Could trans-vaginal sono-elastography help benign-malignant differentiation of cervical masses

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Aims and objectives

Worldwide, cervical cancer is the second most common malignancy in women with almost half a million new cases each year \cite{1,2}. In western countries, the majority of cervical cancer is diagnosed at an early stage of the disease. The International Federation of Gynecology and Obstetrics (FIGO) staging system is the most commonly used clinical staging and remains the standard for staging and treatment decision in patients with cervical cancer \cite{3}. It takes into account the results of the physical examination, colposcopy, histopathology results of biopsy, chest radiography and endoscopy (cystoscopy or sigmoidoscopy). Evidence suggests that surgical and modern imaging stagings are better than clinical staging for identifying the true extent of the disease. However, none of these methods have been incorporated into the FIGO staging system yet. The main reason is that the disease disproportionately affects developing countries, essentially due to the absence of cervical cancer screening, where staging methods are not universally available, standardized, or comparable to those present in developed countries. Moreover, there is also still a lack of consensus about the best imaging modality and the clinical value of surgical staging \cite{4}.

Current imaging assessments of uterine cervical cancer include computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound. Compared with CT, which has a low contrast resolution of soft-tissue, MRI was the ideal modality for visualization of the cervix. However, we cannot usually perform MRI immediately in regard to convenience and the limitations of contraceptive devices. On the other side, ultrasound is gaining clinical interest because it is less time consuming, cheaper and has similar diagnostic accuracy as MRI \cite{5}. Equipped with a high resolution probe, transvaginal ultrasonography (TVUS) may provide a clearer image of the uterine cervix and parametrial tissue \cite{6}.

It is well-known that the malignant tissues are generally harder than adjacent normal tissues, this could distinguish benign from malignant tissues based on their elasticity \cite{7,8,9,10,11}. Qualitative real-time ultrasound elastography is an emerging technique, now readily available on conventional ultrasound systems with modified software. In ultrasound elastography, non-invasive imaging and estimation of tissue elasticity is achieved by measuring local tissue displacements from returning ultrasonic signals before and after application of a compressive force. Under compression, stiff tissues show less deformation or strain than soft tissues. Reflecting the property that malignant tissues have higher stiffness than their benign counterparts, ultrasound elastography has been shown to differentiate malignant from benign lesions in the breast, prostate, pancreas, lymph nodes, liver, and gastrointestinal tract \cite{7,10,12-18}. In addition, there is accumulating evidence that ultrasound elastography has a high accuracy for predicting
malignancy in thyroid nodules [11, 19 - 27]. However, slight effort was done on the detection of cervical cancer until now

**Aim of study:**

The aim of this study was to evaluate the role of TV sono-elastography in differentiation between normal and abnormal (diseased) cervix and if the strain ration (SR) can be used for characterization of cervical carcinoma in postmenopausal women.
Methods and materials

**Patients**

During the period from January 2012 to October 2013, seventy consecutive postmenopausal women were enrolled, their age ranged from 55-70 years with a mean age of 62.5 years. The 70 patients were divided into 2 groups: first, the control group that included 30 healthy women, second the diseased group that included 40 patients. Inclusion criterion for the diseased group was the presence of lesions in the uterine cervix. Patients with history of radiotherapy and cervical cancers with vaginal involvement were excluded to avoid infection and serious vaginal bleeding. All participated patients signed the informed consents required by the human study committee.

**Methods**

Clinical staging and treatments plan of cervical cancers were defined according to the staging system revised by the International Federation of Gynecology and Obstetrics (FIGO) \(^{(28, 29)}\) in 2009. All the enrollments accepted TV-sono-elastography scanning one week before the conization treatment or surgery.

**Acquisition of the elastograms**

Real-time TV sono-elastography was performed by using aplio XG system (Toshiba Medical System, Tokyo, Japan) equipped with a 7.0-MHz intravaginal probe. All the examinations were performed in succession by 2 independent radiologists (M. S. and M. A.). The first radiologist had more than 25 years and the second had 15 years experiences in ultrasonic scanning. They were blinded to the colposcopy findings and physical examination results when performing.

Patients were asked to lie in a lithotomy position with empty bladder. A disposable condom was used to prevent cross infection. The TV ultrasound probe was put into the vagina about 1 cm away from the cervix. Position, shape, size, echo of the cervical lesions were recorded. Color Doppler was used to assess the blood supply of the lesions. The highest sensitivity for detection of color Doppler signals was used, allowing detection of blood flow velocities \# 2 cm/s. After that, the system was switched into elastography mode to evaluate the stiffness of the cervix and the lesions. Support of the anterior pelvic wall was done by the left hand and manual compression on the cervix by the right hand. The parameters were set as follows: density 2; frame rate M; dynamic range 4; Persistence 6; smoothing 2; noise rejection 2; frame rejection 4. The deformity was represented by color transparently overlaid on the conventional B-mode images. The colors range from blue to red in order to show the relative hardness or softness. Tissue with average strain in the region of interest (ROI) was colored in green. Hard tissue areas were shown in dark blue, moderately hard tissue in light blue, moderately soft tissue
areas in yellow, and soft tissue areas in red. On average, 3 (range 2-5) clips and 4 (range 3-6) static images were obtained per lesion for further evaluation. The standard reference ROI was the anterior peri-cervical fat in anterior cervical lesions and the posterior peri-cervical fat in posterior cervical lesions.

**Evaluation of the elastograms**

Strain ratio was employed to evaluate the hardness of the cervical tissue half-quantitatively. All the lesions were assessed at least 3 times by 2 independent observers, based on different static images and the average value was recorded as their final results. Both of the observers were blind to the physical and pathological results.

Area colored in steady dark blue was considered to be involved. Infiltration depths of cervical cancers were measured on the sagittal view. The maximum value of the cranio-caudal measurements was considered for the comparison with the histological measurements.

**Statistical analysis**

Statistical analysis was carried out via Statistical package for social Science (SPSS) version 17 program on windows XP. Qualitative data were represented in the form of number and frequency, while quantitative data were represented in the form of mean ± standard deviation (mean ± SD). Kolmogrov-smirnov test was used to test normality of quantitative data. Student's t test, Mann-Whitney U and Kruskal-Wallis Test were used to compare groups. Receiver operating characteristic (ROC) curve was computed to determine the cutoff value for the malignancy. All tests were considered significant if P value equals or less than 0.05.
Fig. 1: The colors range from blue to red in order to show the relative hardness or softness

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Results

The 70 patients enrolled in the study were classified into control group (n=30) and patients group (n=40). The 40 patients had 27 primary cancer cervix, 5 recurrent cancer cervix, and 8 fibroids.

Mean surface area of all lesions in the patients group was 8.35 ± 4.07 cm². Mean surface area of the primary cancer cervix, recurrent cancer cervix and fibroid lesions were 7.68 ± 3.15 cm², 5.80 ± 2.77 and 12.18 ± 5.27 cm² respectively.

Mean SR of the control group was 2.46 ± 0.46. Mean SR of the diseased group was 10.41 ± 2.59. Mean SRs of the cancer cervix, recurrent cancer cervix and fibroid lesions were 11.51, 10.60 and 6.65 respectively.

Comparison of all SRs revealed that mean SR of the diseased group was significantly higher than the control group (P < 0.0001). Also, mean SR of the malignant lesions (primary and recurrent cancer cervix) was significantly higher than the benign lesions (fibroid) (P < 0.0001).

Twenty four lesions of the 27 primary cancer cervix lesions had high vascularity at power Doppler imaging, 4 lesions of the 5 recurrent cancer cervix lesions had high vascularity and none of the 8 fibroids showed central vascularity with only peripheral vascularity at power Doppler imaging.

Using the SR of 3.4 as a cut off value resulted in 100 % sensitivity, 100% specificity and 100% accuracy for differentiation between control and diseased group.

Using the SR of 8.7 as a cut off value resulted in 93.8% sensitivity, 100% specificity and 95% accuracy in differentiation between malignant and benign lesions.

Table (1) Mean SR cutoff value for the differentiation between normal(control and diseased cervix

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>AUC ±SE</th>
<th>95%CI</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Accuracy (95%CI)</th>
<th>PPV (95%CI)</th>
<th>NPV (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR &gt;3.4</td>
<td>1.00±0.00</td>
<td>0.949-1.00</td>
<td>100% (91.2-100%)</td>
<td>100 (88.4-100)</td>
<td>100 (92.4-100)</td>
<td>100</td>
<td>91.2-100% (88.4-100)</td>
</tr>
</tbody>
</table>
Table (2) Mean SR cutoff value for differentiation between malignant and benign cervical lesions

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>AUC  ±SE</th>
<th>95%CI</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Accuracy (95%CI)</th>
<th>PPV (95%CI)</th>
<th>NPV (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR &gt;8.7</td>
<td>0.98±0.017</td>
<td>0.877-1.00</td>
<td>93.8% (79.2-99.2%)</td>
<td>100 (63.1-100)</td>
<td>95 (81.6-95)</td>
<td>100 (91.1-100%)</td>
<td>80 (53.3-80)</td>
</tr>
</tbody>
</table>
**Fig. 2:** Ultrasound images of a female patient, aged 55 years with normal cervix (control group). B-mode ultrasound image (A), color Doppler image (B) & TV elastogram (C) show healthy cervix with normal vascularity and SR = 1.51.

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Fig. 3: Ultrasound images of a female patient, aged 52 years with multiple uterine and cervical fibroids. B-mode ultrasound image (A) & TV elastogram (B) show multiple well defined hypoechoic fibroid masses in the cervix with its SR = 6.74.

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Fig. 4: Ultrasound images of a female patient, aged 67 years with malignant cervical mass (confirmed to be invasive cervical squamous carcinoma by pathological examination). B-mode ultrasound image (A), color Doppler image (B) & TV elastogram (C) show ill defined mass with increased vascularity and its SR = 13.8.

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Fig. 5: Ultrasound images of a female patient, aged 63 years with malignant cervical mass (confirmed to be cervical squamous carcinoma by pathological examination). B-mode ultrasound image (A), color Doppler image (B) & TV elastogram (C) show ill defined hypoechoic mass with increase vascularity and its SR = 16.38.

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**Fig. 6:** Ultrasound images of a female patient, aged 69 years with recurrent malignant cervical mass (confirmed to be cervical squamous carcinoma by pathological examination). B-mode ultrasound image (A), color Doppler image (B) & TV elastogram (C) show irregular mass of mixed echogenicity with increase vascularity and its SR = 16.28.

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Conclusion

Real-time sono-elastography is a new method to describe the mechanical properties of tissue. Similar to color flow Doppler ultrasonography, a region of interest is defined. The relative stiffness of the tissues within this area is described by colors superimposing on the B-mode image. Real-time elastography can be performed with linear scanners for trans-cutaneous use, rigid endo-cavitary probes and with flexible echo-endoscopes. The probes can be used to compress the tissue. The elasticity modulus is calculated from the resulting deformation of the tissue \[^{30}\].

Several studies have demonstrated that real-time elastography is feasible and improves the diagnostic accuracy for tumors of the breast, the prostate and the thyroid gland. Endosonographic elastography has been employed in the examination of lymph nodes and the pancreas \[^{30}\]. However, to the best of our knowledge, only few articles have assessed the feasibility of its application in evaluating the cervical lesions \[^{6, 10 & 31}\].

Thomas et al \[^{10}\], investigated tissue elasticity of normal and abnormal cervix and concluded that computer-assisted and subjective evaluation of cervical elastography allows differentiation of malignancy from normal findings and cervical tissue is of medium hardness and does not change with age. In the current study. Strain ratio was useful in differentiation between normal cervix (control group) and pathological cervix (diseased group) and using the cut off value of 3.4 resulted in sensitivity, specificity and accuracy of 100 % for differentiation between normal and pathological cervix.

Using the strain ratio of 8.7 as a cut off value resulted in 93.8 % sensitivity , 100% specificity, 95% accuracy, 100% PPV and 80 % NPV for differentiation between malignant (primary and recurrent cancer cervix) and benign (fibroid) lesions. While in the study of Sun et al \[^{6}\], When SR of 4.53 was used as a cut-off point, sensitivity and specificity of elastography were 78.8% and 89.7% in differentiating cervical carcinomas from benign cervical lesions. They confirmed that elastography should be used combined with conventional ultrasound to provide extra information and aid to confirming the diagnoses.

There was no significant difference between strain ratio of primary cervical carcinoma and recurrent cervical carcinoma.

Limitation:
In the present study, Strain ratio was obtained by dividing the mean strain within the lesion by the mean strain from the parametrical tissue, if the lesion was in the anterior cervical wall, the anterior pericervical fat was chosen as the reference tissue and if the lesion was in the posterior cervical wall, the posterior pericervical fat was taken as the reference. Hence, sufficient parametrical tissue was essential. So, When the lesions infiltrated both sides of the pelvic wall, reference tissues are difficult to choose, the value of strain ratio would be questionable. However, we think that un-infiltrated uterus could be used as a reference and we tried that on small number of cases, promising results were obtained and further investigation in that point is needed.

Fibroid was selected as a representation of benign cervical lesions, however, other benign lesions like erosions, polyps and inflammation were studied by Sun et al. [6], and showed significant differentiation between these benign lesions and cervical carcinoma. Also, in our study, four cases of cervicitis were studied which gave similar results, but excluded because of its small number.

We concentrated on feasibility of TV sono-elastography in characterization of cervical carcinoma and we didn't compare its results with that of B- mode ultrasound. This point needs further investigation in the future.

Also, this study included small number of cases with big size masses, future studies with large number of cases and small sized masses are recommended.

**Conclusion:**

TV sono-elastography is a useful technique in characterization of cervical pathology and differentiation between normal and abnormal cervix and between malignant and benign cervical lesions.

We advice the use of TV sono-elastography as an additional tool to other used screening modalities. Large scale research is needed to asses its use as an alternative to biopsy if SR > 3.4.
Personal information

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