Systematic differences between ultrasound and pathological evaluation of thyroid nodules: a method comparison study

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Abstract

Background: The size of thyroid nodules as measured by ultrasound (USS) is routinely used in clinical decision-making. Reports of size discrepancy between USS and pathological (PS) evaluation have not analysed their systematic differences. The objective of this study was to uncover lack of agreement (bias) between USS and PS measurements.

Methods: A retrospective study was performed on 121 patients who had a total or hemi-thyroidectomy for a solitary nodule. Ordinary Least Product (OLP) regression was used to detect and distinguish constant and proportional bias in unidimensional size measurements between USS and PS evaluation. Three-dimensional volume measurements were compared in a subgroup of 31 patients. Pre-specified acceptable limits of interchange were defined as 20% difference.

Results: OLP regression demonstrated no constant or proportional bias between the two methods; regression equation: $USS = (0.863) + (1.040) * PS$. When nodules were grouped by size, discrepancies between the two methods were observed in nodules less than 10mm ($p = 0.004$). However, potential over-treatment of patients with ultrasound size > 10 mm but pathological size < 10 mm only accounted for 4.1% of total patients. Subgroup analysis of volume measurements showed no bias between USS and PS evaluation.

Conclusions: USS and PS measurements were interchangeable, as there was no evidence of constant or proportional bias between the two measurements. However, USS may misclassify the size for smaller nodules and potentially lead to unnecessary workup and treatment. Discrepancy in size measurements between USS and PS should be taken into account in clinical practice, particularly in smaller nodules.

Introduction

High-resolution ultrasound is recommended for all patients with known or suspected thyroid nodules¹. This assesses the risk of malignancy by evaluating nodule size, number, parenchymal characteristics such as echogenicity, calcifications, internal vascularity, margins and the presence of associated cervical lymphadenopathy^{1,2}. Furthermore, ultrasound measured nodule size (USS) plays a critical role in selecting patients for further evaluation with fine needle aspiration (FNA) and surgical decision making.

Current American Thyroid Association (ATA) guidelines give strong recommendations for routine FNA in nodules >10mm if classed as high or intermediate risk on imaging. Fine needle aspiration of lesions >15mm is recommended for nodules with low risk features on imaging (weak recommendation, based on low quality evidence). In solitary nodules between 1-4cm (on US) without extra-thyroidal extension or evidence of lymph node metastases, patients may undergo either lobectomy or total thyroidectomy, depending on patient preference, pre-operative pathology and need for radioactive iodine treatment.

However, it is the histopathological size (PS) in malignant nodules that determines the final TNM classification¹.

There are limited data comparing USS and PS, and these studies have not analysed their systematic differences³⁻⁵. The primary objective of this study was to uncover the lack of agreement (bias) between USS and PS measurements using a method comparison study. The secondary aim was to assess nodules with USS < 10 mm, as size discrepancies may alter management decisions.

Materials and Methods

A retrospective study was undertaken to examine patients who underwent total or hemi-thyroidectomy at our institution for a solitary thyroid nodule between January 2009 and October 2015. Patient demographics, thyroid function, USS, FNA cytology, histopathological diagnosis and PS were recorded. Patients with multiple nodules were excluded from the study to prevent discrepancies due to sonographers and pathologists measuring different nodules in the same specimen.

Pre-operative ultrasounds were performed at our institution and multiple external radiology providers. All ultrasounds were reported by consultant radiologists, and measurements were taken prior to FNA. PS was measured in our pathology department following formalin fixation and cross section by the pathologist. We used the largest recorded USS and PS measurements in 121 patients for unidimensional size comparison. In 31 patients, three-dimensional volume measurements were available for subgroup analysis. The unit of

measurement for USS and PS size and volume is in millimetres (mm) unless otherwise stated. The study was approved by the Western Health Ethics committee.

Statistical Analysis

A scatterplot of ultrasound measurements (USS) on pathology measurements (PS) was constructed and Pearson's product-moment correlation coefficient and the coefficient of determination calculated. No assumption was made that USS or PS measurements were error-free⁶⁻⁹. Ordinary Least Product (OLP) regression was used to uncover systematic differences and, in particular, to detect and distinguish constant (fixed) and proportional bias between the two measurements (method-comparison study)^{10,11}. Constant bias is where one method gives values that are higher (or lower) by a constant amount. Proportional bias is where one method gives values that are higher (or lower) by an amount that is proportional to the level of the measured variable. Assumptions for using OLP regression including linearity and equality of variances in the scatterplot were tested. Subgroup analysis of volume comparison was made where three-dimensional measurements were available. Non-parametric exact (permutation) test for two related samples were used to compare nodules grouped by size. Pre-specified acceptable limits of interchangeable results were defined as 20 per cent.

Continuous data are presented as median (IQR, inter-quartile range). All tests were two-sided, and $p < 0.050$ was considered significant. Statistical analyses were performed using Systat v12 (Systat Software, Inc, Chicago, IL, USA) for OLP regression and StatXact v9.0 (Cytel Software Corporation, Cambridge MA, USA) for categorical data with exact non-parametric methods.

Results

There were 121 eligible patients and demographics are summarised in Table 1. The median age of patients was 47, with a female predominance (66%) and the majority of patients were euthyroid (82%). The median USS was 27mm (IQR 15-39mm) and the median PS was 25mm (IQR13-35mm).

Method Comparison Analysis

A scatterplot of USS and PS measurements is shown in Fig. 1. The correlation coefficient (r) = 0.888; 95% confidence interval (CI): 0.844 to 0.921; $p < 0.001$; and the coefficient of determination (r^2) = 0.789, which implied that 80% of the variation in USS measurements was accounted for by knowing the PS measurements and vice versa.

The variance (or scatter) of USS was constant across all values of PS, an essential assumption for using OLP regression (homoskedastic distribution: χ^2 2.43, df 2, $p = 0.296$). Fig. 2 shows the residual plot of the regression model, the residual is the difference between the observed and predicted value of the USS measurements. The random pattern of the residuals around the horizontal axis supported a linear model.

The results of OLP regression for unidimensional size and volume comparisons are shown in Table 2. The 95% CI for the intercept (-1.831 to 3.557) included a *zero* (0) value implied no constant bias; the 95% CI for the slope (0.951 to 1.129) included a *one* (1) value implied no proportional bias. The regression equation for the model is:

$$\text{USS} = 0.863 + 1.040 \cdot \text{PS}.$$

No constant or proportional bias was uncovered between USS and PS evaluation in the subgroup analysis for volume measurements.

Analysis of nodules grouped by size

Analysis based on PS is illustrated in Fig 3 and Table 3. There was no significant difference between USS and PS for nodules measuring 11-15mm and nodules >15mm. For nodules <10mm there was a significant difference ($p=0.004$) between US and PS measurements.

Thirteen patients had nodules with USS less than 10 mm. Within this group, 8/11 nodules that had FNA were suspicious for, or malignant on cytology. Only one nodule was underestimated with PS 11mm. Nineteen patients had nodules with PS less than or equal to 10mm and the USS ranged from 5-20mm. There was a statistically significant difference on exact permutation test (p value 0.004, median PS 9mm vs. USS 10mm). Sixteen patients had an FNA and ten were suspicious for, or confirmed malignancy. Seven were over-estimated with USS >10 mm. As a percentage of the total patients with USS measuring between 10-20 mm ($n=45$) this only represented 16% (7/45) of nodules that may have been over-treated.

Discussion

The principal finding of this study was that ultrasound measurements were interchangeable with pathological measurements. Analyses of measurements showed no evidence of constant or proportional bias. Published studies comparing USS with PS have not analysed the systematic differences between measurement methods³⁻⁵. However, similar to our study, all of these studies demonstrated a tendency for USS to over-estimate PS.

In a study of 292 patients with papillary thyroid carcinoma by Bachar et al, consistent size discrepancy was noted, although it was only statistically significant in nodules measuring more than 15 mm. They also found that 18.8% of nodules measured to be >10mm on USS were <10mm on final pathology, suggesting that some patients may have potentially been over-treated⁴. Devici et al⁵ compared USS and PS on 664 benign and malignant solitary nodules. Nodules were stratified based on size criteria. This study demonstrated an overall concordance between USS and PS of <50%, except for nodules <10mm where there was a concordance of 78.5%. A study by Sowerby et al³ in 2011 evaluated 263 patients with solitary thyroid nodules. They demonstrated a median overestimation by ultrasound of 5.4 mm compared with pathological size. This was consistent with subgroup analysis for size, pathology and nodularity. For nodules <10 mm, a concordance of 80% was present.

The current ATA guidelines recommend FNA for patients with USS >10 mm with intermediate to high suspicion features on US, and routine FNA for patients with USS >15 mm¹. In our study, we demonstrated a statistically significant difference between PS and USS for nodules >10mm. Seven (4.1%) patients with PS less than 10 mm had an USS >10 mm. This may represent some patients who have potentially been over-treated with FNA and choice of surgery. However, we examined ultrasound size alone, and did not take into account the other nodule characteristics on US or risk factors that may have prompted FNA. There are many important features of thyroid nodules on imaging which are important in addition to size, such as echogenicity, irregularity of borders, shape and patterns in calcification and vascularity. A large proportion (61.5%) of the patients with USS <10 mm had either suspected or confirmed malignancy on pre-operative FNA, which was confirmed on final

pathology in 100% of cases. However, for nodules with USS less than or equal to 10 mm, PS was close to the same size, and management would not have been altered.

There are many possible factors to account for the discrepancy between USS and PS, and it is likely multi-factorial. High-resolution ultrasound is the “gold standard” for assessment of thyroid nodules, for its reliability, cost-effectiveness, accessibility and non-invasive nature. However, limitations include being operator-dependent with an inter-observer variation of up to 48.96% for estimated thyroid volume¹²⁻¹⁵, and its accuracy influenced by poorly defined nodule margins, irregular shapes, multi-nodular goitre and large nodules¹⁶.

A number of factors contribute to PS discrepancy. There may be more than 50% volume increase on serial US following thyroid nodule FNA in up to 35% of patients, possibly due to post aspiration scarring or haemorrhage¹⁷. De-vascularisation of the gland following removal has been postulated to contribute to size discrepancy and nodule shrinkage¹⁶. Shrinkage of specimens following formalin fixation is a phenomenon that has been described in a number of different specimens. A study examining 100 head and neck specimens, including 16 thyroid specimens demonstrated an average shrinkage of maximal diameter of 4.40%¹⁸. The measured nodule size also depends on the plane in which the nodule has been sectioned by the pathologist, and the plane examined by US, particularly as most nodules are not perfectly spherical.

The main limitation of this study was its retrospective nature. Duplicate measurements were not made and assessment of repeatability not available. It is important that nodule

assessment on US is performed and interpreted by experienced endocrine radiologists. Whilst some of the imaging in our study was performed at our institution, a majority of the US were performed at external provider sites. This raises the issue of inter-observer variation.

However, our study is reflective of 'real world experience' where external US results are used in patient assessment and decision-making.

Conclusion

We demonstrated that USS and PS measurements were interchangeable. Analyses of measurements showed no evidence of constant or proportional bias between the two measurements. Potential over-treatment of patients with ultrasound size greater than 10 mm and pathological size less than 10mm only accounted for 4.1% of patients. USS may misclassify the size for the smaller nodules and potentially lead to unnecessary workup and treatment. The decision for investigation and treatment of thyroid nodules is based on a number of factors not solely the USS. However, discrepancy in size measurements between USS and PS should be taken into account in clinical practice.

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Legend for Figures

Fig. 1 Scatter plot of Ultrasound Size versus Pathological Size

Fig. 2 Residual plot of Regression Model

Fig. 3 Analysis of Thyroid Nodules by Pathological Size

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Table 1 Patient demographics and thyroid status of 121 patients with solitary thyroid nodules

Characteristic	
<i>Age, median (years)</i>	
47	
<i>Sex, n (%)</i>	
Male	41 (34)
Female	80 (66)
<i>Thyroid function, n (%)</i>	
Hyperthyroid	20 (17)
Euthyroid	100 (82)
Hypothyroid	1(1)
<i>FNA (Bethesda criteria) n (%)</i>	
Non-diagnostic	13(10)
Benign	42 (35)
Atypia of Undetermined Significance	8 (7)
Follicular Neoplasm/Suspicious of Follicular Neoplasm	8 (7)
Suspicious for Malignancy	18 (15)
Malignant	19 (16)
No FNA	13 (10)
<i>Size, mm, inter-quartile range</i>	
USS median	27 (15-39)
PS median	25 (13-35)
<i>Final Histopathology, n (%)</i>	
Hyperplastic or colloid nodule	26 (21)
Adenoma	35 (29)
Cyst	12 (10)
Malignancy	38 (30)

Table 3 USS and PS grouped by nodule size (mm)

Group by size (PS)	n	USS, median (IQR)	PS, median (IQR)	p exact
d 10	19	10.00 (8.25 – 16.00)	9.00 (7.00 – 10.00)	0.004
11 – 15	20	13.00 (12.00 – 17.00)	13.00 (12.00 – 15.00)	0.213
> 15	82	33.00 (27.00 – 44.00)	31.00 (25.00 – 41.00)	0.141

Figure1.tif

Figure2.tif

Figure3.tiff

Table 2 Results of OLP Regression: USS vs PS measurements

Parameter	Estimate	ASE	Paramter/ASE	Wald 95% CI
<i>Intercept</i> [¶]	0.86	1.36	0.64	-1.83 to 3.56 [†]
<i>Slope</i> [¶]	1.04	0.05	23.09	0.95 to 1.13 [‡]
<i>Intercept</i> [§]	180.27	1889.14	0.10	-3683.45 to 4043.99 [†]
<i>Slope</i> [§]	0.89	0.03	27.97	0.82 to 1.02 [‡]

¶ unidimensional size comparison n=121, § volume comparison n=31, † no constant bias, ‡ no proportional bias, OLP ordinary least product, USS ultrasound size, PS pathological size, ASE asymptotic standard error.

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