31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Screening of Thyroid Nodules by Ultrasound Elastography Using Diastolic Strain Variation

Si Luo[1], Eung-Hun Kim[2], Manjiri Dighe[3] and Yongmin Kim[1,2]
Departments of Electrical Engineering[1] and Bioengineering[2], Department of Radiology[3]
University of Washington, Seattle, WA 98195, USA

Abstract--**The diagnosis for thyroid nodules is currently made via an FNA biopsy. It is estimated that somewhere between 250,000 and 300,000 thyroid FNA biopsies are performed in the United States annually. However, a large percentage (approximately 70%) of these biopsies turn out to be benign. The purpose of this study is to evaluate whether ultrasound elastography can be used as a screening tool to reduce the number of FNA procedures on benign thyroid nodules. Ultrasound data previously acquired from 34 thyroid nodules in 31 FNA-bound patients were used. Pulsation from the carotid artery was used to compress the thyroid nodules, and the strain was calculated off-line. A metric, called diastolic strain variation index (DSVI), was computed for each nodule during diastole as the standard deviation of strain within a thyroid nodule. Based on the derived DSVI value, thyroid nodules were retrospectively classified into 2 types: I) no FNA (observation-only) and II) FNA. The DSVI value of benign nodules (n=22) was significantly higher than that of malignant nodules (n=12) (p=0.0000016). Using an DSVI cut-off value of 0.019%, 18 nodules were classified as type I, all of which were benign, while 16 nodules were classified as type II, 12 malignant and 4 benign. This suggests that ultrasound elastography could have screened out 18 type-I nodules, reducing the number of FNAs by 53%. Because aggressive FNA management of thyroid nodules is costly, thyroid elastography could be employed in the future for more appropriate utilization of healthcare resources in handling thyroid nodules.**

Keywords: thyroid elastography, carotid artery pulsation, strain

I. INTRODUCTION

A thyroid nodule is abnormal growth of cells within the thyroid gland and can be non-cancerous (benign) or cancerous (malignant). The diagnosis for nodule malignancy is currently made via a fine needle aspiration (FNA) biopsy, which draws cytological samples from the nodule using a 25-gauge needle. It is estimated that somewhere between 250,000 and 300,000 thyroid FNA biopsies are performed annually in the United States. However, a large percentage (approximately 70%) of these biopsies turn out to be benign [1]. 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.

US elastography measures the tissue deformation in response to stress to derive and display tissue stiffness. Recent studies demonstrated the potential of applying US elastography to the thyroid gland in noninvasively differentiating between malignant and benign thyroid nodules [2-5]. In a study by Lyshchik et al. [6], the elastic modulus of excised thyroid tissues was shown to correlate with the malignancy of thyroid nodules. They observed that malignant thyroid nodules are 5 times stiffer than normal thyroid tissue while benign nodules are only 1.7 times stiffer than normal tissue. They reported that US elastography could be used for differential diagnosis of thyroid cancer [3].

Previous elastography studies [3,5,7] employed the freehand external compression. Bae et al. [2] developed a new approach where the carotid artery was used as an *in vivo* compression source, taking advantage of its inherent periodic pulsation (e.g., expansion of the carotid artery lumen diameter during systole) and its position (adjacent to the thyroid).

Different from the previous studies where only static strain was used, in this paper we have investigated the use of a thyroid nodule's dynamic properties in nodule classification. We have also evaluated the feasibility of using ultrasound elastography as a pre-FNA screening tool to reduce the number of FNA biopsies being performed on benign thyroid nodules. By detecting those nodules that are almost certainly benign, the number of FNA biopsies performed on benign nodules could be reduced to improve the utilization of FNA in diagnosing malignant nodules.

II. METHOD

A. Ultrasound elastography using carotid artery pulsation

Since the thyroid gland is adjacent to the carotid artery, the inherent periodic pulsation of the carotid artery was used for thyroid elastography [2]. During systole, the carotid artery expands its diameter due to high blood pressure, which compresses the thyroid against the trachea in the medial-lateral direction. Since soft tissues are nearly incompressible, compression in the medial-lateral direction causes thyroid expansion in the anteroposterior and superior-inferior directions. Because ultrasound is highly sensitive to the displacement along the beam (axial) direction, we estimated thyroid strain in the anteroposterior direction.

Figure 1 shows an example of thyroid strain induced by pulsation of the carotid artery. The data were acquired from a healthy volunteer at 270 fps to attain high temporal resolution. An ROI (a red rectangle in Fig. 1) is first placed within the thyroid gland, and its strain is computed by averaging all the strain values in the neighborhood of 2 mm x 2 mm. By repeating this over multiple strain images, a strain vs. time plot is generated as shown in Fig. 1. The thyroid expansion in the axial direction during systole results in positive peaks.

B. Diastolic strain fluctuation

For a single cardiac cycle, a strain vs. time plot (generated from the data acquired at 270 fps) could be divided into three phases as shown in Fig. 2. The zero time instance in Fig. 2

represents the peak of an ECG R wave. Phases I and II correspond to the expansion of the carotid artery lumen diameter during systole. Phase III represents the restoration of the carotid artery in diastole. During Phase I, due to the high blood pressure in the lumen, the carotid artery wall starts to compress the thyroid gland. At the end of the Phase I, a positive peak indicates a time instance where the thyroid has the maximum deformation between two consecutive frames. After this peak, the strain value tends to decrease until the end of Phase II, which means that the carotid artery wall still compresses the thyroid but not as much as it does at the end of Phase I or the beginning of Phase II. Because of the drop in carotid artery lumen blood pressure during diastole, the thyroid recovers to the original state in Phase III.

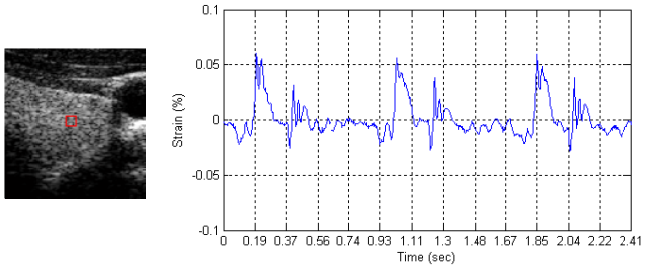


Figure 1. Strain vs. time plot for an ROI within the thyroid. Positive strain indicates expansion in the axial direction and negative strain indicates axial compression.

We believe that the overall shape of the strain vs. time plot reasonably follows the expansion and restoration of the carotid artery lumen diameter. On the other hand, the strain oscillation is noticeable in the strain vs. time plot, especially during the Phase III. The oscillation frequency is much higher than the carotid artery pulsation frequency (e.g., ~1 Hz), indicating it is unlikely that the oscillation is caused by artery pulsation. We hypothesize this frequency stems from the vibration of thyroid tissue at its natural frequency [8].

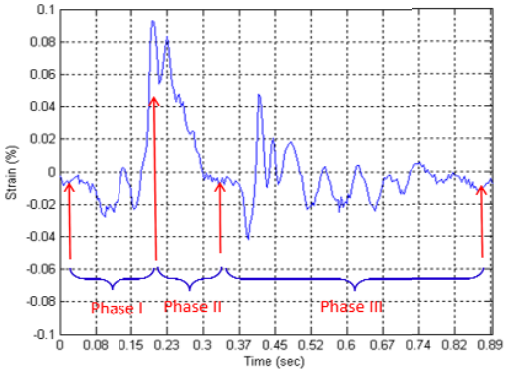


Figure 2. Three phases in a strain vs. time plot.

Figure 3 shows the power spectrum of the strain vs. time plot. The frequency components less than 6.5 Hz accounts for about 75% power in Fig. 3, which is accordant with the fact that the carotid artery is a low-frequency compression source. The main strain oscillation frequency is represented by a distinct peak at the frequency of 14.3 Hz (a blue arrowhead in Fig. 3). This frequency is consistent with other's findings on the vibration of soft tissue in the leg [9]. Since the strain value is relatively low and the strain oscillation is more easily noticeable in Phase III, we define the diastolic strain fluctuation as the variation of strain value in Phase III.

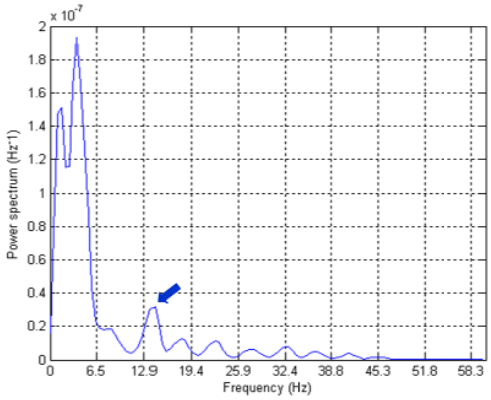


Figure 3. Power spectrum of the strain vs. time plot in Fig. 2.

The mechanical property of thyroid tissue can be modeled as a system with a purely viscous damper and a purely elastic spring connected in parallel [8]. The natural frequency can be calculated by

$$f_n = \frac{1}{2\pi}\sqrt{\frac{k}{m}} \tag{1}$$

where m is the mass and k is the spring constant that is proportional to the thyroid tissue stiffness. The carotid artery pulsation can be represented as

$$F(t) = \sum_{f=f_h}^{\infty} C_f \cos(2\pi f t) \tag{2}$$

where f_h is the heart beat frequency (~1 Hz), f is the frequency of sinusoidal functions and C_f is the corresponding magnitude. Since the carotid artery is a low-frequency compression source, we assume the heart beat frequency f_h has the maximum magnitude $C_{\max}$ and the magnitude decreases exponentially as the frequency increases. Then, the magnitude of thyroid tissue vibration at a certain frequency f can be calculated by

$$X(f) = \frac{C_f}{k}\frac{1}{\sqrt{(1-r^2)^2 + (2\zeta r)^2}} \tag{3}$$

where ζ is the damping ratio and r is defined as

$$r = \frac{f}{f_n} \tag{4}$$

Eq. (3) suggests that a certain frequency component from the carotid artery pulsation would vibrate the tissue at that frequency and the magnitude of vibration is mainly related to

the magnitude of input and tissue stiffness. Since $f_h << f_n$ and $r \ll 1$, the term $\frac{1}{\sqrt{(1-r^2)^2+(2\zeta r)^2}}$ in Eq. (3) approaches 1. Thus, Eq. (3) can be simplified as

$$X \approx \frac{C_{\max}}{k} \tag{5}$$

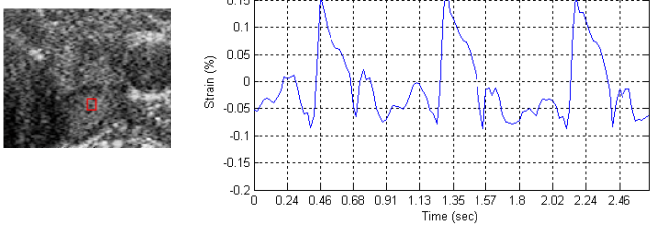
According to Eq. (5), the magnitude of thyroid tissue vibration at the heart beat frequency is inversely proportional to its spring constant or stiffness. Since a malignant nodule is about 3 times stiffer than a benign nodule, the magnitude of vibration for a malignant nodule should be ~3 times less than that for a benign nodule at the heart beat frequency. Figure 4 compares the strain vs. time plot of a benign nodule and a malignant nodule. The ultrasound data were acquired at 45 fps, thus more strain can be seen in Fig. 4. As can be seen, the peak strain of a malignant nodule (~0.05% in Fig. 4 (b)) is about one third of that of a benign nodule (~0.15%, Fig. 4 (a)).

When the thyroid tissue vibrates at its natural frequency, r becomes 1 based on Eq. (4). Assuming the dumping ratio ζ is 0.5 for both benign and malignant nodules, the magnitude of vibration at the natural frequency can be approximated

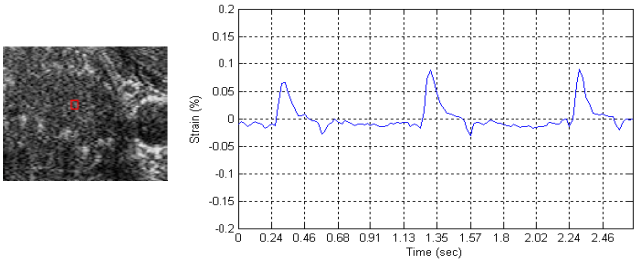
$$X_n(f) \approx \frac{C_f}{k} \tag{6}$$

which suggests that X_n is dependent on both the stiffness of tissue and C_f, which is the magnitude of input component that has the same frequency with the natural frequency of the nodule. Since a malignant nodule is stiffer than a benign nodule, the natural frequency of a malignant nodule is higher than that of a benign nodule based on Eq. (1). As C_f decreases exponentially when the frequency f increases, the input component to vibrate a malignant nodule is actually smaller than that of a benign nodule, which leads to an even smaller vibration magnitude X_n. This explains why the strain variation of a malignant nodule in Fig. 4(b) is not apparent compared to .Fig. 4(a).

To quantify the strain variation in Phase III, a diastolic strain variation index (DSVI) was defined as the standard deviation of strain in diastole. A high DSVI means larger strain variation during diastole and suggests a high probability of being benign. DSVI for the malignant nodule (papillary carcinoma) in Fig. 4(b) is 0.006% whereas that for the benign nodule (follicular cells) in Fig. 4(a) is 0.028%, indicating that the strain variation in diastole for the malignant nodule is much less than that for the benign nodule.



(a)



(b)

Figure 4. Strain vs. time plot for (a) a benign nodule and (b) a malignant nodule.

C. *Screening of nodules*

Based on the calculated DSVI value, each thyroid nodule was classified into 2 different categories for pre-FNA screening purposes. Type-I (observation-only) nodules have a high DSVI value, indicating a high probability of being benign and would bypass an FNA biopsy. On the other hand, type-II nodules have a low DSVI value. Thus, these nodules are referred for an FNA biopsy to determine whether it is malignant or not.

III. RESULTS

We analyzed 34 thyroid nodules from 31 patients, who were referred for an FNA biopsy at our institution. 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 significant carotid atherosclerosis, which was assessed from the presence of carotid plaque, calcification or mural thrombus in the neck. The diagnosis for thyroid nodules was based on FNA results unless a patient subsequently underwent surgery.

US elastography was performed prior to 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 US probe was placed on the thyroid of a patient in the supine position with no external freehand compression since the carotid artery was used as the compression source. For each nodule, the transverse plane showing both the common carotid artery (CCA) and the largest diameter of a nodule was searched using B-mode. Once the imaging plane was identified, quadrature-demodulated I/Q data (before any B-mode and color Doppler processing) were acquired at 45 fps for about 6 seconds. The ultrasound data were processed off-line using the angular strain method (ASM) for elastography [10].

Table 1. DSVI values from malignant and benign nodules

Parameter	**Malignant** (n=12)	**Benign** (n=22)	***p***
DSVI	0.013% ± 0.005%	0.030% ± 0.012%	0.0000016

Table 1 summarizes the DSVI mean and standard deviation for the benign and malignant nodules. The mean DSVI value

(0.030% ± 0.012%) of benign nodules (n=22) is significantly higher than that (0.013% ± 0.005%) of malignant nodules (p= 0.0000016).

A cut-off DSVI value of 0.019% was used. Thus, any nodule with the DSVI value equal to or higher than 0.0019% was classified as type I, while any nodule with the DSVI value less than 0.0019% was classified as type II. Type I consisted of 18 nodules, all of which turned out to be benign. Type II consisted of 16 nodules, with 12 malignant and 4 benign.

The boxplot distribution of DSVI values for benign and malignant nodules is shown in Figure 6. With the cut-off value of 0.019%, a sensitivity of 100% and a specificity of 82% were obtained for detecting malignant nodules.

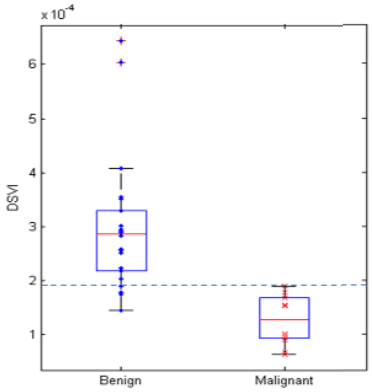


Figure 6. DSVI boxplot distribution of benign (blue dots) and malignant (red x) nodules. The blue dotted line indicates the cut-off value of 0.019%.

IV. DISCUSSION

Thyroid nodules are considered an epidemic due to the large number of imaging studies performed and the increasing incidental detection of these nodules [11]. Since the existing imaging modalities (CT, MRI and US) cannot accurately differentiate between the malignant and benign nodules, an FNA biopsy, which costs typically $1,500 including an US exam, is performed on nodules showing suspicious features. However, the majority of FNA procedures are performed on benign nodules. Thus, by detecting and removing many benign nodules from an FNA procedure altogether, costs associated with FNA biopsies on patients with benign nodules could be substantially reduced. In addition, although FNA is a minimally-invasive procedure, it can take a toll on the patients emotionally, especially in patients who are fearful of procedures requiring the use of needles. Thus, a noninvasive pre-FNA triage tool to screen out benign nodules with a high level of confidence can be of significant benefit to the patients and increasing the efficiency of healthcare expenditures.

Using our elastography method, we were able to capture all the malignant nodules in type II (i.e., 100% sensitivity), while still detecting many benign nodules as type I. Thus, by utilizing US thyroid elastography as a triage tool, it would be possible to limit FNA biopsies to only type-II (high probability of malignancy) nodules, thereby increasing the percentage of malignant nodules being referred for an FNA biopsy.

V. CONCLUSION

US elastography has shown the feasibility as a noninvasive screening tool to reduce the number of FNA biopsies being performed on benign nodules. The diastolic strain variation is used to differentiate malignant nodules from benign nodules. In our retrospective study, 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 53%. To confirm our results, future prospective studies would be needed to confirm the efficacy of elastography as a triage tool to FNA biopsy.

REFERENCE

[1] H. Gharib and J. R. Goellner, "Fine-needle aspiration biopsy of the thyroid: an appraisal," *Annals of Internal Medicine,* vol. 118, pp. 282-289, 1993.

[2] U. Bae, M. Dighe, T. Dubinsky, S. Minoshima, S. Shamdasani, and Y. Kim, "Ultrasound thyroid elastography using carotid artery pulsation," *J. Ultrasound Med.,* vol. 26, pp. 797-805, 2007.

[3] A. Lyshchik, T. Higashi, R. Asato, S. Tanaka, J. Ito, J. J. Mai, C. Pellot-Barakat, M. F. Insana, A. B. Brill, T. Saga, M. Hiraoka, and K. Togashi, "Thyroid gland tumor diagnosis at US elastography," *Radiology,* vol. 237, pp. 202-211, 2005.

[4] M. Dighe, U. Bae, M. L. Richardson, T. J. Dubinsky, S. Minoshima, and Y. Kim, "Differential Diagnosis of thyroid nodules with US elastography using carotid artery pulsation," *Radiology,* vol. 248, pp. 662-669, 2008.

[5] T. Rago, F. Santini, M. Scutari, A. Pinchera, and P. Vitti, "Elastography: New developments in ultrasound for predicting malignancy in thyroid nodules," *J. Clin. Endocrinol. Metab.,* vol. 92, pp. 2917-2922, 2007.

[6] A. Lyshchik, T. Higashi, R. Asato, S. Tanaka, J. Ito, M. Hiraoka, A. B. Brill, T. Sata, and K. Togashi, "Elastic moduli of thyroid tissues under compression," *Ultrason. Imaging,* vol. 27, pp. 101-110, 2005.

[7] B. S. Garra, E. I. Cespedes, J. Ophir, S. R. Spratt, R. A. Zuurbier, C. M. Magnant, and M. F. Pennanen, "Elastography of breast lesions: Initial clinical results," *Radiology,* vol. 202, pp. 79-86, 1997.

[8] Y. C. Fung, *Biomechanics*. New York, NY: Springer, 1981.

[9] J. M. Wakeling and B. M. Nigg, "Modification of soft tissue vibrations in the leg by muscular activity," *J Appl Physiol,* vol. 90, pp. 412-420, 2001.

[10] U. Bae and Y. Kim, "Angular strain estimation method for elastography," *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control,* vol. 54, pp. 2653-2661, 2007.

[11] R. Ortiz, K. H. Hupart, C. R. DeFesi, and M. I. Surks, "Effect of early referral to an endocrinologist on efficiency and cost of evaluation and development of treatment plan in patients with thyroid nodules," *J. Clin. Endocrinol. Metab.,* vol. 83, pp. 3803-3807, 1998.