Differentiation between endometrial carcinoma and atypical endometrial hyperplasia with transvaginal sonographic elastography

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KEYWORDS
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Abstract
Purpose: To assess the value of transvaginal sonographic elastography (TSE) in discriminating between endometrial hyperplasia and endometrial carcinoma.

Materials and methods: A total of 61 women with post-menopausal hemorrhage and/or normal TSE were included. There were 32 women (mean age: 53.1 ± 14.1 years) with endometrial hyperplasia, 14 women (mean age: 60.0 ± 14.0 years) with endometrial carcinoma and 15 women (mean age: 51.9 ± 7.8 years) with no endometrial disease who served as a control group. The strain index (SI) values obtained during TSE in each group were compared using Mann-Whitney U test and Kruskal-Wallis analysis of variance test.

Results: The mean SI values were 0.80 (range: 0.30–1.30) in the endometrial hyperplasia group, 1.80 (range: 0.80–3.20) in the endometrial carcinoma group and 1.00 (range: 0.50–4.00) in the control group. No significant differences were found between endometrial hyperplasia group and control group, but significant differences were found between endometrial carcinoma and hyperplasia groups and between endometrial carcinoma and control groups (P < 0.0001). TSE had a sensitivity of 81.3%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 70% in differentiating endometrial carcinoma from endometrial carcinoma.

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Hyperplasia. The area under ROC curve (AUC) to distinguish between endometrial carcinoma and endometrial hyperplasia was 0.933 (95% CI, 0.853—1.000) using a threshold SI value of 1.05. The AUC to distinguish between endometrial carcinoma and control was 0.881 (95% CI, 0.735—1.000) using a threshold SI value of 1.15.

Conclusion: Our results indicate that TSE can provide important information that help discriminate between endometrial carcinoma and endometrial hyperplasia.

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Sonographic elastography is an imaging technique that provides information regarding tissue elasticity by measuring the hardness and stiffness of tissues by external compression and decompression that may predict malignancy [1].

Due to the progressive decrease of ovarian hormone production during the post-menopausal period, endometrial cavity becomes thinner and atrophy along with no cyclic changes are observed. Kurjak et al. reported a mean cavity thickness of 2.3 mm on transvaginal sonographic elastography (TSE). A thickness < 5 mm is considered normal in this post-menopausal period [2,3]. The causes of post-menopausal bleeding are endometrial carcinoma, endometrial polyps, endometrial hyperplasia and/or atrophy, leiomyomas, hormone therapy and treatment with tamoxifen [4]. Transvaginal sonography is the first line imaging modality in the evaluation of post-menopausal bleeding because other imaging techniques such as computed tomography and magnetic resonance imaging have limited predictive values [5,6].

The reference standard to differentiate benign from malignant endometrial abnormalities remains endometrial biopsy with histopathological analysis [6]. Benign endometrial hyperplasia represents 5—10% of the causes of post-menopausal bleeding. In women with atypical hyperplasia, malignancy has to be ruled out as a concomitant well-differentiated adenocarcinoma can be present in up to 25% of women [7,8].

Sonographic elastography is a technique that is conceptually based on tissue elasticity [9]. Sonographic elastography is used for tissue characterization via the application of compressions due to elasticity degrees, quantitative measurement of elasticity and stiffness of compressible tissues in different areas [10,11]. There are different types of elastography that include strain elastography, acoustic radiation force impulse elastography (ARFI), shear-wave elastography (SWE) and transient elastography (TE) [12—15]. In strain elastography the compressions and decompressions were manually performed by the user manually and the resulting variable is the strain index (SI). SI is the strain ratio of the lesion and adjacent normal tissue. ARFI, SWE and TE use shear-waves to measure tissue elasticity. Shear-waves are created by the sonographic transducer electronically and present the strain or stiffness of the tissue independently from normal adjacent tissue. There is no ratio in shear-wave method. ARFI and SWE calculate the transverse shear-waves, but method of measurement is not displayed on the same way. Unlike other methods, TE does not provide B-mode image.

Elastography was first introduced for the differential diagnosis of malignant breast lesions. In this regard, fibroadenomas are less rigid than squamous breast cancers [9]. In the liver, degree of fibrosis causing rigidity in the liver can also be measured by elastography [16,17]. Bojunga et al. reported that elastography significantly decreased the number of unnecessary fine-needle aspiration biopsies in thyroid nodules [18]. Not only the thyroid but also the musculoskeletal system and abdominal organs are now evaluated by elastography [19—22].

In this study, we aimed to assess the role of TSE in differentiating endometrial hyperplasia from endometrial carcinoma;

Materials and methods

Institutional review board approval and written informed consent forms were obtained for this prospective study.

A total of 136 women who had TSE between February 2013 and October 2013 were initially included in the study. All women were referred to the imaging department for TSE because of post-menopausal hemorrhage and/or for routine ultrasonographic examination of the pelvis. Ages and menopause ages of all women were reported and TSE was performed with the same protocol by the same radiologist who had 15 years of experience for pelvic ultrasound and five years of experience for TSE. The patients underwent both B-mode ultrasound and TSE examinations in the supine position with a digital sonography scanner (Logiq E9, GE Healthcare, Wisconsin, USA) equipped with real-time tissue elastography software, by using 5—7.5 MHz multifrequency transvaginal transducer.

During TSE, mild repetitive compression and decompressions were manually performed. The apparently normal myometrium adjacent to the measured endometrial surface was also included in the elastographic box for all patients. The imaging files of each patient were re-analyzed. The most appropriate time for compression before measurement was predicted as 5—7 bars range. First of all, the normal sonographic appearing myometrium then the endometrium were measured inside the box by inserting region of interest (ROI). We took care to adjust the ROI to the maximum homogeneous and thick tissue to avoid the ROI bias. In order to optimize the width of ROI, the same ROI size was handled to both myometrium and endometrium (Figs. 1—3). SI was automatically measured and recorded for each woman. Three random SI measurements were performed and the mean value was used as the final value.

Inclusion criteria of this research for all patients were that the histopathological correlation had to be done within
three weeks after the TSE examination. Biopsy of the patients who were suspicious for endometrial carcinoma with TSE (there was no suspicious result in the biopsies, so the re-biopsy was not needed), was re-examined and patients with the direct diagnosis of carcinoma without any focuses of hyperplasia were included in the research which were coded with blue as type 4 elasticity pattern, whereas endometrial adenocarcinomas with hyperplasia and/or hematoma, carcinoma arising from endometrial polyps were excluded which were coded with mixture of green, yellow and red codes as type 2 elasticity pattern. Women using hormonal therapy and tamoxifen, women with submucosal leiomyomas, women with the diagnosis of endometrial atrophy and women without any histopathological diagnosis were excluded from the study. Finally, 61 women were included in the study population. The
endometrial carcinoma group comprised 14 women with histologically confirmed endometrial carcinoma either after probe curettage or after abdominal hysterectomy. The endometrial hyperplasia group comprised 32 women. The control group comprised 15 post-menopausal women with normal endometrial thickness.

**Statistical analysis**

For each continuous variable, Kolmogorov-Smirnov Test for normal variables was performed. Parametric or non-parametric analyses were applied depending on the distribution of each characteristic. For the comparison of two groups, Student’s t test was applied since all parametric assumptions were fulfilled. Kruskal-Wallis analysis of variance test was performed for comparison of more than two groups. In this circumstance, Mann-Whitney U Test with the Bonferroni correction was applied for pairwise statistics. Quantitative were reported as mean ± standard deviation (SD) or median (interquartile range: q3—q1) depending on the statistical methods. In addition, receiver operating characteristics (ROC) curve was fitted in order to characterize the group differences in terms of sensitivity and specificity. Threshold SI values were also searched for using ROC curve analysis and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. For each statistical procedure, level of significance was set at P < 0.05. All statistical calculations and tests were performed with SPSS (Version 18.0) software. MS Excel (Version Microsoft Excel for Mac 2011) was used for the designs of graphics.

**Results**

The mean age of the women was 51.93 ± 7.84 (range: 39–68 years) years in the control group, 53.13 ± 14.11 (range: 30–90 years) years in the hyperplasia group and 60.07 ± 14.04 (range 30–76 years) in the endometrial carcinoma group. No differences in age were found between the hyperplasia group and the endometrial carcinoma group (P = 0.081). Median endometrial thickness was 15.00 mm (interquartile range [IR]: 13; range: 8.30–64.00 mm).

The median SI values were 0.80 (IR: 0.60; range: 0.30–1.30) in the endometrial hyperplasia group, 1.80 (IR: 1.05; range: 0.80–3.20) in the endometrial carcinoma group and 1.00 (IR: 0.40; range: 0.50–4.00) was in the control group. No significant differences were found between endometrial hyperplasia and control group, but a significant difference was found between endometrial carcinoma group and hyperplasia and control group (P < 0.0001). A ROC-1 analysis was made to determine the optimal threshold SI value to distinguish between endometrial carcinoma and endometrial hyperplasia. Using a threshold SI value of 1.05, sensitivity was 92.9%, specificity was 71.9%, PPV was 59.1% and NPV was 95.8%, with a corresponding area under the curve (AUC) of 0.933 (95% CI, 0.853–1.000) (Fig. 4).

A ROC-2 analysis was obtained to determine the optimal threshold SI value to distinguish between endometrium carcinoma and control group. Using a threshold SI value of 1.15, sensitivity was 85.7%, specificity was 93.3%, PPV was 92.3% and NPV was 87.5%, with a corresponding area under the curve (AUC) of 0.881 (95% CI, 0.735–1.000) (Fig. 5).

The elasticity patterns of endometrial carcinoma and hyperplasia were distributed as follows: 26/32 endometrial hyperplasias (81%) showed types 1 and 2 elasticity pattern, while 14/14 endometrial carcinomas (100%) showed type 3, 4 or 5 elasticity patterns [26].

**Discussion**

Our research was based on the fact that malignant lesions display higher rigidity and stiffness than benign lesions [23]. In the present study, we evaluated the post-menopausal patients who had thickened endometrium by using both
Elastography in endometrial carcinoma and endometrial hyperplasia

Figure 4. A ROC-1 analysis was fitted to determine the optimal cut-off SI value in order to distinguish endometrium carcinoma from endometrial hyperplasia. Sensitivity was 92.9%, specificity was 71.9%, positive predictive value was 59.1% and negative predictive value was 95.8%. The area under the curve (AUC) was 0.933 using a threshold value of 1.05.

Figure 5. A ROC-2 analysis was obtained to determine the optimal cut-off SI value for endometrium carcinoma and control group. Sensitivity was 85.7%, specificity was 93.3%, positive predictive value was 92.3% and negative predictive value was 87.5%. The area under the curve (AUC) was 0.881 using a threshold value of 1.15.

Sonographic and elastographic methods, obtained color-coded schemes for each patient. We compared the strain rates of each group (endometrial carcinoma and endometrial hyperplasia) with the control group. Our findings underlined significant statistical differences among the study groups in terms of SI and elasticity patterns of tissues. Previous reports about the differentiation between benign and malignant lesions of various organs indicated that nucleus/cytoplasm ratio was increased due to the increased number of tumor cells, leading to increased stiffness of tumor tissues [24–27].

Sonographic elastography has been used in many studies investigating breast cancer, liver fibrosis, cervical lymphadenopathies, thyroid cancer, prostate and kidney tumors. Sonographic elastography provided significant outcomes in those studies [21,22,28–33]. Sonographic elastography is applied to the diagnosis of cancers in the breast, thyroid, prostate, kidneys as well as the characterization of lymph nodes, myocardial and cervical pathologies. However, only a few studies have addressed the potential of sonographic elastography for the investigation of endometrial pathologies [23,34–38].

Endometrial carcinoma takes the fourth place in ranking of malignancy in women after breast, colon and lung carcinoma. Approximately 70% of endometrial carcinomas are seen during the post-menopausal period. Endometrial thickening is the most frequent finding of endometrial carcinoma on transvaginal ultrasound. Endometrial hyperplasia is generally homogeneous, but however, can be focal or asymmetrical nodular hyperplasia. Thickening of endometrial cavity on ultrasound is a non-specific finding, which has to be histopathologically confirmed by biopsy [38,39]. Sessile endometrial polyps, submucosal myomas and intraluminal hematomas can be differentiated from endometrial carcinoma [40,41]. Endometrial carcinoma can be diffuse, focal or nodular, or may present as polyloid mass. If myometrial invasion is present, sub-endometrial halo sign can be visualized but this sign is not specific [41].

In our study, SI values and color code mapping of ES supplied important information in the differential diagnosis of endometrium carcinoma and hyperplasia. There are different color-coded elasticity patterns in the literature. Asteria et al. described four color codes, while Rago et al. and Alam et al. described five color codes [28,42,43]. In the color mapping, we fitted the scoring model as five color codes according to Alam et al. [28]. With regard to this scoring, red color indicated extreme soft tissue components-green color indicated moderate soft tissue and blue color indicated the tough tissues. Tissues reveal different patterns according to colors as pattern 1, 2, 3, 4 and 5. Pattern 1 shows absent or very small blue area(s); pattern 2 shows small scattered blue areas, total blue area < 45%; pattern 3 shows large blue area(s), total blue area ≥ 45%; pattern 4 shows peripheral blue area and central green area; pattern 5 shows blue area with or without a green rim. The mean SI values for endometrial hyperplasia and carcinoma were 0.80 and 1.80, respectively in our study. Normal endometrium SI value was 1.00. Barr et al. studied elasticity patterns and B-mode ultrasound results of 413 benign and 222 malignant breast lesions and achieved a sensitivity of 98.6 and a specificity of 87.4% to differentiate benign lesions from malignant.
ones [44]. Our results regarding sensitivity and specificity ranges were similar.

In real-time ultrasound elastography, color-coded mapping was first applied on breast masses, and this scoring scheme was adapted to other organs [45]. Lyshchik et al. proved that benign, malignant, and cystic thyroid lesions had different elasticity values [46]. In our study, endometrial carcinoma group had greater stiffness than hyperplasia with color-coded map. Types 3 and 4 color-mapping scheme was mostly present for endometrial carcinoma and types 2–3 for endometrial hyperplasia. None of the endometrial carcinomas had types 1 and 2 elasticity patterns. In such cases, types 3 and 4 patterns regarded 81.3% sensitivity, 100% specificity, 100% PPV and 70% NPV for the diagnosis of endometrial carcinoma. These results stated that elastography had high diagnostic profile in the exact differentiation of benign and malignant endometrial lesions.

Dudea et al. evaluated the relative strain rates and stiffness indexes of the superficially located lymph nodes [47]. They reported that the strain rates of the malignant lesions were significantly higher than benign lesions [47]. Klotz et al. used shear-wave elastography in a study that included 167 BI-RADS 3 or higher breast lesions. They reported that shear-wave elastography can improve breast tumor management [33]. The results of Ciledag et al. showed that elastography had important contribution for differentiating benign from malignant ovarian cystic tumors and also facilitated the detection of solid areas for further biopsy [1].

Yijin Su et al. reported high sensitivity and specificity of ARFI method in the evaluation of cervical cancers [48]. In our study, we performed elastography by using a transvaginal approach instead of a transabdominal approach. The probe pressure applied during transabdominal elastography was directly dependent to the operator, thus the magnitude of the compression might change from one operator to another. However, when elastography was applied using a transvaginal approach, the pressure was relatively stable compared to the transabdominal application. Moreover, transabdominal elastography outcomes were often affected by the thickness of the skin-subcutaneous soft tissue while these limitations were not seen in TSE. Since the probe pressure was negligible for the TSE method, to our experience, it would be rational to discover a possible cut-off point for diagnosing endometrial pathologies.

There were some limitations of this research. First, hematomas of endometrial cavity which could be seen with both carcinoma and hyperplasia cases could not be easily differentiated by ultrasonography and elastosonography due to changes of SI in terms of different stages of hematomas and bleeding period. Second, we did not have evaluated inter- and intra-observer variability, which could cause statistical bias. Third, we did not test the inter-observer reproducibility of TSE. But a study in the literature mentions that there was no significant inter- or intra-observer variability in the strain elastography [29].

Conclusion

In conclusion, TSE is a complementary method providing advantages especially for an early diagnosis of endometrial pathologies. In our study, significant SI differences were observed between women with endometrial carcinoma, endometrial hyperplasia and controls. These findings indicate that TSE can provide important contribution to the exact diagnosis of endometrial abnormalities. Our results also indicate valuable thresholds SI values for the diagnosis and depiction of such conditions.

Disclosure of interest

The authors declare that they have no competing interest.

References

Elastography in endometrial carcinoma and endometrial hyperplasia


