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ABSTRACT

Objective: The aim of my study was to prospectively compare static two-dimensional (2D) and three-dimensional (3D) ultrasonographic (US) images with regard to interobserver agreement and diagnostic performance for the evaluation of thyroid nodules.

Methods: Between February 2011 and August 2011, 2D and 3D US images were preoperatively obtained from 85 consecutive patients (mean age, 51 years; age range, 28–83 years) who were referred for thyroidectomy. Three radiologists, who did not perform the examinations, independently evaluated 2D and 3D US images of 61 malignant and 30 benign nodules (confirmed via histological examination) and graded the nodules in a 3-tiered classification as to the probability of malignancy. Interobserver variability and diagnostic performance were compared between 2D and 3D US.

Results: 3D images were similar to or better than 2D US images
for diagnosis of malignant nodules in terms of sensitivity (75.4% vs. 59% for reader 1, 80.3% vs. 65.6% for reader 2, and 80.3% vs. 59% for reader 3) and specificity (73.3% vs. 70% for reader 1, 76.7% vs. 76.7% for reader 2, and 80% vs. 83.3% for reader 3). For detection of extracapsular invasion, interpretation using 3D images was more sensitive and specific compared to 2D images with the exception of specificity for reader 2: the sensitivity and specificity was 71.4% vs. 67.9% and 63.5% vs. 43.0%, respectively, for reader 1; 57.1% vs. 25% and 73.0% vs. 84%, respectively, for reader 2; and 75% vs. 53.6% and 61.9% vs. 57.1%, respectively, for reader 3. The sensitivity of 3D US for determining both malignant nodules and extracapsular invasion was statistically greater than that of 2D US (P < 0.001). Interobserver agreement between the 3 radiologists for the determination of extracapsular invasion was better for 3D images (κ = 0.79) than for 2D images (κ = 0.36). Interobserver variability for nodule descriptions and detection of
malignant nodules by using 3D and 2D images was fair to substantial.

**Conclusions:** 3D US has potential for superior interobserver agreement and has better diagnostic performance with regard to the evaluation of thyroid nodules.

**Keywords:** thyroid, sonography, nodule

**Student number:** 2011–21828
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INTRODUCTION

Thyroid nodules are common findings in the daily practice of medicine. The prevalence of thyroid nodules has been reported to include approximately 50% of the population at autopsy and 13–67% of living adults when screened with ultrasonography (US)\(^1\)\(^-\)\(^4\).

US is widely accepted as the preferred imaging technique for the initial evaluation of thyroid nodules. US evaluation can guide decision-making with regard to whether a thyroid nodule should be aspirated, and it can help differentiate between benign and malignant nodules\(^1\)\(^,\)\(^5\). However, the known limitations of ultrasonography with respect to thyroid nodule evaluation include subjectivity, operator dependency, and considerable interobserver variability\(^6\)\(^,\)\(^7\).

Three-dimensional (3D) US is a relatively new imaging technique that can scan target organs with a single sweep of an ultrasound beam and record accurate US information and the
relative position of each tomographic section. The accuracy of this
data can allow for the determination of exact relationships between
anatomic structures. Furthermore, 3D US provides images in
multiple planes from stored volume data by using a software
including planes that are not possible to view with conventional 2D
US\textsuperscript{8-10}. Several prior studies have reported that 3D US
examination may be useful for overcoming these limitations of
conventional 2D US in organs other than the thyroid gland\textsuperscript{9-12}. As
for the thyroid gland, some studies have shown that 3D US is an
effective adjunct to traditional 2D US in examining the thyroid
nodules\textsuperscript{12,13}. However, previous studies have not documented
whether these benefits affect the final diagnostic assessment of
thyroid nodules and correlate to histological examination.

Therefore, the objective of my study was to compare (i)
prospectively obtained static 2D and 3D US images with regard to
interobserver agreement and (ii) diagnostic performances of 2D and
3D US for the evaluation of thyroid nodules while using histological examination as the reference standard.

MATERIALS AND METHODS

Patients

The institutional review board approved this prospective study and all enrolled patients provided informed consent. From February 2011 to August 2011, 85 consecutive patients (73 women and 12 men) who had been scheduled for thyroid surgery were enrolled. Their mean age was 51 years (age range, 24–83 years). Surgical treatment was indicated on the basis of the following criteria: mechanical compression of the aerodigestive tract, hormonal complications (hyperthyroidism), and/or suspected malignancy that had been diagnosed by ultrasonography-guided fine-needle aspiration biopsy (FNAB).
Ultrasonography

Four radiologists (K.S.A, W.J.Y, L.J.H, and S.H.Y with 3 years of experience in thyroid US) performed US on the patients by using a scanner (ACCUVIX XQ; MEDISON Co. Ltd, Korea) equipped with a 6-12-MHz linear array transducer for 2D US and a 6-12-MHz dedicated volume transducer for 3D US. The scanning protocol for the 2D US consisted of transverse and longitudinal imaging of each nodule that was more than 5 mm in diameter or that showed any suspicious ultrasonographic features (taller-than-wide shape, a spiculated margin, marked hypoechogenicity, microcalcifications, and/or macrocalcifications)\textsuperscript{14}. The 2D and 3D US images were obtained from an identical plane with the same depth, focus position, and gain settings. A volume box size was chosen to cover one lobe of the thyroid gland and half of the isthmus. The volume scan was automatically acquired by using slow-tilt movement of the sectorial, mechanical transducer.
In cases in which the thyroid gland was not fully covered during the single volume scan, additional scanning was performed with some overlap. The same scanning protocol was repeated for the contralateral thyroid lobe. The order of the US examinations (i.e., either 2D US first or 3D US first) was randomly determined. The scan times for 2D and 3D US were recorded.

**Imaging Review**

No time limitation was set for the review. Three radiologists (Y.T.J., C.S.H., and K.J.H. with 5, 7, and more than 10 years of experience in thyroid US, respectively), reviewed the stored 2D and 3D US images. It is important to note that none of radiologists had been involved in performing the US scans. Before this study, each underwent a training session that consisted of 20 unrelated cases. The training session was performed in order to create a standard for the qualitative assessment of the thyroid nodules.
Blinded to the patient demographical data and FNAB findings, the study coordinator (K.S.C., a radiologist with 4 years of experience in thyroid US) displayed 2 representative transverse and longitudinal images of each thyroid nodule on a picture archiving and communication system (PACS) for review of the 2D US data. Three orthogonal, reconstructed (transverse, sagittal, and coronal) images on a SonoView workstation were presented for analysis of the 3D US data. The reviewers interpreted the 2D US images on the PACS and the 3D US images on the SonoView workstation (independently and with a 4-week interval between reading the 2D US data and the 3D US data).

All 3 radiologists categorized the following characteristics of each thyroid nodule according to the guidelines established by the Thyroid Study Group of the Korean Society of Neuroradiology and Head and Neck Radiology\textsuperscript{14}: spongiform appearance; internal content (solid, predominantly solid, predominantly cystic, or cystic);
echogenicity (markedly hypoechoic, hypoechoic, isoechoic, or hyperechoic); margin (smooth, spiculated/micro-lobulated, or ill-defined); shape (ovoid to round, taller-than-wide, or irregular); calcification (none, microcalcification, macrocalcification, or rim calcification); and level of suspicion concerning extracapsular invasion according to the degree of capsular abutment by using a 5-point scale (0, 0% of the tumor abuts the thyroid capsule; 1, 1–25%; 2, 26–50%; 3, 51–75%; and 4, 76–100%). Grades 3 and 4 were regarded as confirmation of extrathyroidal invasion. Finally, they provided a level of suspicion concerning the probability of malignancy (probably benign, indeterminate, or suspicious for malignancy).

**Statistical Analyses**

To assess and compare the diagnostic performance of 2D and 3D US in determining malignancy and extracapsular invasion, receiver
operating characteristic (ROC) curve analysis was performed using
MedCalc (Mariakerke, Belgium). ROC curves and non-parametric
estimates were obtained using the Az at a 95% confidence interval
via the method developed by Hanley and McNeil. The statistical
significance of the differences between 2 Az values was calculated
using the z test. The sensitivity, specificity, likelihood ratio for a
positive test result, and likelihood ratio for a negative test result of
the 2 modalities were directly calculated for each reader with
histological examination as the reference standard. The calculated
values were then compared using the McNemar’s test. The paired
t-test was used to compare scan times between the 2 techniques
and the Student’s t-test was used to compare size differences
between benign and malignant nodules. In every statistical
analysis, P < .05 was considered indicative of significant differences.

The interobserver agreements between the 3 radiologists for
descriptions of thyroid nodules were calculated using Fleiss κ
statistics in the Minitab software package, version 15 (Minitab Inc., US). A $\kappa$ value of 0.20 or less was considered slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement.

RESULTS

Lesion Diagnosis

Ninety-one thyroid nodules of 85 patients that were confirmed by histological review were included. Thirty nodules were benign (18 were hyperplastic nodules, 5 follicular adenomas, 6 chronic lymphocytic thyroiditis, and 1 Hurthle cell adenoma). For the benign nodules, the diameters ranged from 0.3 to 4.6 cm, with a mean size of 1.64 cm. Sixty-one nodules were malignant (all were papillary carcinomas). For the malignant nodules, the diameters
ranged from 0.3 to 3.1 cm, with a mean size of 0.85 cm (Table 1). Malignant nodules were significantly smaller than benign nodules (P < 0.001).

**Diagnostic Performance**

3D images were similar to, or better than, 2D US images for the diagnosis of malignant nodules in terms of sensitivity, specificity, and determination of the likelihood ratio for positive (+LR) and negative (−LR) test results (Table 2, Fig 1). A statistically significant difference between the 2 techniques was found with regard to sensitivity (P < .001).

The Az values of the 3 readers were as follows: 0.67 for 2D images and 0.75 for 3D images for reader 1, 0.74 for 2D images and 0.77 for 3D images for reader 2, and 0.77 for 2D images and 0.79 for 3D images for reader 3 (Table 2). These differences were not statistically significant for all readers (P > .05).
Table 3 shows the diagnostic performance of the 3 readers for detection of extracapsular invasion. Interpretation using 3D images was significantly more sensitive than the interpretation results using 2D images ($P < 0.001$). The Az values were greater for the 3D images for all 3 readers. However, differences did not reach statistical significance ($P > .05$).

**Reader Agreement**

The radiologists showed fair to substantial agreement for descriptions of US features and diagnoses of thyroid nodules by using 2D and 3D US images (Table 4). In terms of the detection of extracapsular invasion, substantial agreement was found for 3D US images, while fair agreement was found for 2D US images. Similarly, in terms of diagnosis of malignancy, agreement between the 3 readers was slightly better for the 3D images than for the 2D images. For other nodule features, interobserver variability for 3D
US images was similar or better than that for 2D US images.

Scan time

The mean ± SD time per patient for the 3D US scanning was 55.47 ± 4.21 s (range, 14–236 s) and that for the 2D US scanning was 85.47 ± 6.02 s (range, 5–224 s). Comparison of the mean time per patient between the 2 techniques showed a statistically significant difference (P < 0.001). Therefore, 3D scanning resulted in a net time savings of 30 s per patient (only 64.9% of the time taken for traditional 2D sonography).
<table>
<thead>
<tr>
<th>Pathological diagnosis</th>
<th>No. of lesions (%)</th>
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<tbody>
<tr>
<td>Benign</td>
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<tr>
<td>Nodular hyperplasia</td>
<td>18 (60.0)</td>
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<tr>
<td>Follicular adenoma</td>
<td>5 (16.7)</td>
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<tr>
<td>Chronic lymphocytic thyroiditis</td>
<td>6 (20.0)</td>
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<tr>
<td>Hurtle cell adenoma</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>30 (100)</strong></td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>61 (100)</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>61 (100)</strong></td>
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</table>

Table 1. Distribution of the 91 thyroid nodules confirmed by histological analysis.
<table>
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<tr>
<th>Reader</th>
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<th>-LR</th>
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<tr>
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<td>2D</td>
<td>3D</td>
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<td>3D</td>
<td>2D</td>
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<tr>
<td>1</td>
<td>59.0</td>
<td>75.4</td>
<td>70.0</td>
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<td>1.97</td>
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<td>80.3</td>
<td>83.3</td>
<td>80.0</td>
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Table 2. Performance of the 3 radiologists assessing 91 thyroid nodules with two- and three-dimensional ultrasonography for the diagnosis of malignancy.
Figure 1. Images of a 63-year-old woman with a 7-mm, malignant, thyroid nodule.

In two-dimensional axial (A) and longitudinal (B) scan reviews, 2 radiologists assessed this nodule as benign. However, on the three-dimensional reviews using multi-planar images (C) 3 radiologists diagnosed this nodule as malignant because of the spiculated margin and taller-than-wide appearance.
Table 3. Performance of the 3 radiologists assessing 91 thyroid nodules with two- and three-dimensional ultrasonography for detection of extracapsular invasion.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>+LR</th>
<th>-LR</th>
<th>A1 Value</th>
<th>95% CI</th>
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<td>2D</td>
<td>3D</td>
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<td>67.9</td>
<td>46.0</td>
<td>63.5</td>
<td>1.26</td>
<td>1.96</td>
<td>0.7</td>
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<td>25.0</td>
<td>84.1</td>
<td>73.0</td>
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<td>57.1</td>
<td>61.9</td>
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<td>$k$</td>
<td>95% CI</td>
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<tr>
<td>Spiciform</td>
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<td>75.54, 91.33</td>
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<tr>
<td>Echogenicity</td>
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<td>0.52</td>
<td>45.25, 66.44</td>
<td></td>
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<tr>
<td>Calcification</td>
<td>0.52</td>
<td>52.99, 73.56</td>
<td>0.61</td>
<td>56.39, 76.53</td>
<td></td>
<td></td>
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<tr>
<td>Suspicion of invasion</td>
<td>0.36</td>
<td>43.08, 64.36</td>
<td>0.79</td>
<td>61.00, 80.41</td>
<td></td>
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<tr>
<td>Suspicion of malignancy</td>
<td>0.44</td>
<td>47.43, 68.50</td>
<td>0.57</td>
<td>50.75, 71.55</td>
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</table>

Table 4. Radiologists’ agreement for descriptions and diagnoses of 91 thyroid nodules.
DISCUSSION

In this report, I compared commonly used 2D US images with the recently developed 3D US images in order to assess their ability to accurately evaluate thyroid nodules. Jang et al.\textsuperscript{12} in their retrospective study reported better diagnostic performance and improved interobserver and intraobserver agreement with 3D US (in comparison with 2D US) based on cytopathological results. Similarly, in my prospective study based on the histological evaluation of thyroid nodule specimens, I found that the performance of the radiologists for the diagnosis of malignancy with 3D US data trended towards being more accurate than that with static 2D US images. Seven nodules incorrectly categorized as benign with 2D US images were correctly categorized as malignant with 3D US images by at least 1 of the 3 radiologists. Four nodules diagnosed as malignant with 2D US exams were correctly diagnosed as benign with 3D US exams by at least 1 of the 3
In addition, for the evaluation of the extracapsular invasion, the 3D images were found to be superior to the 2D images in all diagnostic performances (with the exception of the specificity recorded for radiologist number 2). With 3D US images, there was found to be a significant improvement in the sensitivity for detection of malignancy and extracapsular invasion. I presume that 3D US images that encompass the entire thyroid nodule could provide solid clues for the diagnosis of malignancy. Calcification, a key factor for differentiating benign nodules from malignant ones, was found more frequently and confidently by the radiologists in my study. Another advantage was that additional images in multiple planes provided by the 3D US (not possible with conventional 2D US) gave more opportunities to detect spiculated and/or micro-lobulated margins. In terms of the prediction of extracapsular invasion, I suggest that increased contact between the tumor and the thyroid capsule demonstrated on additional planes with 3D US reflects a
higher probability of extracapsular invasion and 3D US images facilitate a better understanding of the spatial relationship between the lesion and the adjacent structures. Because extrathyroidal invasion is a well-known prognostic factor and independent risk factor of recurrence\textsuperscript{17,18}, preoperative assessment of the presence of extrathyroidal invasion is crucial for optimal treatment. If a thyroid cancer extends beyond the thyroid, total thyroidectomy is recommended\textsuperscript{19–21}. Therefore, my results could be used in clinical practices while developing treatment plans.

In my study, generally good agreement was obtained for interobserver variability of the 3 radiologists with respect to the 3D US images. Radiologists’ agreement with regard to the suspicion of malignancy and extracapsular invasion was higher for 3D US than for 2D US. For other descriptions of nodular features, interobserver variability for 3D US images was similar to or better than agreement for 2D US images (as reported by Jang et al).
Recent studies by Benacerraf et al.\textsuperscript{22-24} suggest that 3D US may be most useful as a stand-alone technique that eliminates the need for time consuming, preparatory 2D US. These previous studies have shown significant improvements in workplace efficiency when 3D US is used in obstetric screening and transvaginal studies.

Similarly, the findings of this study suggests that a 3D US examination can be performed in a shorter period of time than that necessary for the traditional 2D US examination, demonstrating better time efficiency (especially in cases with a large number of thyroid nodules).

The 3D US definitely has advantages over traditional 2D US. The 3D US images were automatically obtained in the form of volume data with commercially available, volume dedicated, transducers. Subsequently, the stored 3D data allows radiologists and clinicians to review images at remote sites, as needed\textsuperscript{9,25}. In addition, it allows for the comparison of interval changes more precisely by
using full data sets, thereby improving the accuracy of the evaluation of thyroid nodules during follow-up visits\textsuperscript{8,9}.

In many thyroid-imaging clinics, US examination is performed by a US technologist. The physicians then evaluate the thyroid nodules with stored 2D US images. My results show either superiority or noninferiority with respect to the evaluation of thyroid nodules by 2D US and suggest that 3D US examination could be used as a substitute for the 2D sonographic data review method in the current healthcare environment.

My study has some limitations. I did not compare the real time assessment of 2D and 3D US in the evaluation of thyroid nodules. However, my study has the significant finding that 3D US is comparable or better than 2D US with regard to interobserver agreement and diagnostic accuracy in retrospective review. In addition, the shorter scanning time of 3D US is advantageous. I also did not compare 2D and 3D US for the evaluation of cervical
lymphadenopathy (which is essential in the workup of patients with thyroid cancers). Hence, further studies in this direction are needed.

In conclusion, 3D US has the potential to present better interobserver agreement and better diagnostic accuracy than 2D US for the evaluation of thyroid nodules.
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국문 초록

서론: 갑상선결절은 초음파를 시행한 인구의 13~67%에서 발견되는 비교적 흔한 내분비 질환으로 보고되어 있다. 갑상선 초음파는 갑상선결절의 진단을 위한 매우 중요한 검사로 널리 이용되고 있으나, 검사자의 주관적 판단에 의존하여 검사자 간 차이가 있다라는 단점을 가지고 있다. 고식적 이차원 초음파의 이러한 한계점을 극복하기 위한 방안으로, 최근 삼차원 초음파가 대두되고 있는데, 삼차원 초음파를 이용한 갑상선 결절 진단의 정확성과 진단적 유용성에 대해서는 아직까지 연구가 부족한 실정이고 이에 저자는 갑상선결절에서의 삼차원 초음파의 진단적 유용성을 고식적 이차원 초음파와 비교하여 알아보고자 하였다.

방법: 2011년 2월 1일부터 8월 31일까지 갑상선 수술을 시행하기 위해 입원한 환자들 중에서 수술 전 초음파를 시행한 85명의 환자를 대상으로 하였다. 수술로 확인된 61개의 양성 결절과, 30개의 악성 결절에 대하여 촬영된 이차원, 삼차원 초음파 영상을 각각 세 명의 영상의학과 의사가 독립적으로 판독하였으며, 갑상선 결절에 대한 초음파 지표와 악성
예측도, 피막 침습 여부를 판정하였다.

결과: 갑상선 암의 진단에 있어서 삼차원 초음파의 민감도 (관찰자 1-75.4% vs 59%; 관찰자 2-80.3% vs 65.6%; 관찰자 3-80.3% vs 59%)와 특이도 (관찰자 1-73.3% vs 70%; 관찰자 2-76.7% vs 76.7%; 관찰자 3-80% vs 83.3%)는 이차원 초음파와 비교하여 비슷하거나 높은 결과를 보였다. 피막 침습 여부의 진단에 있어서도 관찰자 2의 특이도를 제외하고, 모든 관찰자에서 삼차원 초음파의 진단적 지표들이 이차원 초음파보다 높은 값을 보였다. 특히 갑상선 암과 피막 침습 여부의 진단에 대한 민감도는 통계적으로 유의하게 삼차원 초음파가 높았다. 갑상선결절의 초음파 지표에 대한 기술과, 진단에 있어 삼차원 초음파는 높은 관찰자간 일치도를 보였다.

결론: 갑상선결절을 진단함에 있어 삼차원 초음파가 이차원 초음파와 비교하여 열등하지 않은 진단력과 관찰자간 일치도를 보여준다.

주요어 : 갑상선, 초음파, 결절
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