned, follow-up investigations of thyroid nodule volumes are most often done by different investigators. Moreover, to avoid introducing a bias through recognizing a probands diagnosis by double determination at the same day we did not address the intraobserver reliability in our study. Also, our observer variation study was performed on the same day to avoid the possibility of day-to-day measurement variation. The aim of our study was not to determine the true thyroid or nodule volumes by submersion of the resected thyroid lobes or nodules because follow-up investigations by ultrasound should contribute to preserve a (benign) functioning organ.

### *Ellipsoid method/formula*

Each lobe was measured separately. Measurements of the thyroid gland volume started with the cross sectional screen picture. The maximal width of the lobe was measured between the most medial (imaginary line that was vertically drawn along the lateral part of the trachea) to the most lateral part of the lobe on the screen picture. The maximal depth of the lobe was measured in the same screen image vertically in the middle half of the lobe. The length was assessed in the longitudinal screen image as the maximal length from the most cranial to the most caudal part of the lobe (17,19). The isthmus was ignored as previously described (17). Moreover, in the cross-sectional and longitudinal screen pictures the maximal width, depth, and length of the nodules were measured. Thereby, the observers searched for the maximal

extension of the nodules. Thereafter, volumes were calculated using the formula of the rotation ellipsoid:

$$V_{\text{ellipsoid}} = \pi/6 * D_{\text{length}} * D_{\text{width}} * D_{\text{depth}}$$

*Planimetric method/formula*

Each observer outlined the area of each lobe or nodule manually with the track ball. The lobe including the isthmus was measured in the cross-sectional and longitudinal screen image. At each step, the two-dimensional ultrasound image of the thyroid gland or nodule was outlined and the image was integrated automatically by the computer to give the longitudinal and cross-sectional area ( $A_{\text{long}}$  and  $A_{\text{cross}}$ ). In the longitudinal and cross sectional screen image the maximal depth of the lobe or nodule was measured ( $D_{\text{long}}$  and  $D_{\text{cross}}$ ). The area of the lobe or nodule was quantified by counting the pixels in the outlined region and multiplying by the pixel area (17,19,26). The nodules were also measured in the longitudinal and cross-sectional screen image. We determined the volumes using the two-dimensional formula of planimetry:

$$V_{\text{plan}} = \frac{\pi}{6} * D_{\text{long}} * 4 \frac{A_{\text{long}}}{\pi * D_{\text{long}}} * 4 \frac{A_{\text{cross}}}{\pi * D_{\text{cross}}}$$

*Spherical method (for determining nodule volumes)*

Estimation of the thyroid nodule volume by using the largest diameter ( $D_{\text{max}}$ ) is also used in clinical studies on the assumption that the shape of the nodule is a sphere (27). The largest radius ( $D_{\text{max}}/2$ ) is found subjectively in the longitudinal or cross-sectional view as the maximal extension of the nodule.

*Statistics*

Measurement errors are proportional to the mean of the volumes observed by the three investigators. To estimate the interobserver coefficient of variation (CV), we used the logarithmic method as proposed by Bland et al. (28–30). After logarithmic transformation of the data, the within-subject variance can be assumed to be the same for all patients. We therefore estimate this common within-subject variance (CLWSVAR) by calculating the mean of all within-subject variance estimates on the log scale. A confidence interval for this estimate is derived observing that the estimate of CLWSVAR divided by the true value is distributed as  $\chi^2 (n*(m-1)) / (n*(m-1))$ . The CV then is estimated as  $\sqrt{\text{CLWSVAR}} - 1$ . A confidence interval for the estimate of

the CV is calculated by back-transforming the confidence interval for CLWSVAR. Note that simply taking the mean of the estimates of the within-subject coefficient of variation on the original scale (18,25) leads to a marked underestimation of the interobserver coefficient of variation as can be confirmed by simulation ([www.users.york.ac.uk/~mb55/meas/cv.htm](http://www.users.york.ac.uk/~mb55/meas/cv.htm)). We used SPSS 11.0 statistical software (SPSS Inc., Chicago) and Excel (Microsoft, Seattle, IL WA).

**Results**

The mean age of our study population consisting of 42 probands was  $49.26 \pm 11.48$  years ( $\pm$  standard deviation [SD]), ranging from 24 to 69 years.

The interobserver variation for determining thyroid volume was 23.69%, ranging from 19.69% to 27.82% for the ellipsoid method (Table 1) and 17.82%, ranging from 14.83% to 20.88% for the planimetric method (Table 1).

The three sonographers identified 51 versus 53 versus 58 thyroid nodules in 23 probands with uninodular thyroid lobes and in 17 probands with multinodular thyroid lobes. Data of two probands were excluded because of withdrawn consent.

The investigators agreed concerning the measurement of 38 thyroid nodules identified as the largest nodule. The interobserver variation of the ultrasonographers for the calculation of the thyroid nodule volume ( $n = 38$ ) was 48.96%, ranging from 39.83%–58.67% for the ellipsoid method and 48.64%, ranging from 39.57%–58.28% for the planimetric method. The interobserver variation for the determination of the greatest diameter of a thyroid nodule ( $n = 38$ ) was 15.95%, ranging from 13.26%–18.7%. To highlight the influence of the associated measurement error for each dimension of the nodules on the mathematical product of three separate measurements for the ellipsoid method, the much smaller interobserver variation for single dimensions of thyroid nodules in comparison to nodule volume variation is given in Table 2.

Moreover, we modeled the probability for interobserver agreement in thyroid nodule detection and thyroid nodule volume estimation.

Figure 1 displays the data for the ellipsoid method plotting deviations of single volume measurements from the mean against mean nodule volumes. As to be expected absolute deviations increase with mean nodule volumes (left panel) while logarithmic deviations show a band-structure indicating that errors are approximately independent from the underlying nodule volume. Plots for the planimetric method looks similar.

TABLE 1. INTEROBSERVER VARIATION FOR THE DETERMINATION OF THE THYROID VOLUME BY THE ELLIPSOID METHOD AND BY THE PLANIMETRIC METHOD

	<i>Interobserver variation by the ellipsoid method</i>	<i>Interobserver variation by the planimetric method</i>
Left lobe	27.73 (22.98, 32.65)	28.12 (23.24, 33.18)
Right lobe	35.63 (29.38, 42.17)	32.05 (26.42, 37.92)
Total thyroid volume	23.69 (19.69, 27.82)	17.82 (14.83, 20.88)

Thyroid volumes obtained by the ellipsoid method and by the planimetric method. Interobserver variations are given for each lobe and the total thyroid volume. Values for interobserver variation are percentages. Values in brackets denote the 95% confidence interval of the interobserver variation.

T1

T2

F1

TABLE 2. INTEROBSERVER VARIATION OF SINGLE DIMENSIONS OF THYROID NODULES IN COMPARISON TO NODULE VOLUME VARIATION

	<i>Interobserver variation</i>
Nodule volume	48.96 (39.83, 58.67)
Mediolateral diameter	21.21 (17.56, 24.96)
Anteroposterior diameter	20.99 (17.38, 24.70)
Craniocaudal diameter	19.89 (16.48, 23.38)

Dimensions obtained by using the ellipsoid method. Interobserver variations are given for each single dimension and for the total thyroid nodule volume. Values for interobserver variation are percentages. Values in brackets denote the 95% confidence interval of the interobserver variation.

**T3** As illustrated in Table 3 the probability to identify a thyroid nodule in an uni- or multinodular thyroid/ thyroid lobe depends on the greatest diameter of a nodule. If a nodule was greater than 15mm in diameter all sonographers identified the same nodule, while only one third of nodules smaller than 10 mm in greatest diameter could be identified as the same structure.

To further clarify the influence of the thyroid nodule size on the probability to identify these structures by different observers we used the greatest nodule diameter as the predictor in a logistic regression assuming (Table 3) that observer agreement is depending on nodule size values. Figure 2 shows a regression analysis revealing that the probability for the identification of the same thyroid nodule by all sonographers is 90%, if the nodule is at least 15 mm in greatest diameter. Because Table 3 did not reveal a dif-

**F2** ference between detection of thyroid nodules in uni- or multinodular thyroids, regression analysis was performed for all thyroid nodules. The predictor variables X (diameters) were able to provide information for predicting Y as given in Figure 2.

In addition to these findings, there was a lack of influence through echogenicity or thyroid volume on the thyroid nodules observer variation ( $p > 0.4$ ).

**Discussion**

Many clinical trials have investigated the changes of thyroid nodule volumes without pharmacotherapy or in response to therapies with levothyroxine or iodine. During most of these trials the nodule volumes were determined by several investigators (12,23,27,31–33). However, to our knowledge there are no prospective blinded trials available that compare the interobserver reliability of thyroid nodule measurement although this information would be crucial for the interpretation of these study results. In our investigation, the interobserver variability was similar for the planimetric method in comparison to the ellipsoid method for thyroid nodule volume estimation (48.64% versus 48.96%) as well as for thyroid volume measurement (17.82% versus 23.69%). The interobserver variation of both two-dimensional methods for thyroid volume estimation was similar to previous investigations (18,19). Because the measurement error is related to the magnitude of the measurement, statistic methods used in previous investigations could underestimate the interobserver reliability (18,25). A logarithmic transformation of the data, as used in our investigation, solves this problem (28,30).

Some authors reported an increase in nodule volume of 30% or more as indicative for nodule volume changes (23,27).

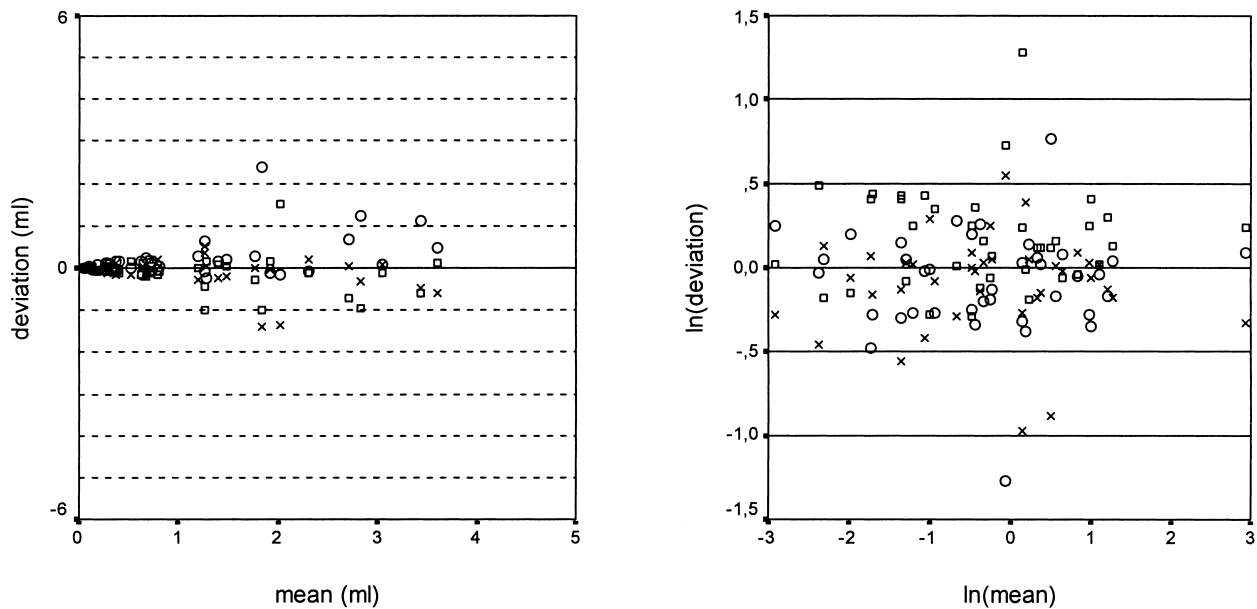


FIG. 1. Deviation of the nodule volumes determined by the three investigators from the mean nodule volume. The x-axis represents the mean nodule volumes in milliliters on the original scale (left) and on the logarithmic scale (right). The y-axis represents the deviation from the mean in milliliter on the original scale (left) and on the logarithmic scale (right) for the three observers. Volumes in Figure 1 are estimated by the ellipsoid method. □, Investigator 1; ×, Investigator 2; ○, Investigator 3.

TABLE 3. PROBABILITY TO IDENTIFY THE SAME THYROID STRUCTURE DEPENDING ON ITS DIAMETER

Diameter	Overall number of nodules as identified at least by 1 observer (=agreement cases +nonagreement cases)	Total number of nodules identified by all sonographers (=agreement cases)	Probability to identify the same nodule (=agreement cases/nonagreement)
1. Overall thyroid nodules in uninodular as well as multinodular thyroids			
> 15 mm	18	18	100,00%
10–15 mm	22	16	73,00%
< 10 mm	18	6	33,00%
2. Thyroid nodules in uninodular thyroids			
> 15 mm	15	15	100,00%
10–15 mm	16	11	68,75%
< 10 mm	15	6	40,00%
3. Thyroid nodules in multinodular thyroids			
> 15 mm	4	4	100,00%
10–15 mm	5	3	60,00%
< 10 mm	3	1	33,33%

Probability for consens of the 3 ultrasonographers in identifying a thyroid nodule. Cases of agreement (percentages, column 4) are total numbers of nodules unanimously identified by all sonographers (column 3) divided by the overall numbers of nodules identified at least by one investigator (column 2).

Furthermore, many study protocols do not give details for the interobserver reliability (12,23,27,31–34). If we assume that the interobserver reliability for thyroid nodule measurement is approximately 50% we have to consider that we can just reliably say that the nodule volume changed at all if nodules were found to increase or decrease their volumes 50% or more. Therefore, the cut off for thyroid nodule vol-

ume reduction or nodule growth 50% or more as used in most studies (13,31,33,35–37) investigating the effect of thyroid hormones on thyroid nodule volume reduction after treatment periods of 6–18 month appears to be appropriate and safe. Smaller rates of thyroid nodule volume reduction ( $\leq 50\%$ ) were not described in most studies (12,33–35,37) because of unknown observer reliability in ultrasound measurement of thyroid nodules. Moreover, the probability to identify the same thyroid structure by different investigators depends on the volume (or diameter) of a nodule. Because several authors investigated the outcome of pharmacotherapy on thyroid nodule volume or diameters in patients harboring small thyroid nodules, that is less than 1.5 cm in diameter (11,33–35), some nodules could have remained unidentified or could have been misclassified in these studies. Also reports of thyroid nodules that disappeared after treatment (13,31,37) could be attributable to an ultrasound detection failure.

Because of the necessity to distinguish the nodule from the surrounding thyroid, we expected a significant influence through echogenicity or thyroid volume on the thyroid nodules observer variation. Surprisingly, we found no influence through echogenicity or thyroid volume on the variation coefficient.

What do our results mean for further follow-up investigations? With an interobserver variability for thyroid nodule volume measurements in the order of 50% as seen in this study, the observation of a 50% volume change on follow-up by an independent investigator means that there is a chance of approximately two thirds that the underlying “true” volume did not change at all. However, it is reasonable to assume, that the reproducibility between two investigations is better, if the previous ultrasound findings are known. For that reason authors should disclose their ultrasound procedures. They should specify if there were data from previous ultrasound findings available for the second investigator. Results of studies and metaanalyses investigating thyroid nodule growth or reduction and describing rates

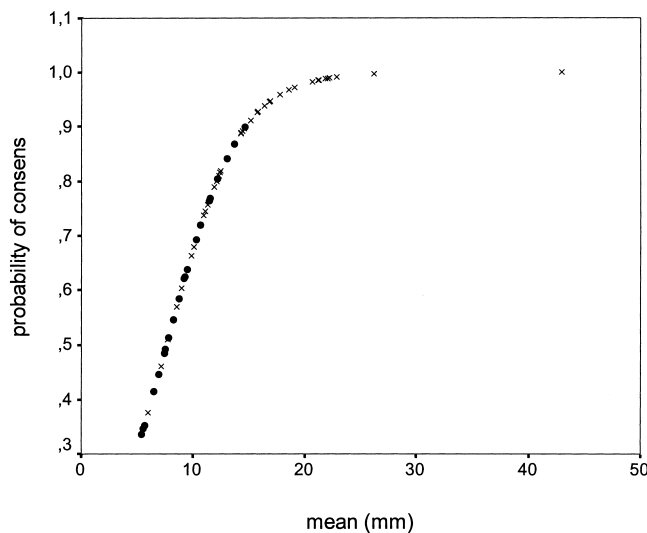


FIG. 2. Regression analysis for the identification of the same thyroid nodule by all sonographers. The x-axis represents the mean diameter of the thyroid nodules. At a given mean diameter of a thyroid nodule (x-axis) the slope of the regression line and the intercept with the y-axis represent the probability to identify the same thyroid nodule in uninodular and multinodular thyroids by all sonographers. Consens takes on a value of 1 if all three observers agreed in identifying a thyroid nodule and 0 for failure to agree. ● consens = 0, × consens = 1.

of nodule volume growth/reduction 50% or less need to be questioned. Rates of nodule volume modification 50% or less and lack of information for ultrasound procedures introduce a bias (23,27,34,37).

Moreover, a distinction should be made between the importance of interobserver variation for the estimation of a treatment effect in a single individual and the possibility of detecting smaller treatment effects in a study group of patients despite the inaccuracy of two-dimensional ultrasound. The individual management decisions should not be based on nodule volume changes of less than 50%. Clinical trials may detect smaller difference in mean volume change. However, this requires substantial sample sizes, for example, to detect a 10% difference in mean volume change when interobserver variability is about 40% requires approximately 340 patients per group. In addition, the clinical significance of such a finding may be disputable.

The use of color-flow Doppler could enhance the detectability of small thyroid nodules (<1.5 cm). The quality and reproducibility of two-dimensional ultrasound examinations are limited by the subjectivity and experience of the investigator. The problems for the investigator are to interpret two-dimensional images at some (arbitrary) angle in the lobe and to integrate the information of multiple plan images in a three-dimensional anatomic structure (26). The three diameters that are required for the volume determinations are measured in at least two images. Most sonographers use measurements of the depth, width and length of the thyroid gland from two orthogonal views and assume an ellipsoid shape as described. This clinical practice can lead to considerable interobserver variability and moreover to incorrect diagnoses (26,38) because organs are not correctly described by simple geometric figures. It is known, that the difference between thyroid volume estimation by three-dimensional versus two-dimensional ultrasound compared to submersion of the resected thyroid lobe is lower for the three-dimensional method. The standard deviation of the normalized volume differences (thyroid volume ultrasound measurement versus submersion of the resected thyroid lobe) was 9.7% for three-dimensional ultrasound versus 26.9% for two-dimensional ultrasound (19). However, three-dimensional ultrasound has not been compared to the two-dimensional method for thyroid nodule volume determination and is still today not widely available.

In conclusion

- The interobserver variation of thyroid nodule ultrasound measurement is approximately 50%.
- Future investigations should carefully describe changes in nodule volume less than 50% since probably only volume changes of at least 49% or more can be interpreted as nodule shrinkage or growth or as therapy effects.
- The clinical interpretation of a shrinking/growing thyroid nodule based on volume determinations by ultrasound is not well established because it is difficult to reproduce a two-dimensional image plane for follow-up studies.
- Only thyroid nodules with a greatest diameter of at least 15 mm are associated with a 90% probability of being identified by different investigators.

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