Clinics in Oncology

Research Article
Published: 10 Dec, 2020

Ultrasound Strain Elastography Features in Patients with Early and Advanced Stages of Cervical Cancer

*Kolbrún Pálsdóttir[1,2], Ole Mogensen[1,2] and Elisabeth Epstein[1,3]**

[1]Department of Women's and Children's Health, Karolinska Institute, Sweden

[2]Division of Pelvic Cancer, Karolinska University Hospital, Sweden

[3]Department of Clinical Science and Education, Karolinska Institute, Sweden

Abstract

Ultrasound Strain Elastography (SE) can be added to conventional ultrasonography as a complement to examine tissue strain. The clinical value of SE in patients with cervical cancer has not been thoroughly studied. The objective of this study was to explore the SE features in patients with cervical cancer, and to assess if SE can improve tumor delineation. SE features were explored prospectively in 30 women with all stages of cervical cancer. Tumor delineation was assessed using SE images and conventional Ultrasound (US) including power Doppler. Other SE features studied were tumor size, elasticity score, and strain ratio. SE improved tumor delineation in 40% (8/20) of early and 70% (7/10) of advanced tumors. Size agreement between SE and histology was excellent. An elasticity score of 4 to 5 was found in 45% (9/20) with early stage and 80% (8/10) with advanced disease (p=0.068). The maximal strain-ratio was significantly lower in early stages compared to advanced stages (1.9 SD ± 0.83 *vs*. SD ± 1.2, p<0.009). The results indicate that SE features differ in early and advanced stage disease, that SE may help in tumor delineation in advanced stage disease, and provide more accurate size measurements as compared to conventional US alone.

Keywords: Strain Elastography; Cervical carcinoma; Strain ratio; Elasticity score; Transvaginal ultrasonography

OPEN ACCESS

Correspondence:
Elisabeth Epstein, Department of Clinical Science and Education, Karolinska Institute and Department of Obstetrics and Gynecology, Södersjukhuset, Sjukhusbacken 10, 118 83 Stockholm, Sweden, E-mail: elisabeth.epstein@sll.se

Received Date: *07 Nov 2020*
Accepted Date: *07 Dec 2020*
Published Date: *10 Dec 2020*

Citation:
Pálsdóttir K, Mogensen O, Epstein E. Ultrasound Strain Elastography Features in Patients with Early and Advanced Stages of Cervical Cancer. Clin Oncol. 2020; 5: 1757.

Introduction

Accurate methods for staging women with cervical cancer are necessary in order to triage them for the right therapy. Staging of cervical cancer has been based on clinical examination with palpation under anesthesia according to the International Federation of Gynecology and Obstetrics (FIGO) criteria from 2009 [1]. However, clinical palpation is inaccurate and underestimates the disease stage in 15% to 40% of all cases [2,3]. Previous studies have confirmed the high accuracy of TVU in staging and identifying early stage tumors [4,5]. Still, tumor delineation can be difficult on grayscale images, especially when the tumor is small or iso-echoic to the surrounding cervical stroma. There is evidence indicating comparable accuracy of TVU with MRI to detect parametrial invasion [5,6]. Ultrasonographic Strain Elastography (SE) is a method of assessing the elasticity of tissues that has been proposed as a complement to conventional Ultrasonography (US) [7]. SE measures the strain, i.e. the difference in length during compression. The relationship between the compression/stress, and the strain can be calculated using Young's modulus, E=stress/strain, which estimates the stiffness of a certain tissue [8]. The image of Two-Dimensional (2D) SE displays tissue stiffness in a continuum of colors ranging from red (soft- high strain) to green (intermediate - equal strain) to blue (hard - no strain). However, there is yet no color standard, and some SE-systems have an inverse color scale [9]. According to newly published revised FIGO staging criteria US or Magnetic Resonance Imaging (MRI) should now be relied upon to more accurately stage cervical cancer and provide guidance to appropriate treatment [10]. Therefore, SE is a method that may objectively improve accuracy of staging and subsequently assist in referring women with cervical cancer for appropriate treatment.

SE has been extensively studied in patients with breast cancer, where it can complement the conventional B-mode US to help differentiate between benign and malignant lesions [11-13]. Moreover, in addition to conventional US, SE appears to increase the accuracy of targeted biopsies in patients with suspected prostate cancer [14,15]. Only a few studies of SE and cervical cancer have been published [16-19]. According to European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines [20], SE has this far no clinical indication in gynecology. Previous

studies have shown that healthy cervical tissue (all ages) was of medium hardness, i.e. having the same stiffness as the surroundings, whereas malignant tumors were harder as compared to normal cervical tissue; SE contributed to the delineation [16-18]. There are to the best of our knowledge no studies comparing cervical tumor measurements with conventional US and SE, using histology as golden standard. The aim of our study was to describe the SE features in a cohort of women with early and advanced stage cervical cancer, and to assess if, SE can be utilized to optimize tumor size measurements and improve tumor delineation.

Materials and Methods

This prospective, single center study included thirty-six patients with a histologically confirmed diagnosis of invasive cervical cancer. The patients were examined and clinically staged according to the 2009 FIGO staging system at the regional reference center for gynecological malignancies [1], Karolinska University Hospital, Stockholm, Sweden, between January 2013 and July 2015. Patients with all clinical stages were eligible. The study was approved by the local Ethics Committee (EPN-2011/1925), and all participating women provided their informed written consent. Six patients were excluded as no remaining tumor was reported in the final histology examination after radical surgery. Baseline demographic data, patient age, and clinical stage was collected prospectively and registered in the study Case Report Form (CRF), together with the sonographic data. The final histological diagnosis was based on radical hysterectomy or trachelectomy, for patients with early stage disease or on biopsy for patients with advanced stage disease. The maximal tumor size was measured on the surgical specimen after a formalin fixation by reference pathologist; the findings referred to were achieved from real life data and were not intentionally measured by one pathologist for study purpose.

All patients were initially examined by an expert sonographer (EE) with 21 years experience. The conventional ultrasound examination was performed using a GE Voluson E8 US system (GE Medical Systems, Zipf, Austria) with a 5 MHz to 9 MHz transducer (RIC5-9D). The SE was then performed with a Philips IU22 US system (Philips Healthcare, Best, The Netherlands) with a 3 MHz to 10 MHz transducer (C10-3v). Standardized settings were applied for the SE examination. The US examination was performed according to Fischerova previously described transvaginal or transrectal method [21], with the woman lying in a lithotomy position, having emptied her bladder prior to the examination. Still images with measurements, videos of the conventional grayscale, power Doppler ultrasound examination, and SE videos were recorded and retained for all patients. The results of the conventional grayscale Transvaginal Ultrasound (TVU) were assessed at the time of examination, whereas the SE videos were analyzed after the completion of the study. Grayscale and power Doppler were first used to scrutinize the tumor location and extent. The size of the tumor was measured by TVU and tumor extension subjectively assessed. The tumor was measured in three dimensions in millimeters. In sagittal projection two measurements were done: Cervical fundal diameter and anterior-posterior diameter. In the transverse plane, the lateral diameter was measured. These measurements were used to study the agreement between conventional US alone and histology.

SE assessment and evaluation

When performing the SE, the transvaginal probe was gently introduced into the vagina and inserted until the cervix appeared. The cervical region was then magnified. The probe was positioned with the lesion of interest in the center in a sagittal projection. Placing light compression on the cervix, SE images and videos 15 sec to 30 sec long were saved and later exported. No adverse events were reported by the patients during or after the examination. The strain elastography videos were retrospectively analyzed off-line using Philips software package QLAB®, (release 10, Philips Ultrasound, Bothell, WA, USA) by an examiner (KP) that had not been involved in the real time examination.

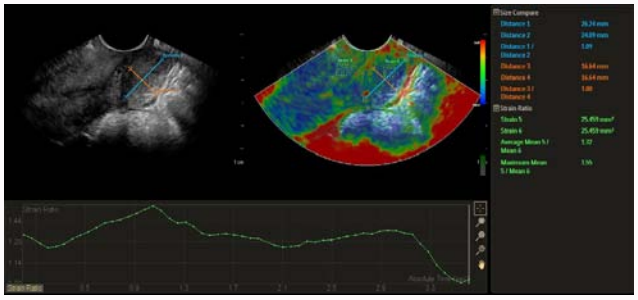

Figure 1: A patient with stage IB1 tumor. The tumor size is measured by combining grayscale and SE images on a dual split screen. To calculate the strain ratio, 5 mm × 5 mm Region of Interest (ROI) boxes were placed in the tumor and in the adjacent healthy cervical stroma.

The videos for each case were reviewed, where the grayscale and SE images appeared side by side on a split screen. While playing the video, the examiner subjectively determined if the SE examination improved the certainty in the assessment of tumor delineation as (yes/no), compared to using the grayscale recordings only. From the videos, a representative still image was captured where the SE image appeared stable. These captured still images were used to measure the maximal cervical-fundal diameter and anterior-posterior diameter in millimeters after the tumor was identified. As the measurements were set in the SE image, it simultaneously appeared on the grayscale image, making it possible to adjust and optimize the size measurement using both modalities together (Figure 1).

Further evaluation was done of the SE images by calculating both the average and maximal strain ratio between the tumor lesion and the normal surrounding tissue. Three patients with early stage disease were excluded from this analysis due to missing raw data. Two pre-fixed 5 mm × 5 mm squares were used, to mark the ROI's (region of interest) and they were placed at an area in the tumor and in the adjacent normal cervical stroma, unless the cervix was completely infiltrated then the reference box was placed in the lower uterine segment. Both ROI´s were located at the same distance from the probe, as close to the probe as possible (Figure 1). Calculation of the strain ratio was performed on the videos automatically by QLAB, after placement of ROI's. By dividing the strain value of the ROI in the healthy stroma by that of the tumor [22], the software calculates a mean strain ratio that represents the strain during the whole video, and a maximal strain ratio that only represents the time where the highest strain ratio is found between the two ROI's.

The next step was to classify the tumors by an elastography scoring system. An accepted method that has been proposed for breast lesions by Itoh et al. was applied, based on the colors of images in the SE videos. Itoh's recommendation were followed by capturing still images from the videos at the early phase of compression, as this gives the best contrast between the lesion of interest and the

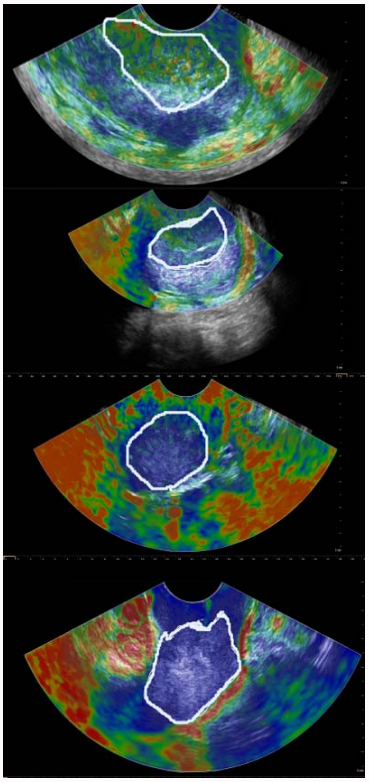

Figure 2: Tumors with elasticity scores from 2 to 5 (lowest scores above, highest scores below).

surrounding tissue. On these images the tumors were assigned an elasticity score according to the following system: Elasticity score 1 indicates an even green color in the lesion of interest that does not differ from the surrounding tissue; score 2 shows a mosaic of green and blue in the focal lesion; score 3 characterizes a lesion with a central blue area surrounded by a green periphery; score 4 identifies a totally blue lesion; and score 5 is assigned when the lesion of interest and the surrounding tissue are blue [11]. See Figure 2 for examples of tumors with different elasticity scores.

Statistical analysis was performed with statistical program SPSS (version 25, IBM Corporation, Armonk, NY, USA). As data were non-normally distributed [23], Mann-Whitney test was applied for continuous variables. The chi square test was used to compare elasticity score. Following Bland-Altman measurement comparison, 95% limits of agreement were used to compare the measurements from different modalities. Linear regression was done to look for proportional bias by measuring a beta coefficient. The Bland-Altman plots are made in Graph Pad Prism (version 6.0 for Windows, Graph Pad Software, La Jolla, CA, USA). A value of $p<0.05$ was considered statistically significant.

Results

The median age of the patients was 46 years (range 26 to 71), 20/30 (67%) were early stage (IA2, n=1, IB1, n=19), and 10/30 (33%) advanced stages (IIA n=3, IIB n=5, III n=1, IV n=1), 21/30 (70%) had squamous cell carcinoma whereas adenocarcinoma was diagnosed in 9/30 (30%). Patients with FIGO stage ≤ IB1 (n=17; 66.7%) had robotically-assisted radical hysterectomy or radical trachelectomy and pelvic lymph node dissection. All patients with advanced disease stage ≥ IB2 (n=10) and two with stage IB1 received primary radio-

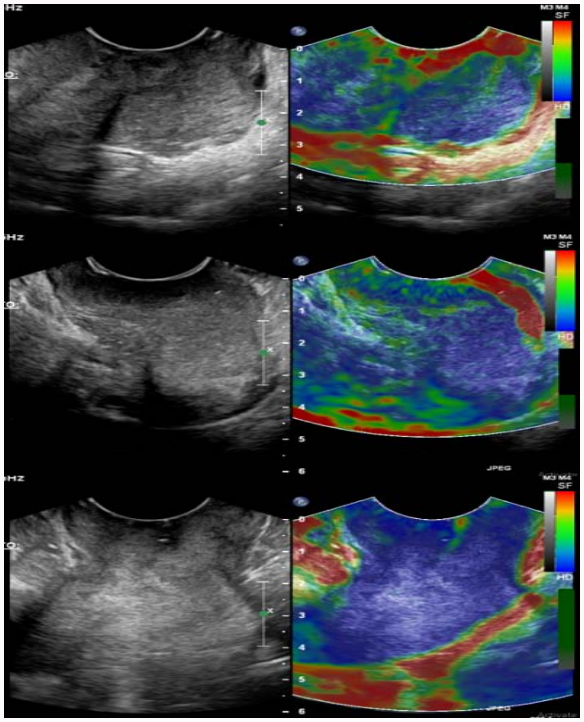

Figure 3: Examples of three instances where SE increased certainty for delineating tumor borders, all were locally advanced tumors ≥ stage IB1.

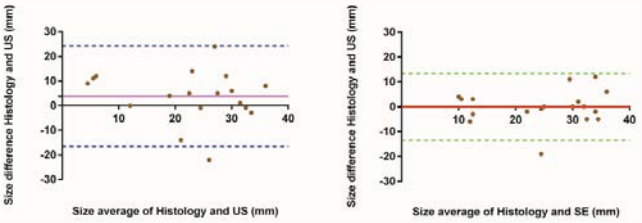

Figure 4: Bland-Altman plot showing 95% limits of agreement in millimeters between histology and conventional Ultrasonography (US), Strain Elastography (SE).

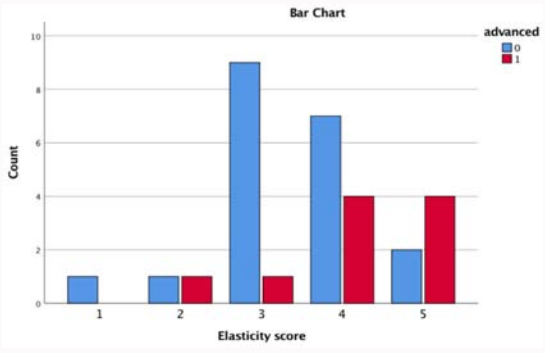

Figure 5: Strain ratio in early (blue) n=20 and advanced (n=10) stage disease (red).

chemotherapy. One patient refused any further treatment other than cone biopsy.

Adding SE to the grayscale images was helpful in demarcating tumor borders in 50% of all cases (15/30). SE was helpful 40% (8/20) of cases with early stage disease (mainly where the tumors were isoechoic to the surrounding tissue), and in 70% (7/10) of the advanced stage

Table 1: Strain ratio and elasticity score in early and advanced cervical cancer.

Strain ratio	Early stage (n=20*)	Advanced stages (n=10)	p-value
Strain ratio, mean	1.34 (± 0.57)	1.86 (± 0.74)	0.075**
Strain ratio, maximum	1.87(± 0.83)	3.06 (± 1.18)	0.009**
Elasticity score			
Score low (1-3)	11	2	0.068***
Score high (4-5)	9	8	

* When calculating strain ratio, three patients with early stages were excluded due to missing raw files; ** Mann-Whitney test; *** Chi-square test

cases (Figure 3). Comparing tumor size measurements by SE with size measured by histology using 95% limits of agreement (Figure 4), there was a mean size difference of - 0.11 mm (95% CI: – 13.37 to 13.59), with no significant bias (p=0.657). Maximal size on conventional grayscale compared with histology had a mean size difference of 3.9 mm with 95% limits of agreement between – 16.5 and 24.3, and not significant bias (p=0.488) (Figure 4). Table 1 show the strain ratio and elasticity score (Figure 5) of early and advanced stage cervical cancer. An elasticity score of 4 to 5 was found in 45% (9/20) with early stage and 80% (8/10) with advanced disease (p=0.068), Figure 5, Table 1. The maximal strain-ratio was significantly lower (p<0.009) lower in early stages (1.9; SD ± 0.8), compared to advanced stages (3.1; SD ± 1.2) (Table 1).

Discussion

In this pilot study we found that SE features differ in early and advanced stage disease, that SE may help in tumor delineation in advanced stage disease, and provide more accurate size measurements as compared to conventional US alone.

Our findings are supported by Ma and colleagues who found an almost equal accuracy of MRI (79%) as with TVU combined with SE (77%) for diagnosing parametrial involvement, in a series of 52 women with all stages of cervical cancer [19]. In the present study, excellent agreement of tumor size measurements comparing SE to histology, with only a slight tendency for over sizing smaller tumors with SE and underestimating size of larger ones. Conventional US generally slightly underestimated the size of the tumors, regardless of stage. There seems to be a small advantage in complementing conventional US with SE for size estimation which can be of great importance in the preoperative staging especially for women who wish for fertility sparing surgery.

One of the strengths of this study is having one examiner do all the ultrasound examinations. This optimizes the standardization of the examination, which is especially important, as it is known that the amount of pressure applied affects the results of the SE. To our knowledge, this relationship has not been studied before in cervical tissue. However, Barr and Zhang examined 10 patients with breast cancer and found that the stiffness of the surrounding benign tissue increased with increasing external pressure, while the stiffness of the harder cancer lesions was unaffected of the pressure applied [24]. For validation of the examination settings and to study reproducibility, it would have been optimal if the same examiner had repeated the examination at the same or at a different occasion on the same patient. This is however not feasible in clinical settings.

Further strengths of this study are the cohort of patients included all stages of cervical. To diminish the risk of bias comparing conventional imaging alone or supplemented by SE, conventional tumor size measurements were done prospectively during the primary examination, while the combined assessment were performed by another examiner (KP) months after, thus showing the true additional value of the SE. Thus, the analyses done retrospectively, but without knowledge of tumor size estimation by other modalities. The greatest limitations to the study were a) small number of patients examined and b) the lack of standardization when comparing measurements taken from US modalities with histological results.

A scoring system was applied based on elasticity colors that has been validated for breast cancer lesions [11] and studied in cervical cancer by Lu et al. Elasticity scores 3 to 5 in 90% of the patients is comparable to the results where malignant lesions had a score of 3 to 5 in 91% (40/44) of their cases. In their prospective series of 84 patients (40 benign, 44 malignant) the SE was used to clinically distinguish malignant lesions from benign lesions and the authors proposed that the method could be useful even where histological diagnosis is not provided. In our setting, this would not be a relevant indication, as all patients with suspicious cervical lesions undergo various biopsy procedures to obtain an exact diagnosis before being subject to any further treatment. In addition, applying elasticity scores on cervical cancer lesions seems to be more complicated as compared to breast cancer lesions. Normal breast tissue is mostly fat and glandular tissue which is soft and easily deformed by external pressure. Healthy cervical tissue is fibrotic and less elastic, which may be a physiological limitation as the difference in elasticity between normal and malignant tissue is small. This is a likely explanation why some patients with early stage disease were classified with an elasticity score of 1 to 3 even if a tumor was present. In summary, the clinical relevance for elasticity score seems uncertain.

A much lower average (1.5) and maximum (2.3) strain ratio was found in this study compared to the findings of the two previous, where SE was used to differentiate between benign and malignant disease [16,17]. Both found that a cut-off for strain ratio of 4.5 could be used to separate benign and malignant tumors with a specificity of approximately 80% and a sensitivity of 90%. The main difference between the study of Sun et al. and the actual study is that they used the softer parametrium as a reference, which, by definition, should give a higher strain ratio value. The parametrium was not chosen as a reference here, as the images were in sagittal projection where the parametrium is not represented. Another important difference is the choice of software and ultrasound equipment was not the same in the studies so differences in calculated values are expected. Additional differences between this study and the two earlier ones are a dissimilar study population [16,17], including a mix of women with benign cervical tumors, premalignant conditions as well as different stages of cervical cancer.

Acknowledgement

We thank Margareta Häggström at the former Department of Obstetrics, Karolinska University Hospital, Solna, Stockholm, for her assistance.

This paper was supported by ALF - Grants no. 561101, 562101, 563101 Stockholm County Council and Radiumhemmets Research Funds (Grant no. 154112).

References

1. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. Int J Gynaecol Obstet. 2009;105(2):107-8.

2. Lagasse LD, Creasman WT, Shingleton HM, Ford JH, Blessing JA. Results

and complications of operative staging in cervical cancer: experience of the Gynecologic Oncology Group. Gynecol Oncol. 1980;9(1):90-8.

3. Qin Y, Peng Z, Lou J, Liu H, Deng F, Zheng Y. Discrepancies between clinical staging and pathological findings of operable cervical carcinoma with stage IB-IIB: A retrospective analysis of 818 patients. Aust N Z J Obstet Gynaecol. 2009;49(5):542-44.
4. Fischerova D, Cibula D, Stenhova H, Vondrichova H, Calda P, Zikan M, et al. Transrectal ultrasound and magnetic resonance imaging in staging of early cervical cancer. Int J Gynecol Cancer. 2008;18(4):766-72.
5. Epstein E, Testa A, Gaurilcikas A, Di Legge A, Ameye L, Atstupenaite V, et al. Early-stage cervical cancer: tumor delineation by magnetic resonance imaging and ultrasound - a European multicenter trial. Gynecol Oncol. 2013;128(3):449-53.
6. Moloney F, Ryan D, Twomey M, Hewitt M, Barry J. Comparison of MRI and high-resolution transvaginal sonography for the local staging of cervical cancer. J Clin Ultrasound. 2016;44(2):78-84.
7. Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: A quantitative method for imaging the elasticity of biological tissues. Ultrason Imaging. 1991;13(2):111-34.
8. Hoskins PR. Principles of ultrasound elastography. Ultrasound. 2012;20(1):8-15.
9. Carlsen JF, Ewertsen C, Saftoiu A, Lonn L, Nielsen MB. Accuracy of visual scoring and semi-quantification of ultrasound strain elastography--a phantom study. PLoS One. 2014;9(2):e88699.
10. Matsuo K, Machida H, Mandelbaum RS, Konishi I, Mikami M. Validation of the 2018 FIGO cervical cancer staging system. Gynecol Oncol. 2019;152(1):87-93.
11. Itoh A, Ueno E, Tohno E, Kamma H, Takahashi H, Shiina T, et al. Breast disease: Clinical application of US elastography for diagnosis. Radiology. 2006;239(2):341-50.
12. Schaefer FK, Heer I, Schaefer PJ, Mundhenke C, Osterholz S, Order BM, et al. Breast ultrasound elastography--results of 193 breast lesions in a prospective study with histopathologic correlation. Eur J Radiol. 2011;77(3):450-6.
13. Zhi H, Xiao XY, Ou B, Zhong WJ, Zhao ZZ, Zhao XB, et al. Could ultrasonic elastography help the diagnosis of small (</=2 cm) breast cancer with the usage of sonographic BI-RADS classification? Eur J Radiol. 2012;81(11):3216-21.
14. Brock M, von Bodman C, Palisaar RJ, Loppenberg B, Sommerer F, Deix T, et al. The impact of real-time elastography guiding a systematic prostate biopsy to improve cancer detection rate: A prospective study of 353 patients. J Urol. 2012;187(6):2039-43.
15. Kapoor A, Kapoor A, Mahajan G, Sidhu BS. Real-time elastography in the detection of prostate cancer in patients with raised PSA level. Ultrasound Med Biol. 2011;37(9):1374-81.
16. Sun LT, Ning CP, Liu YJ, Wang ZZ, Wang LD, Kong XC, et al. Is transvaginal elastography useful in pre-operative diagnosis of cervical cancer? Eur J Radiol. 2012;81(8):e888-92.
17. Lu R, Xiao Y, Liu M, Shi D. Ultrasound elastography in the differential diagnosis of benign and malignant cervical lesions. J Ultrasound Med. 2014;33(4):667-71.
18. Thomas A, Kummel S, Gemeinhardt O, Fischer T. Real-time sonoelastography of the cervix: tissue elasticity of the normal and abnormal cervix. Acad Radiol. 2007;14(2):193-200.
19. Ma X, Li Q, Wang JL, Shao J, Zhu YC, Ding W, et al. Comparison of elastography based on transvaginal ultrasound and MRI in assessing parametrial invasion of cervical cancer. Clin Hemorheol Microcirc. 2017;66(1):27-35.
20. Sidhu PS, Cantisani V, Dietrich CF, Gilja OH, Saftoiu A, Bartels E, et al. The EFSUMB guidelines and recommendations for the clinical practice of Contrast-Enhanced Ultrasound (CEUS) in non-hepatic applications: Update 2017 (long version). Ultraschall Med. 2018;39(2):e2-e44.
21. Fischerova D. Ultrasound scanning of the pelvis and abdomen for staging of gynecological tumors: A review. Ultrasound Obstet Gynecol. 2011;38(3):246-66.
22. Ophir J, Alam SK, Garra B, Kallel F, Konofagou E, Krouskop T, et al. Elastography: Ultrasonic estimation and imaging of the elastic properties of tissues. Proc Inst Mech Eng H. 1999;213(3):203-33.
23. Research on the menopause. Geneva; 1981. Report No.: Series 670.
24. Barr RG, Zhang Z. Effects of precompression on elasticity imaging of the breast: Development of a clinically useful semiquantitative method of precompression assessment. J Ultrasound Med. 2012;31(6):895-902.