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Accuracy of ^{123}I Na Thyroid Imaging in calculating thyroid volume

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Conflict of Interest: None

Abstract:

Introduction

Hyperthyroidism is often managed with radioactive iodine therapy. The dose of ^{131}Iadministered to the patient is determined based on the calculated size of the thyroid gland in gram and 24 hour iodine uptake. Ultrasonography is a validated modality for determination of thyroid volume. Though necessary for assessing degree of ^{123}I uptake, nuclear scintigraphy also allows for the capability of estimating thyroid volume. Here we compare volume measurements calculated based on ultrasonography and nuclear scintigraphy in a cohort of hyperthyroid patients.

Methods

This prospective study designed to evaluate 110 consecutive hyperthyroidism patients who were undergoing thyroid ultrasound and ^{123}I scintigraphy. Scintigraphy was performed after oral administration of approximately 11 MBq ^{123}Isodium, and uptakes at 2 and 24 hours were measured. At 24 hours, the patients underwent thyroid scan with a nuclear medicine camera with LEHR (low energy high resolution) collimator next to the patient's chin. Thyroid measurements were calculated via the formula for determining a prolate ellipsoid. The formula was modified for RAIU as it is a planar image. Volumes calculated with these two modalities were subsequently analyzed and compared by linear regression. All patients had undergone ultrasonography with an average three months from nuclear scan. All of our patient ^{131}I dosages were based on the thyroid measurements obtained by thyroid scintigraphy.

Results

We included 110 patients (95 females, 15 males) with age range 20-95 years and average age 56 +/- 17.4 years old. Diagnoses included 66 patients with nodular goiter, and 44 patients with Graves' Disease. There was a linear relationship between measurement of thyroid gland weight by two modalities which can be explained in the following formula: log US(g) = 0.841 + 0.649*log NM(g).

Conclusion

We have validated that this method has helped obtain more accurate measurements of the thyroid gland by thyroid scintigraphy. Additionally, we have derived conversion factors that convert the estimated thyroid volume calculated from thyroid scintigraphy to the expected ultrasound value.

Key words: Graves' Disease; Toxic Nodular Goiter; Anti-thyroid medication (ATD); Thyroid Scintigraphy (RAIU); Thyroid ultrasound, Radioactive Iodine Therapy (RAI)

Introduction:

Hyperthyroidism is one of the most common endocrine disorders in the United States - affecting more than 1 in 100 people (*1*). Thyrotoxicosis describes the syndrome that occurs secondary to systematically elevated thyroid hormone levels, and is characterized by symptoms such as fatigue, heat intolerance, tremor, and weight loss among others (*2*). The two major causes of hyperthyroidism are Graves' disease and Toxic nodular goiter (*3,4*) while Hashimoto's thyroiditis accounts for the majority of cases that occur as a result of passive release (*5*). The diagnoses of these hyperthyroid conditions are made with the aid of thyroid scintigraphy, also known as thyroid scan or Radioactive Iodine Uptake (RAIU) (*6*).

Per the American Thyroid Association (ATA), there are three clinical options for treating hyperthyroidism: anti-thyroid medication (ATD), surgical thyroidectomy, and radioactive iodine treatment (RAI) (*7*). Importantly, treatment with radioactive iodine is only feasible in the context of thyroid hormone overproduction - such as Grave's disease or toxic multinodular goiter.

Treatment for hyperthyroidism generally occurs in a stepwise fashion, and begins by achieving a euthyroid state with antithyroid medication (*8*). While ATD such as Methimazole and Propylthiouracil (PTU) can be effective in achieving euthyroidism in hyperthyroid patients, this treatment is not a definitive approach to treating hyperthyroidism (*9,10*). The remission rate after a standard 12-18 months treatment is only between 50-55%, with some patients requiring ATD for up to 6 years if used as the sole method of treatment. Thus, in the event of recurrence post-ATD regimen, which has been shown to occur in over 52% of patients, either RAI or surgical thyroidectomy is recommended (*11*).

Surgical thyroidectomy is a highly effective treatment method but is only indicated in certain circumstances. These indications include abnormal cytology upon Fine Needle Aspiration

(FNA), very large goiters, goiters that cause airway obstruction or dysphagia, and pregnancy (*12*). In the absence of these indications for surgical thyroidectomy, RAI treatment is the definitive treatment of choice if anti-thyroid medication proves ineffective. RAI is especially used in post-menopausal women and male patients, as there is no risk of fetal abnormalities like there is in fertile female patients who may unwittingly be pregnant at the time of treatment *(13)*.

For the past 80 years, since Dr. Saul Hertz first used ^{131}I as a treatment for hyperthyroidism in 1941 (*14*), radioactive iodine therapy has been the most commonly utilized definitive treatment for hyperthyroidism *(15,16*). The dose of ^{131}I administered to the patient is determined by two factors: the percentage of ^{123}I uptake in the thyroid at 24 hours of a RAIU study and the calculated size of the thyroid gland in grams (*17*). For the calculation of the thyroid mass in grams, the density of thyroid is generally assumed to be 1g/cm^3 (*18*). More specifically, the equation for ^{131}I dose calculation (converted to MBq) in RAI is (*17*):

$$\frac{2.8 - 7.4\ \text{MBq}\ \ x\ thyroid\ weight\ (g)}{\%\ of\ 123I\ uptake\ at\ 24\ hours}$$

As such, it is crucial that the weight of the thyroid can be determined with great accuracy in order to establish a safe and effective dose for RAI.

Ultrasonography is a validated modality for determination of thyroid volume (*19,20*). Though necessary for assessing degree of ^{123}I uptake in RAIU studies, nuclear scintigraphy also allows for the capability of estimating thyroid volume. This study compares volume measurements calculated based on ultrasonography and nuclear scintigraphy in a cohort of patients with hyperthyroidism.

Patients and Methods

From January 2018 to December 2019, this prospective study evaluated 110 consecutive hyperthyroid patients, all of which had undergone thyroid ultrasonography and ^{123}I scintigraphy within 1 day to 6 months of each other (91 days on average). IRB approval for review of the patients' records was obtained. However, consent forms were not obtained from patients because thyroid ultrasound is a routine evaluation of all hyperthyroid patients in order to rule out thyroid malignancy prior to potential ^{131}I therapy. Patients with clinical diagnosis of hyperthyroidism and elevated thyroid function tests were referred. Patients with diagnoses of thyroid carcinoma were excluded. Thyroid imaging was performed at 24 hours post administration of approximately 11.1 MBq ^{123}I Na in anterior, left anterior oblique, and right anterior oblique views. Patients were in supine position with the neck extended and imaged at the level of the chin using Millenium Camera with Low Energy High Resolution (LEHR) parallel hole collimators (GE Healthcare, Milwaukee, WI) to best evaluate thyroid gland dimensions. In patients with normal or high count rate, the images were obtained for 35,000 counts. In patients with a low count rate, a 10-minute image was obtained. Ultrasonography was conducted using dedicated Philips IU 22 ultrasound L12-5 Linear transducers (Philips, Amsterdam, Netherlands). Thyroid measurements were calculated from the formula for each Thyroid Lobe Volume = 0.5 x Length x Width x Depth in ultrasound. This formula for calculating thyroid lobe volume is derived from the geometric method for calculating the volume of a prolate ellipsoid (*21*). In a similar fashion, thyroid volumes from ^{123}I scintigraphy were calculated by the formula Thyroid Lobe Volume = 0.5 x Length x Width x Width. The volumes of both lobes and, if present, that of the isthmus are added together, resulting in the total thyroid volume. Representative images used for thyroid volume estimation for both Grave's disease and multinodular goiter are shown in Figures 1 and 2, respectively. All thyroid scans and calculations were reviewed and analyzed by three experienced nuclear medicine physicians. All ultrasound imaging was performed and reviewed by the expert radiologists in the Radiology Department. Volumes calculated with these two modalities were subsequently analyzed.

Statistical Analysis

Paired t-test was used to compare the thyroid gland weight between the ultrasound and thyroid scan. Pearson correlations were calculated between the thyroid gland weights measured by ultrasound and thyroid scan. Linear regression models were used to explore the relation between measurement of thyroid gland weight by the thyroid scan and ultrasound. To achieve normality, reduce variability, and fit the model better, logarithm transformations were used for measurements by the thyroid scan and ultrasound in the linear regression model. All statistical analyses were done using Stata v17.0 (StataCorp LLC, College Station, TX).

Results

We included 110 patients (95 females, 15 males) with age range 20-95 years and average age 56 +/- 17 years old. Diagnoses included 66 patients with nodular goiter, and 44 patients with Graves' Disease. The mean thyroid gland weight for patients with Graves' disease via ultrasound measurement was 33.1 +/- 50.1 grams and by thyroid scan 50.0 +/- 45.6 grams ($p = 0.001$).

For patients with nodular goiter, however, the mean thyroid weight calculated by ultrasound measurement was 34.1 +/- 18.9 grams, while the thyroid scan method resulted in a mean of 47.8 +/- 28.7 grams ($p<0.001$). In both Graves' and nodular goiter patients, there was a good correlation between the measurements of the thyroid scan and ultrasound ($r = 0.8327$ and $r = 0.7174$ respectively, $p < 0.001$). The overall correlation coefficient regardless of diagnosis is 0.7804 ($p < 0.001$). There was a linear relationship between measurement of thyroid gland weight by two modalities (regardless of diagnosis) which can be explained in the following formula: $\log US(g) = 0.84 + 0.65*\log NM(g)$ ($r = 0.59$, $p < 0.001$ for the slope, Figure 3C). Moreover, there are separate linear relationships between measurement of thyroid weight between the two modalities with respect to the diagnosis of either Graves' disease or nodular goiter.

For Graves' patients, $\log US(g) = 0.77 + 0.62*\log NM(g)$ ($r = 0.57$, $p < 0.001$, Figure 3B) while for nodular goiter patients, $\log US(g) = 1.03 + 0.63*\log NM(g)$ ($r = 0.61$, $p < 0.001$, Figure 3A). Figure 3 shows the relationship hold up better for smaller thyroid glands 20 - 55g (exp(3) to exp(4)) with narrowed 95% CI. Linear regressions for log US(g) using log NM(g) as predictor are shown in the Table by diagnosis and all patients.

Figure 1 depicts the imaging for both ^{123}I thyroid scintigraphy (NM) and thyroid ultrasonography (US) of a 27-year-old female patient with hyperthyroidism. The thyroid scan showed uniform uptake throughout the enlarged lobes of the thyroid gland, consistent with Graves' disease. Thyroid uptake at 2 hours was 26.5% (N = 5-10%) and at 24 hours 62.2% (N = 10-35%). Ultrasound showed bilaterally enlarged lobes with no nodules.

Figure 2 depicts the imaging for both ^{123}I thyroid scintigraphy (NM) and thyroid ultrasonography (US) of an 89-year-old female patient with hyperthyroidism. The thyroid scan showed non-uniform uptake in the right lobe of the gland, consistent with multi-nodular goiter. Thyroid uptake at 2 hours was 4.2% (N = 5-10%) and at 24 hours 16.3% (N = 10-35%), consistent with subclinical hyperthyroidism. Ultrasound showed bilaterally enlarged glands with right upper pole nodule.

Discussion

Here we have shown the ability to obtain accurate thyroid volume measurements using planar ^{123}I scintigraphy and imaging with Gamma Camera using High Resolution Parallel Hole collimator. We used a modified ellipsoid formula based on dimensions obtained from a single anterior view as well as a modified acquisition protocol characterized by placing a wide-view gamma camera at the patient's chin with the neck in hyperextension. We reasoned that these changes would aid in curtailing the volume overestimations that we had previously seen with scintigraphy at our institution. The ability to assess thyroid volume via scintigraphy has been well investigated and previously reported (*22-24*). However, the standard methodologies used for estimation generally result in inaccuracies in measurement - either under or overestimating volume depending on the formula used for estimation and the architecture of the gland under assessment[22]. Ultrasound has been shown to result in more accurate volume estimations and, for this reason, has generally been adopted as the gold standard imaging modality for volume estimation prior to RAI therapy (*23,25,26*).

To improve the accuracy of scintigraphy-based volume estimations, linear regression was used to compare volumes obtained with scintigraphy to those obtained from ultrasound. Regression analysis revealed a fairly strong linear relationship between the volumes derived from ultrasound with those derived from scintigraphy Figure 3C. Importantly, this relationship allowed for the derivation of a correction factor, such that volumes obtained with scintigraphy could be corrected to more closely align with those obtained from ultrasound. This correction factor - which in our study predominantly corrected for the overestimation of scintigraphy relative to ultrasound - allows for accurate volume estimation with scintigraphy alone (Figure 3A-C). Importantly, this estimation can be made more accurate by stratifying patients by Grave's and nodular goiter, as the slopes of the regression lines obtained differ between these two patient cohorts (Figure 3 B,C). This, in turn, could streamline the pre-procedural workup in patient's awaiting radioiodine therapy, as scintigraphy could be used to determine radioiodine uptake and thyroid volume simultaneously. While ultrasound is generally considered accessible and cost effective[24], scintigraphy is a requirement prior to RAI therapy. Extending its role to estimate volume in addition to radioiodine uptake would spare patients an additional test, a net gain to both patients and the health systems treating them.

Currently, there is debate on whether hyperthyroidism is better treated with standardized or calculated doses of ^{131}I. Standardized doses treat based on general size (small, medium, large) and treatment with 185, 370, or 555 MBq doses of ^{131}I, respectively. Calculated doses utilize a formula that accounts for thyroid weight and RAIU uptake to determine treatment dose. In a study done by Peters et al, they determined outcomes are dependent on radiation dose absorbed, which is inversely proportional to thyroid size (*26*). As such, patients with standardized doses had lower treatment success in larger-sized thyroid goiters, compared to patients who received calculated doses. While an additional study found the two methods to be equal in effectiveness, this study did not take into account differences in thyroid volume (*27*). Furthermore, with the importance of personalizing treatments to the patient's own gland size, nodularity, treatment history, and longevity of illness, utilizing a set dose for all patients may not adequately treat the patient, or expose patients with smaller thyroids to unnecessary levels of radiation. Therefore, taking into account each patients' thyroid volumes and diagnoses helps to individualize treatment.

While our methodology improves volume estimation via scintigraphy, it, itself, requires that a series of previous ultrasound measurements be available on which regression analysis can be performed. For this reason, volume estimation using this correction factor suffers from the limitations inherent to ultrasound as a modality: a tendency to underestimate volume and a lack of precision relative to slightly more robust modalities such as CT and MRI (*25,28,29*). While CT and MRI have shown superior performance with respect to volume estimation, both suffer from shortcomings. MRI is expensive and time consuming while CT increases exposure to unnecessary radiation. the negative aspects of these two imaging modalities, relative to ultrasound, make their use less desirable in the setting of pre-procedural thyroid volume estimations. It is generally uncommon for CT and MRI to be used as stand-alone modalities for the estimation of thyroid volume. When these modalities are used for evaluation of the thyroid, it is usually in response to an incidental finding *(30)*. This was demonstrated in our study, where only 3 out of all 110 subjects had received CT scans specifically for evaluation of the thyroid. Though reports from these 3 scans commented on the heterogeneity and the overall appearance of the thyroid, only one of these scans reported a thyroid measurement for comparison with ultrasound and scintigraphy. No patients received an MRI specifically for evaluation of the thyroid - all thyroid evaluations stemmed from incidental findings on studies ordered for alternative indications. Thus, although some in the field have shown CT and MRI to be the most accurate modalities in thyroid volume determination, the data needed to create a correction factor to convert volumes obtained with thyroid scintigraphy to more closely align with measurements obtained via CT and MRI were not available at our institution *(28)*. The task of creating such a correction factor should be further investigated at an institution in which thyroid volume estimations conducted by CT and MRI are more commonplace.

Conclusion

The accurate measurement of the thyroid gland can be determined by imaging with a gamma camera with LEHR parallel hole collimator and accurate patient positioning. By this technique, we have validated thyroid scintigraphy as an accurate modality for determining thyroid weight prior to decision making in treatment of hyperthyroidism. Additionally, we have derived conversion factors with which the estimated thyroid volume calculated from thyroid scintigraphy can be converted to the expected ultrasound value. These conversion factors provide physicians with the potential to streamline the treatment pathway for patients with hyperthyroidism by obviating the need for an ultrasound thyroid volume estimation pre-RAIU study.

Key Points

QUESTION: Can I-123 thyroid scintigraphy be utilized to accurately assess thyroid volumes prior to treatment with I-131Na?

PERTINENT FINDINGS: In this prospectively designed study, the authors would like to share their experience in the evaluation of hyperthyroidism patients undergoing thyroid ultrasound and I-123 scintigraphy, which evaluated gland size with a nuclear medicine camera with a low energy high resolution collimator next to the patient's chin. Thyroid volumes calculated with ultrasound and nuclear medicine scintigraphy showed a statistically significant linear relationship between measurement of thyroid gland weight by the two modalities, creating a formula conversion factor that can accurately assess for thyroid weight using scintigraphy alone.

IMPLICATIONS FOR PATIENT CARE: Currently, ultrasound is used to determine thyroid volumes prior to treatment, but utilizing an already-needed I-123 scan to evaluate both uptake values and thyroid volumes gives physicians the potential to remove the need for an additional ultrasound prior to treatment. This change would not only streamline the treatment process, but also improve cost-effectiveness of hyperthyroidism management and decrease the financial and temporal burden placed on patients.

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Graphical Abstract

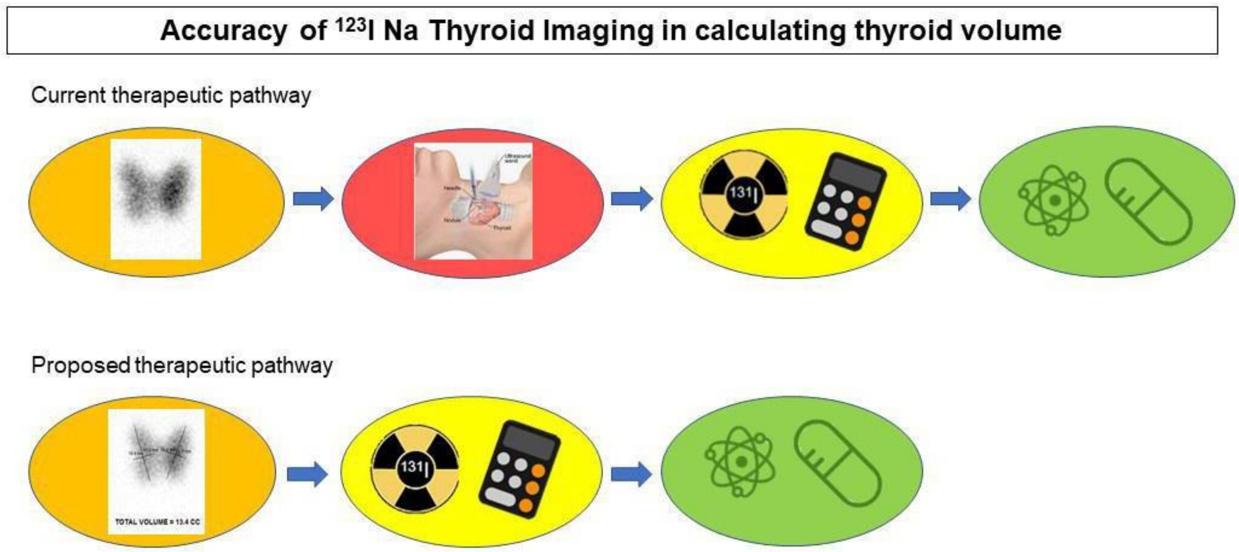
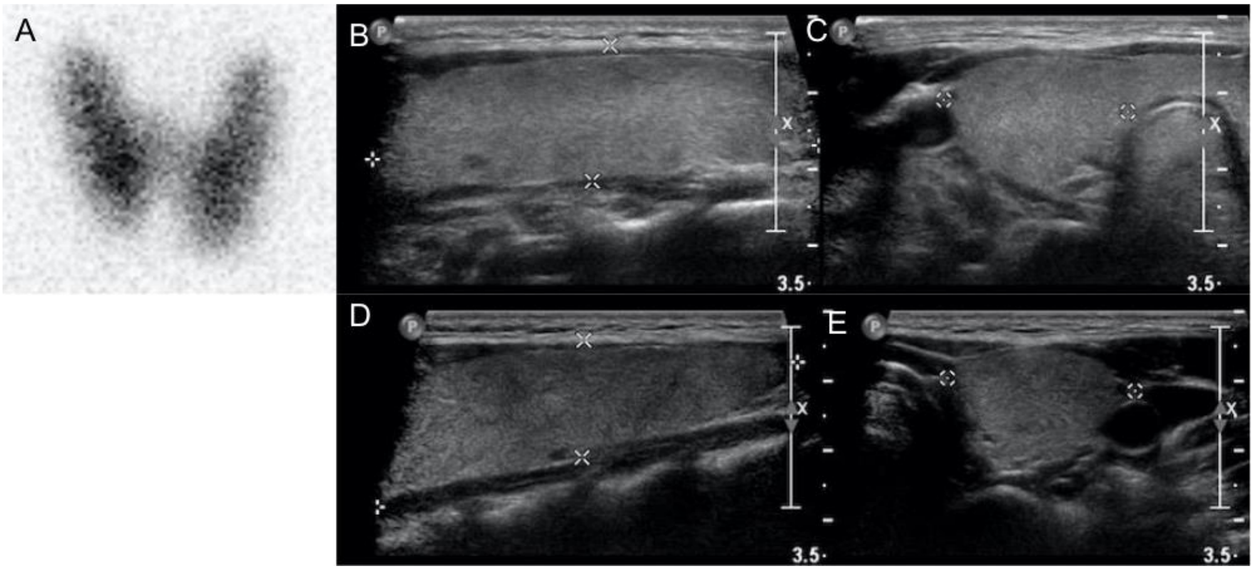
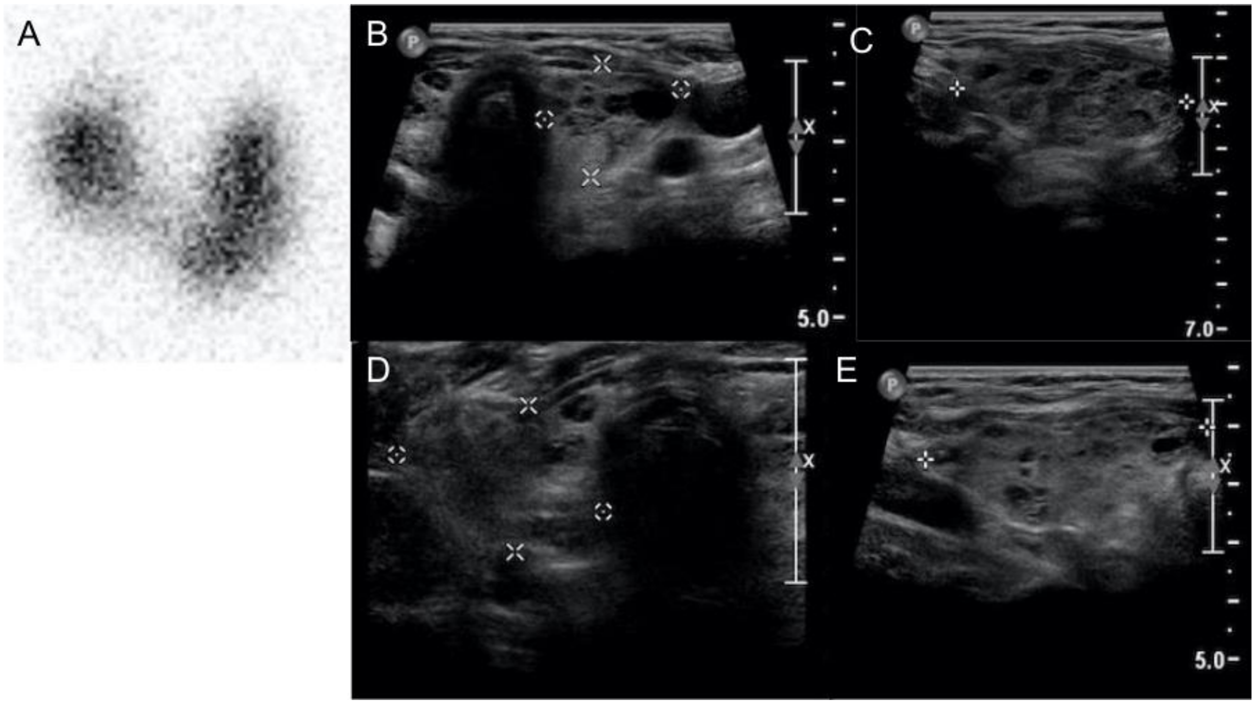


Figure 1: Planar ^{123}I scintigraphy imaging (NM) and Ultrasonography (US) of a patient with Graves' disease.



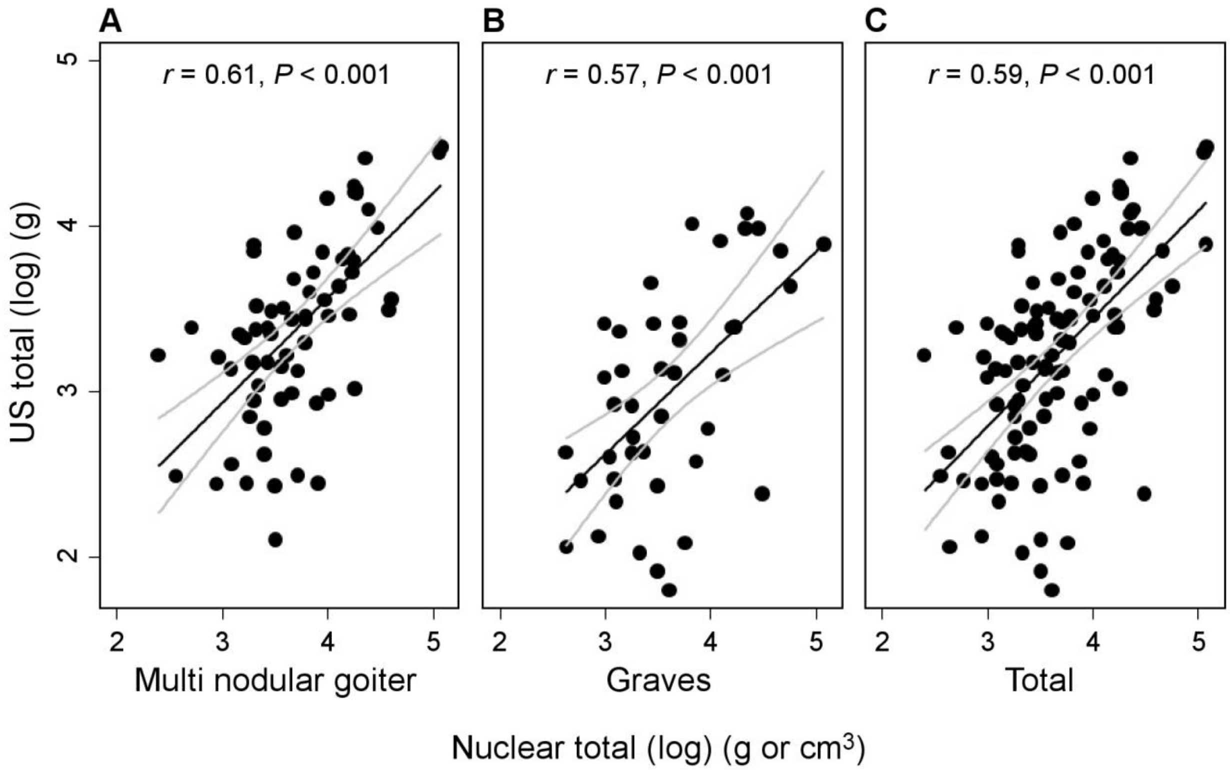
A – Thyroid scan: (Right Lobe = 6.19x2.52 + Left Lobe = 6.48x25.4)
B – US left lobe (Length x Width =6.4 x 1.7)
C – US left lobe (Depth =2.7)
D – US right lobe (Length x Width = 5.9 x 1.8)
E – US right lobe (Depth = 2.4)

Figure 2: Planar ^{123}I scintigraphy imaging (NM) and Ultrasonography (US) of a patient with multi nodular goiter.



A – Thyroid scan: (Right Lobe = 5.4x2.9 + Left Lobe = 4.3x2.4)
B – US left lobe (Length x Width= 5.1 x 2.0)
C – US left lobe (Depth = 2.4)
D – US right lobe (Length x Width = 5.2 x 1.7)
E – US right lobe (Depth = 2.5)

Figure 3



A – Linear relationship between volume estimations from log US(g) and log NM(g) in patients with nodular goiter
B – Linear relationship between volume estimations from log US(g) and log NM(g) in patients with Graves' disease
C – Linear relationship between volume estimations from log US(g) and log NM(g) from all patients included in the study, regardless of diagnosis as nodular goiter or Graves' disease

Table 1: Linear regression for log US (g) using log NM (g) as a predictor by diagnosis.

Diagnosis	**Intercept**	**S.E**	**p**	**Slope**	**S.E**	**p**
Multi nodular goiter	1.031	0.381	<**0.001**	0.632	0.101	**0.028**
Graves	0.775	0.512	0.14	0.613	0.140	<**0.001**
Total	0.841	0.321	**0.01**	0.649	0.086	<**0.001**

The bolded p values are considered statistically significant.