Utility of the Ultrasound Elastographic Systolic Thyroid Stiffness Index in Reducing Fine-Needle Aspirations

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Objective. The purpose of this study was to evaluate whether ultrasound elastography performed by using carotid pulsation as a compression source and generating the systolic thyroid stiffness index (STSI) can be used as a pre–fine-needle aspiration (FNA) screening tool. Methods. Ultrasound data previously acquired from 62 thyroid nodules in 59 patients who underwent a thyroid FNA were used. Pulsation from the carotid artery was used as the compression source, and the strain was calculated offline. A metric called the STSI was computed for each nodule during systole. On the basis of the derived STSI value, thyroid nodules were retrospectively classified into 2 types: I, no FNA (observation only); and II, FNA. Results. The STSI value of malignant nodules (n = 12) was significantly higher than that of benign nodules (n = 39; P < .00002). Using an STSI cutoff value of 10, 31 nodules were classified as type I, all of which were benign, whereas 20 nodules were classified as type II, 12 malignant and 8 benign, with sensitivity of 100% and specificity of 79.4%. This suggests that ultrasound elastography could have screened out 31 type I nodules, reducing the number of FNAs by 60.8%. Conclusions. Thyroid ultrasound elastography has the potential to substantially reduce the number of FNA biopsies by detecting type I benign nodules. Patients with suspicious type II nodules would be referred for an FNA. Future prospective studies are needed to confirm the efficacy of thyroid ultrasound elastography as a triage tool to FNA. Key words: elastography; thyroid nodule; ultrasound.

Thyroid nodules are a common medical problem, with studies reporting as high as 50% of the population having a thyroid nodule at autopsy. Thyroid nodules are typically asymptomatic and increasingly incidentally discovered during imaging examinations. It is clinically important to diagnose the small malignant population (≈5%) from the rest of the asymptomatic benign nodules, which do not require surgery, which is currently performed by a fine-needle aspiration (FNA) biopsy. Gharib estimated that somewhere between 250,000 and 300,000 thyroid FNA biopsies are performed in the United States annually. However, a large percentage (≈70%) of these biopsies in nodules prescreened by ultrasound turn out to be benign. Thus, considering the increasing number of thyroid nodules being detected and the vast number of benign nodules undergoing FNA biopsies, the challenge lies in judiciously deciding which nodules should be aspirated.

Abbreviations
ASM, angular strain method; CCA, common carotid artery; FNA, fine-needle aspiration; ROC, receiver operating characteristic; ROI, region of interest; SRU, Society of Radiologists in Ultrasound; STSI, systolic thyroid stiffness index; TSI, thyroid stiffness index
Multiple studies published on the ability of ultrasound to distinguish between benign and malignant nodules suggest that the range of sensitivity for ultrasound is 69% to 75%, even after considering the feature with the highest sensitivity, ie, solid composition; however, this feature has a fairly low positive predictive value of only 15.6% to 27% for malignancy. Currently, multiple guidelines exist for managing incidentally discovered and clinically indicated thyroid nodules for an FNA. According to the American Thyroid Association guidelines, any thyroid nodule that is 10 mm or greater in diameter should be evaluated using an FNA, whereas the Society of Radiologists in Ultrasound (SRU) guidelines strongly recommend an FNA of solid nodules greater than 10 mm when microcalcifications are present, greater than 15 mm if a nodule is solid or if coarse calcifications are present, and 20 mm or greater if mixed solid and cystic components exist within a nodule. In addition, the American Association of Clinical Endocrinologists guidelines state that an FNA should be performed on all hypoechoic nodules of 10 mm or greater with irregular margins, chaotic intranodular vascularity, a taller-than-wide shape, or microcalcifications, all of which have been associated with increased risk but are not diagnostic of malignancy. Although all of the guidelines agree on using the nodule size and ultrasound characteristics as criteria for an FNA, there is still discordance between these multiple guidelines on which ultrasound features should prompt an FNA.

Ultrasound elastography measures the tissue deformation in response to compression and derives and displays tissue stiffness. It has been applied to various organs and tissues, eg, as an adjunctive tool to sonography and mammography in the detection and characterization of breast masses. Recent studies showed the potential of extending ultrasound elastography to the differentiation of thyroid nodules. Rago et al showed specificity and sensitivity as high as 100% and 97%, respectively, whereas Bae et al and Dighe et al used in vivo compression caused by the inherent carotid artery pulsation rather than conventional external compression. In our previous study, we used the thyroid stiffness index (TSI) to quantify the stiffness of nodules, which was calculated by averaging all of the strain frames generated. In the thyroid, the maximum deformation (strain) occurs during systole when the carotid artery lumen diameter increases maximally because of the high systolic pressure. From data analysis, it was clear to us that excluding the diastolic portion of the elastographic data set helped reduce fluctuation. Hence, we decided to analyze the data by picking out only the systolic portions from the data sets and produced a new index called the systolic thyroid stiffness index (STSI). We believe that because the strain fluctuation in the data sets is potentially reduced by excluding the diastolic portions, the STSI is more accurate in differentiating between benign and malignant nodules.

All articles in the literature describe the accuracy of detecting malignant nodules; however, in addition to detecting malignant nodules, in this study we evaluated the feasibility of using the STSI generated from ultrasound elastography as a pre-FNA screening tool to reduce the number of FNA biopsies being performed on benign thyroid nodules. By detecting nodules that are almost certainly benign, the number of FNA biopsies being performed on benign nodules could be reduced and could lead to better use of health care resources.

Materials and Methods

Patients

Fifty-nine patients (62 nodules), who were referred for an FNA biopsy following the SRU guidelines, were recruited for the study at our institution. Results from 58 of these 59 patients were reported in our previous article. One additional patient was recruited after our previous article was published. Two patients had elastography performed on multiple nodules, 1 on 3 nodules and another on 2 nodules. The mean age of patients was 51 years, ranging from 20 to 76 years. The largest dimension of the smallest nodule was 1.0 cm, and the largest dimension of the largest nodule was 6.0 cm, with a mean size of malignant nodules of $2.4 \times 2.2 \times 2.3$ cm and a mean size of benign nodules of $2.5 \times 1.8 \times 1.9$ cm. The study was approved by the Institutional Review Board at our institution. Before enrollment, an informed consent was obtained from each participant.
None of the enrolled patients had major carotid atherosclerosis, which was assessed by the presence of carotid plaques, calcifications, or mural thrombi in the neck. The diagnosis for thyroid nodules was based on FNA results unless a patient subsequently underwent surgery. Eleven patients were excluded from the final study results: 1 for inadequate elastography data acquisition and 10 for inadequate sample results on an FNA. For 14 patients who underwent surgery, the final diagnosis of their nodules (n = 17) was based on the histopathologic assessment of the excised thyroid tissue. One patient had 3 nodules with papillary carcinoma, and another patient had 2 nodules that were aspirated and were benign on histopathologic assessment. Of the 17 excised nodules, 11 were diagnosed as papillary carcinoma, and another patient had 2 nodules that were aspirated and were benign on histopathologic assessment.

Systolic Thyroid Stiffness Index

In articles published by our group previously (Bae et al20 and Dighe et al24), we used the TSI to quantify the stiffness of nodules. All of the strain frames generated for this method (~200) were averaged. From this single averaged frame, the TSI was calculated as the ratio of the highest strain near the carotid artery to the lowest strain in a nodule. A higher TSI value represents a stiffer thyroid nodule.20,24,26 Elastography measures the amount of tissue deformation under applied stress, and in the thyroid, the maximum deformation (strain) occurs during systole when the carotid artery lumen diameter increases maximally because of the high systolic pressure.18,20,27 Similar to the previous quantitative measure, TSI, published by our group, we produced a new index called the STSI. The STSI is defined as the ratio of the highest strain near the carotid artery and the lowest strain in a thyroid nodule but only at systole rather than averaging all of the strain frames. Figure 1 illustrates several steps in computing an STSI value of a thyroid nodule. Figure 1A shows a typical ASM-generated strain frame during systole. Two regions of interest (ROIs), 1 near the carotid artery (for the highest strain, within 5 mm of the outer border of the carotid artery) and the other within the thyroid nodule (for the lowest strain), were selected manually using both the strain (Figure 1A) and B-mode (Figure 1B) images during systole. The B-mode image was used to delineate the boundary of the nodule and the area near the carotid artery, whereas the strain image provided the strain distribution information, eg, within the nodule. For each ROI, a strain value was generated by aver-

Ultrasound Elastography

Ultrasound elastography was performed before the FNA procedure with a clinical ultrasound machine (HI VISION 5500; Hitachi Medical Systems America, Twinsburg, OH) with a 7.5-MHz linear array transducer. The ultrasound probe was placed gently on the thyroid of a patient in the supine position in a transverse orientation. For each nodule, the transverse plane showing both the common carotid artery (CCA) and the largest diameter of the nodule was searched using B-mode imaging. Once the imaging plane was identified, quadrature-demodulated in-phase/quadrature-phase data (before any B-mode and color Doppler processing) were acquired for about 6 seconds. During data acquisition, care was taken to not apply any external compression because carotid artery pulsation was used as the compression source. This was done by carefully placing the transducer over the thyroid with an ample amount of coupling gel. The sonographers who acquired the elastographic data had more than 10 years of ultrasound scanning experience and more than 2 years of experience acquiring elastographic data. The ultrasound data were processed offline using the angular strain method (ASM) for elastography, and about 200 strain frames (for 6 seconds) were produced.28
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Figure 1. Procedure for computing the STSI value of a thyroid nodule. A, Estimate strain frames from quadrature-demodulated in-phase/quadrature-phase data using the ASM. B, Place ROIs near the CCA wall, where strain is high (area between the red diamonds), and within a thyroid nodule, where strain is low (the thyroid [Th] is located between the CCA and the trachea [Tr]). C, Generate the axial strain versus time plot for each ROI (red corresponds to strain near the CCA, and blue corresponds to strain within the nodule), and select the peak strain during systole from both strain plots for STSI calculation.

Aging all of the strain values in a 2 × 2-mm area. By repeating this over multiple strain images, strain versus time plots similar to Figure 1C were generated. The STSI value was derived by dividing the strain value near the carotid artery at systole (indicated by the red arrow in Figure 1C) by the corresponding strain value in the nodule (indicated by the blue arrow in Figure 1C).

Classification of Nodules
Similar to the TSI, as shown in previous articles, a higher STSI value suggests a stiffer thyroid nodule, which increases the likelihood of a nodule’s malignancy.20–24,26 On the basis of the calculated STSI value, each thyroid nodule was then retrospectively classified into 2 different categories for FNA screening purposes: I, no FNA (observation only); and II, FNA. Type I (observation-only) nodules would have a low STSI value, indicating that they would have a high probability of being benign. On the other hand, type II nodules would have a high STSI value and hence would have a possibility of being malignant. The cutoff STSI value to differentiate type I nodules from type II nodules was determined through receiver operating characteristic (ROC) curve analysis. A cutoff value that led to low false-negative results was desired to minimize the number of malignant nodules being misclassified as type I.

Statistical Analysis
The data were analyzed using both MATLAB (The MathWorks, Natick, MA) and Excel (Microsoft Corporation, Redmond, WA). Parametric tests were used to determine whether the mean STSI value and others of the benign group were different from (ie, less than) those of the malignant group. A 1-tailed Welch t test was used because of the unequal variance between benign and malignant groups. \( P < .05 \) was considered statistically significant.

Results
Table 1 summarizes the mean and SD of the STSI and strain measured within the nodule and near the carotid artery. The mean STSI value of malignant nodules (n = 12) was significantly higher than that of benign nodules \( (P = .00002) \). The strain of malignant nodules \( (0.07\% \pm 0.03\%) \) was...
significantly lower than that of benign nodules (0.19% ± 0.11%; \(P = 1.3 \times 10^{-7}\)). The strain near the carotid artery was approximately 1.1%. However, there was no significant difference in the strain near the carotid artery between malignant and benign nodules (\(P = .25\)).

Figure 2 shows an ROC curve to differentiate between benign and malignant nodules. The area under the ROC curve for diagnosing papillary carcinoma was 0.942 (95% confidence interval, 0.83–0.98). A critical value of STSI of 10 corresponds to sensitivity of 100% and specificity of 79.5%; hence, a cutoff STSI value of 10 was selected. Thus, any nodule with an STSI value of less than 10 was classified as type I, whereas any nodule with an STSI value equal to or greater than 10 was classified as type II. Type I consisted of 31 nodules with a mean STSI value of 5.45 ± 2.45, ranging from 1.19 to 9.71, all of which turned out to be benign. Type II consisted of 20 nodules with a mean value of 15.97 ± 5.57, ranging from 10.87 to 35, with 12 malignant and 8 benign. The box plot distribution of STSI values for benign and malignant nodules is shown in Figure 3, and the overall distribution of nodules is shown in Figure 4.

Discussion

Among multiple subspecialty groups, there is a discrepancy in the guidelines used to decide whether a thyroid nodule should undergo an FNA biopsy. For example, a nodule whose size is between 10 and 14 mm may or may not get an FNA depending on its ultrasound features and the guideline used. Although conventional ultrasound features, such as solid and hypoechoic nodules along with the presence of calcifications, have been shown to be useful for predicting thyroid malignancy, they are present in benign nodules as well. Even after combining multiple ultrasound features together, the positive predictive value of ultrasound is not very high. This was evident in our study population, where 76.5% (39 of 51) of the FNA-referred nodules were benign. Table 2 lists some ultrasound features that are associated with malignancy and their prevalence in both benign and malignant nodules from our study population. We did not have any completely cystic nodules in our study population; however, we did have 24 nodules with a mixed solid-cystic appearance, out of which 4 nodules had thick-walls and 2 had thick irregular septations, and the rest were solid with some cystic components. Of these nodules, only 3 were diagnosed as malignant and had an STSI of greater than 10.

In our previous article, we used the pulsation of the carotid artery as the compression force on the thyroid. We then averaged all of the strain frames generated for a single acquisition (≈200), and from this single averaged frame, the TSI was

![Figure 2. ROC curve for distinguishing between malignant (n = 12) and benign (n = 39) nodules. The area under the curve is 0.942.](image)
calculated as the ratio of the highest strain near the carotid artery to the lowest strain in a nodule. A higher TSI value represents a stiffer thyroid nodule. Because elastography measures the amount of tissue deformation under applied stress, and because in the thyroid the maximum deformation (strain) occurs during systole when the carotid artery lumen diameter increases maximally because of the high systolic pressure, we found that excluding the diastolic portion of the elastographic data set helped reduce variation. Hence, we decided to analyze the data by picking out only the systolic portions from the data sets and produced a new quantitative number called the STSI. Using our elastographic method, we were able to capture all of the malignant nodules (ie, 100% sensitivity) while still detecting many benign nodules, even though these benign nodules showed 1 or more features to indicate an increased likelihood of malignancy on ultrasound imaging. Figure 5 shows an example of how ultrasound elastography was able to differentiate between the benign and malignant nodules that exhibited similar ultrasound features (presence of calcifications and predominantly solid nodules). All 4 nodules illustrated in Figure 5 were referred for an FNA biopsy under the SRU guidelines using only conventional ultrasound. However, with ultrasound elastography, we were able to differentiate between the benign and malignant nodules on the basis of their STSI values.

In our retrospective study, using an STSI cutoff value of 10, we obtained sensitivity of 100% and specificity of 79.4%, a positive predictive value of 60%, and a negative predictive value of 100%. Thirty-one of the 51 nodules (79.5% of 39 benign nodules) that were scheduled for an FNA were classified as type I. Thus, these nodules would have been correctly identified as benign, and we could have avoided an FNA in these nodules. According to our study results, the STSI has a high negative predictive value of 100%, and because a type I nodule has a high probability of being benign, we hypothesize that patients with a type I nodule maybe safely be followed with ultrasound to assess the change in size or characteristics over time, as shown in Figure 6. Using these guidelines, based on thyroid elastography with carotid compression and the STSI, would have reduced the number of FNA biopsies by 60.8% in our study population. Only 20 (8 benign and 12 malignant) nodules that were classified as type II would have undergone an FNA. Thus, by using thyroid ultrasound elastography as a triage tool, it would be possible to limit FNAs to only type II (high probability of malignancy) nodules, thereby decreasing the percentage of benign nodules being referred for an FNA.
In addition to reducing FNAs on benign nodules, thyroid elastography may reduce potential delays in the diagnosis of malignancy in a nodule compared with the current practice. According to the existing guidelines, nodules that are smaller than 10 mm are unlikely to get an FNA in most institutions and are instead followed over time. However, using our elastography method, we hypothesize that it may be possible to detect malignant thyroid nodules smaller than 10 mm if the STSI value is greater than 10. This could be important in managing thyroid nodules because previous studies29–31

Table 2. Ultrasound Features of 51 Nodules

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid vs cystic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid</td>
<td>15</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Mixed</td>
<td>16</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Cystic</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Echogenicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyper</td>
<td>5</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Iso</td>
<td>12</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Hypo</td>
<td>15</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Calcification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>25</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Present</td>
<td>6</td>
<td>11 (7)</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate numbers of malignant nodules.

Figure 5. Transverse sonograms of thyroid nodules (arrows) recommended for an FNA biopsy by the SRU guidelines. A, Hypoechoic solid nodule with central areas of calcification with an STSI of 20.1, which was malignant (papillary carcinoma) on FNA and histopathologic assessment. B, Hypoechoic nodule with peripheral calcifications with an STSI of 5.6, which was benign (follicular lesion) on FNA. C, Hypoechoic solid nodule without calcifications with and STSI of 17.2, which was malignant (papillary carcinoma) on FNA and histopathologic assessment. D, Hypoechoic solid nodule without calcifications with an STSI of 4.1, which was benign (follicular lesion) on FNA.
showed that the papillary microcarcinomas (papillary carcinomas measuring <10 mm in diameter) can represent up to 30% of all papillary carcinomas, and these microcarcinomas are shown to metastasize to the lymph nodes in as many as 1 of every 3 patients. Thus, the capability of detecting thyroid cancers smaller than 10 mm with ultrasound elastography could decrease the possibility of metastasis and improve the patient’s prognosis. With elastography, the smallest lesion that would be accurately diagnosed in our study was 1 cm, which was a limitation related to the use of the SRU guidelines because only lesions larger than 1 cm are suggested to undergo FNA according to the SRU guidelines.

Choosing which nodule to biopsy in patients with multiple nodules or multinodular goiters is also frequently a challenge. Typically, a noncystic nodule with either suspicious ultrasound features or a cold appearance on a nuclear medicine scan is chosen for an FNA. Ultrasound elastography can be used in screening all of these nodules and detecting suspicious (type II) nodules among them. This would help select the nodule(s) most likely to be malignant from the multiple nodules for an FNA. We believe that this should increase the yield of FNAs by targeting only the suspicious nodules instead of targeting the largest nodule, which may or may not be the most suspicious.

Because FNA of thyroid nodules can be costly, thyroid elastography could ensure more appropriate use of health care resources in managing thyroid nodules. Thyroid nodules are also considered an epidemic due to the large number of imaging studies and the increasing incidental detection (annual incidence rate of 0.1%) of these nodules. Because the existing imaging modalities (computed tomography, magnetic resonance imaging, and ultrasound) cannot accurately differentiate between malignant and benign nodules, an FNA, which costs more than $1200, including an ultrasound examination in our institution, is performed only on nodules showing suspicious features on ultrasound imaging as per the SRU guidelines. However, even after using the ultrasound features and SRU criteria, most nodules on thyroid FNAs turned out to be benign, eg, 76.9% in our study population. Thus, by giving a diagnosis of benignity with high specificity and sensitivity on ultrasound elastography and not performing an FNA procedure on these nodules, costs associated with FNAs for patients with benign nodules can be reduced.

Figure 6. Possible clinical decisions for managing thyroid nodules using ultrasound elastography as a pre-FNA screening tool.
cessing time to a few hours (between 2 and 3). The only manual part of our examination at present is placing 2 ROIs on the region with the lowest strain within the nodule and the region with the highest strain near the carotid artery. We are, however, exploring the possibility of automating this process.

We have taken a different approach to the application of elastography in managing thyroid nodules by specifically targeting the detection of benign nodules and removing them from an FNA pool. In many previous studies, ultrasound elastography was evaluated with the goal of eventually replacing the FNA procedure in detecting malignant nodules. However, FNA is presently considered the standard procedure for managing thyroid nodules and has been shown to be accurate for diagnosing thyroid nodules when used in conjunction with ultrasound.

Our study with elastography is not intended to replace FNA but to improve the use of FNA by screening out nodules that are highly likely to be benign, thereby decreasing the number of FNA biopsies performed per malignant nodule detected.

In using the STSI, one limitation is the manual placement of 2 ROIs to estimate the strain near the carotid artery wall and in the thyroid nodule, which may introduce some variability. Because the STSI is calculated as the division of 2 strain values, which are sensitive to noise, the small variation in strain values could be amplified to introduce larger STSI variations. However, by asking the operator to point to approximate areas (one near the carotid artery [within 5 mm] and another within the thyroid nodule) rather than pinpointing the exact ROI locations and having an algorithm automatically determine the optimal ROIs within the neighborhood, it would be possible to reduce the operator variability in selecting ROIs. Our study had 11 papillary carcinomas and 1 lymphoma. The smaller number of papillary carcinomas was a limitation of our study; however, this was in part due to the smaller prevalence of malignancy in the larger number of benign nodules seen in the thyroid gland. Another limitation of our study was the possibility of a patient’s having a calcified atherosclerotic carotid artery, in which case we may not be able to use our technique. Our study results have shown that hypertension does not affect the results of elastography using our technique because the carotid artery acts as an internal control. Although the compression on the carotid artery would be higher in a patient with hypertension, because we calculate the STSI as a ratio, this effect would be negated. Another limitation would be a nodule within the isthmus because it is very distant from the carotid artery without the advantage of having the trachea medially for the compression. A completely calcified nodule will have a higher STSI even though it may be benign; however, this would be a limitation of other elastographic methods as well.

Ultrasound elastography has shown feasibility as a noninvasive screening tool to reduce the number of FNA biopsies being performed on benign nodules. By providing new guidelines based on the stiffness of a nodule, in conjunction with the ultrasound features, thyroid elastography may lead to an improvement in managing thyroid nodules compared with the existing guidelines alone. On the basis of our results, we have shown in an FNA-bound population that it would be possible to detect and screen a substantial number of benign nodules, thus reducing the number of FNA biopsies by 60.8% (31 of 51 nodules). To confirm our results, future prospective studies would be needed to confirm the efficacy of elastography as a triage tool to FNA.

References

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