Cervical Elastography

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1. Introduction

An important characteristic of tissue is its plasticity or elasticity which can be changed by pathophysiological processes. In particular, ageing processes, the appearance of acute and chronic inflammation, or malignant processes have a lasting effect on the elastic nature of tissue. Over the last 20 years sonographic and magnetic resonance tomographic procedures aiming to display these changes have been, and are still being, developed.

The first idea for using Elastography for breast cancer, was based on the knowledge that palpation is used to estimate the hardness of the tissue, where a malignant finding is characterised by a particular "hardness". It is now possible to display the elasticity in real-time, and this method in used in clinical practice[1)-5)]. Changes in tissue elasticity in different organs are currently being intensively investigated. Work on the evaluation of elastography to estimate age and pathophysiological changes to the uterine cervix have not been published to date; the publications below present the first data with this new approach.

1.1 Real-time cervical Elastography

The elasticity image within a defined region of interest (ROI) around the cervix is superimposed as an overlay of the B-mode image. Hard tissue has been defined as blue, and deformable, soft tissue as a red coloration. In a first approach, both age-related factors of cervical elasticity in a normal group of patients and malignant changes to the cervix were investigated. A second study to characterise the cervix of pregnant women is also discussed below.

2. Description of the physiological and pathological cervical findings

2.1 Physiological and pathological cervical findings

The evaluation of the rigid cervix in case of tumour can be assessed using an endocavity probe. Physiologically the cervix is made up of collagens with a small amount of muscular fibres. Collagen fibres are stabilised, for example, during pregnancy by decortine (PGS2) and dissolved by biglycan (PGS1) in the last trimester. Thus, as well as the age of the woman, physiological processes also lead to changes in elastic characteristics. A standard procedure for the diagnosis and early recognition of cervical cancer, apart from the cytological smear test, is the bimanual examination. Transvaginal ultrasound is used as an additional technique for diagnosing cervical cancer. We investigated whether real-time Elastography is able to display the physiological elastic changes of the cervix relating to the patient's age, or changes with cervical cancer or suspicious cytology findings, in comparison to a normal group.

In this first original work we investigated whether cervical elasticity is subject to typical pre- and post-menopausal age-related changes and whether normal appearances can be determined. In addition, selected pathologies were examined with real-time Elastography.

2.2 Study design

115 inpatients underwent a sonographic examination of the cervix using B-mode sonography and Elastography. Ninety women had normal gynaecological findings (normal group). Twenty five women had a focal pathological cervical finding (22%). The histological diagnoses of the pathologies can be seen in Table 1.

Table 1 : Diagnosis of the 24 patients with cervical pathology (*the anatomical borders of the cervix could not be identified in one case)

Diagnosis (n=24)*	FIGO-classification	CIN-classification
cervical cancer (n=13)	1 (FIGO 0) 4 (FIGO Ib) 8 (FIGO III)	
cervical intraepithelial neoplasia (CIN) (n=11)		1 (CIN II) 10 (CIN III)

2.3 Ultrasound technology

All patients were examined with a high end ultrasound device (HITACHI EUB-8500, Wiesbaden, Germany) and a 8～4MHz frequency vaginal probe (EUP-V53W, HITACHI). The examination was carried out with an empty bladder and the vaginal probe was inserted without pressure.

2.4 Image examination

Firstly, each cervix (n=115) was imaged in B-mode in a sagittal section. After, a dual image displaying both the B-mode and the corresponding elastogram (n=230) in the sagittal section was stored. All Elastography images were analysed both by computer and subjectively assessed by two independent experts experienced both in clinical practice and diagnosis.

Using the B-mode image, an Elastography ROI was drawn to cover the cervix and the cervical canal. For the computer-aided image analysis, only the image defined by the ROI was considered afterwards. For the segmentation of the 3 basic colours red, green and blue in the preliminary test, threshold values were determined and analysed for each of the 115 individual images. The percentage share of the three individual colours over the total area was calculated using morphometry software "Leica QWin Standard" (Leica Microsystems Imaging Solutions Ltd, PO Box 86, 515 Coldhams Lane, Cambridge, CB1 3XJ, United Kingdom). The aim of the measurement was to establish the percentage colour distribution of the normal and pathological cervix according to the age of the patient.

Apart from the computer controlled percentage colour evaluation, the presence of a pathological finding was subjectively evaluated based on the colour distribution in the ROI. To standardise the subjective image evaluation, a scoring system was defined similar to that used by Matsumura et al. for breast lesions. This subjective allocation was equivalent to an analogue scale. The findings were described both in images and in words (Fig. 1, 2).

For statistical evaluation, the calculated percentage shares of the colours red and green over the entire area were used to establish an elastic tissue quotient (TQ)

$$TQ = \%\ \text{red share} / \%\ \text{green share}$$

The aim of the measurement was to identify slight differences in the elastic properties of the tissues. This quotient was afterwards correlated by means of Analysis of Variance (Anova, $p < 0.05$) with the age of the patients. The colour blue (hard tissue) was considered separately for pre- and post-menopausal normal findings and focal pathologies.

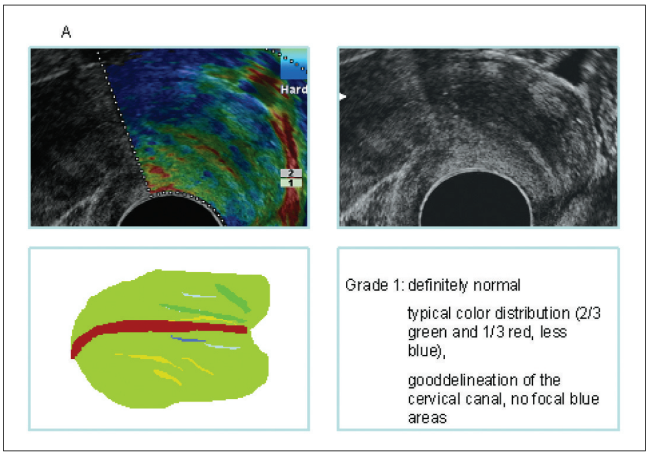

Fig. 1 : The normal cervix in the elastogram and B-mode image

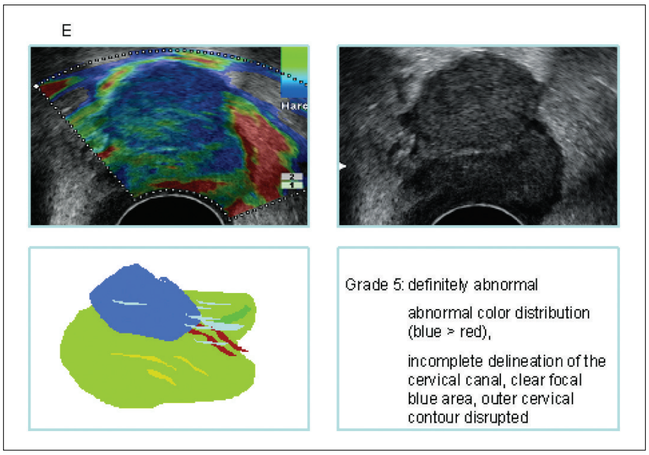

Fig.2 : Cervical carcinoma (FIGO III) in the elastogram and B-mode image

2.5 Image examination results

The colour distribution of the cervix in the normal group determined by the computer analysis showed a dominance of green (67±13%), followed by blue (26±13%) and then red for soft tissue (7±6%) (Fig. 1). In the cervical pathologies group, there was a similar distribution of the colour spectrum over the total area of the ROI. The green part represented 64±15%, the blue part 28±16% and the red part 8±6% (Fig. 2). In total, soft parts (green and red) outweighed the hard blue part in both groups.

If one considers all cervical carcinomas then it is possible to see a significant difference (p=0.025) in the blue part between the normal group (n=89, 26±13%) and the carcinoma patients (n=13, 34±15%), whilst the 11 CIN findings (cervical intraepithelial neoplasia) did not significantly differ (19 ± 12%, $p > 0.05$) from the normal group and had the least blue part of all groups. In the group of post-menopausal women (n=47) in the tumour group there were only invasive carcinomas (n=7), which showed the highest blue part of all groups (40 ± 13%) and could be clearly differentiated (p=0.007) from the post-menopausal normal group (n=40, 25 ± 13%).

In the subjective consideration of the cervical findings, comparable results were also obtained. Here, the experts particularly concentrated on focal hard parts (blue colour coding) and poor visualisation of the anatomical structures such as the cervical canal and the organ contour. The subjective assessment showed a major significance in the comparison between the normal group (1.8 ± 0.7) and the cervical pathologies (3.5 ± 0.9) (p=0.000089). The Pearson correlation coefficient (r^2=0.744) showed a good correlation of the subjective scoring with histological findings and with focal pathologies of the cervix. In particular, there were clearly higher scores for the cervical carcinomas ('probable' to 'definite' pathological findings, score 4-5) in comparison to the CIN findings, which were all evaluated with probably normal (score 2) to indifferent (score 3) and thus were not rated as focal pathologies, as in the computer-aided analysis.

2.6 Age-related cervical elasticity

The distribution of the basic colours relating to the menopausal status of the patients showed no significant results for the normal group. For the pre-menopausal women (n=49) with an average age of 39 years the basic share was 66 ± 13% and for the post-menopausal women (n=40) with an average age of 63 years, it was 68% ± 12%. The blue and red parts were characterised in a similar way to the normal group without age influencing the colour distribution.

There was also no significant difference in the calculated elastic tissue quotient (TQ) in the comparison ($p > 0.05$) between the pre-menopausal (TQ=0.114) and post-menopausal (TQ=0.106) women. Moreover, the correlation with hormone taking, previous pregnancies, or small interventions on the cervix, showed no significant differences in the colour distribution. In total, there was a relatively stable colour distribution independent of the patient age in the normal group.

3. Elastography in pregnancy

3.1 Physiological and pathological cervical findings in pregnancy

Premature birth as a multi-factorial occurrence is the most frequent cause of perinatal morbidity and mortality. Despite intensive care during pregnancy and the detection of those at-risk of premature delivery, in most industrialised nations the incidence of delivery before 37 weeks is increasing. The complex interaction between cervical insufficiency, membrane activation and onset of labour is the probable cause of premature birth. Diagnosis is particularly valuable for early recognition of cervical insufficiency. The standard procedure is transvaginal sonography. Numerous studies have shown that the cervix length decreases and the width increases during pregnancy. It has been proved that the shorter the cervix in the 2nd trimester, the greater the likelihood of premature birth.

We investigated whether an additional diagnostic criterion, such as the elasticity of the cervix, could help in daily practice. Firstly, a pregnant normal group was examined. The data described below has been submitted for publication but has not yet been published.

3.2 Study design

Patients diagnosed as at-risk were examined at consultation with a transvaginal ultrasound scan. If there were positive sonographic findings, Elastography was also carried out. From this non-selective "normal group" of 61 patients, 9 patients were recognised to have cervical insufficiency. Cervical insufficiency is defined here as a cervix length of < 3cm from the 2nd trimester.

3.3 Ultrasound technology

All patients were examined (as in X.2.3) with a high end ultrasound device (HITACHI EUB-8500) and a 8～4MHz vaginal probe (EUP-V53W, HITACHI).

3.4 Ultrasound examination

Firstly, each cervix (n=61) was imaged in sagittal section in B-mode. The cervix length was measured when the cervical canal was seen as a fine line between the os internum and externum and the size of the front and back uterine orifice lips were equal.

Secondly, a dual image displaying both the B-mode and the corresponding elastogram (n=122) in the sagittal section was stored (Fig. 3). We thus obtained 183 representative images for assessment. All the Elastography images were both computer analysed and assessed subjectively as described in X.2.3.1.

In addition, the funneling shape was described subjectively. Here, it was necessary to differentiate between no funnel (0), a T-funnel (1), V-, Y-funnel (2), or a U-funnel (3) (Fig. 4).

For further statistical evaluation, the red and green colours over the entire area were used to establish an elastic tissue quotient (TQ) using the calculated percentage shares:

$$TQ = \%\ \text{red share} / \%\ \text{green share}$$

The aim of the measurement was to identify slight dif-

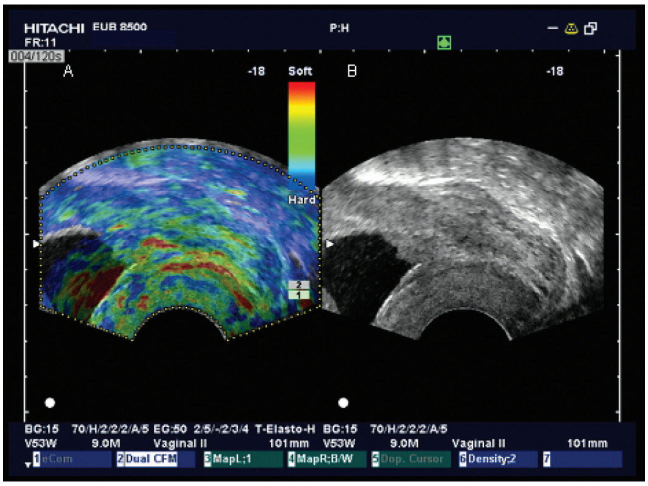

Fig. 3 :
Representative dual image of the cervix of a pregnant woman. Fig. 3 shows the cervix which is of intermediate tissue elasticity (proportion of green) surrounding the soft cervical canal (red-yellow). Fig. 3 shows the B-mode scan.

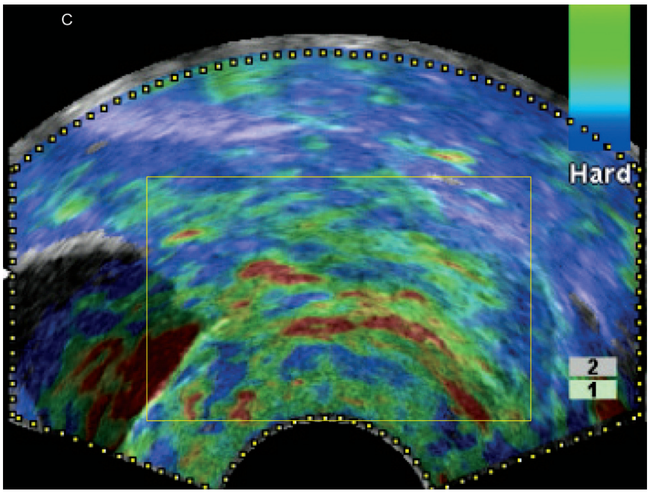

Fig. 4 :
Example of cervical insufficiency with a U-funnel, illustrating the higher elasticity of the funnel and the cervical canal (markedly increased proportion of red).

ferences in the elastic properties of the tissues. This quotient was afterwards correlated by means of Analysis of Variance (Anova, $p < 0.05$) both with the age of the pregnant women and weeks gestation.

3.5 Age-related elasticity differences during pregnancy

The colour distribution of the cervix in the normal group determined by the computer analysis showed a dominance of the green part (67.1 ± 12.5%), followed by the blue part (26.5 ± 12.9%) and the red coloured part (6.4 ± 3.7%). The colours of the soft elasticity area (green and red) were thus the dominant percentage with 73.5% as opposed to the hard parts (blue). With the increasing age of the pregnant women in the normal group there was a significant decrease of the TQ (p=0.026). The tissue elasticity was, in contrast, not dependent on the duration of the pregnancy, i.e. there was no significant change in the TQ (p=0.233) of the cervix in relation to gestation.

There was no significant connection in the ANOVA analysis in relation to the regression between the progression of the pregnancy at the cut off before and after week 26.

3.6 Findings concerning cervical insufficiency

The colour distribution of the cervix in this group determined by the computer analysis showed a dominance of the green part (71.4 ± 9.3%), followed by the blue part (22.6 ± 9.6%) and the red coloured part (6.1 ± 3.7%). The colours of the soft elasticity area (green and red) were in turn the dominant percentage with 77.5% as opposed to the hard parts (blue). As a trend, in comparison to the normal group, there were more elastic parts (77.5% versus 73.5%), there was however no statistically significant difference.

The funnelling shape could be clearly seen by Elastography (Fig. 4). The funnel and the cervical canal were seen in the Elastography in the soft (red) part of colour map. The changes in shape of the funnel correlated well with the reduction of the cervical length (on average 20mm) measured in B-mode. In follow up, it was shown that the patients with funnel level 3 delivered before the 37th week.

In comparison with the subjective consideration of the Elastography images, a good agreement of the results of both experts with the computer analysed data was shown in the univariate correlation. As regards the agreement of both experts determined by a grade test, there was agreement for the colour red and the funnel definition ($p > 0.05$).

4. Discussion of the results of the cervical Elastography

Currently diagnosis of cervical cancer is made by bimanual palpation, cytology and colposcopy, The diagnostic value of transvaginal ultrasound is low, so an improved imaging method is very much sought.

In the first clinical studies presented here[6] age-related changes of the cervix were investigated in a normal group consisting of pre- and post-menopausal healthy women and these findings were compared with structural cervical changes. Due to the ability of malignant tumours to change the elasticity of the tissue, special attention was paid to changes in the hard blue colour both during the computer-aided analysis and the subjective scoring. Invasive carcinomas had, in the computer-aided analysis, a significantly larger blue part, whilst the findings for cervical intraepithelial neoplasia did not differ from normals. The computer program used to standardise the evaluation is very suitable for invasive tumour staging. It should be noted that as regards precancerous cells without major hardness differences, as seen with the CIN findings, no significant differentiation was made by the computer program.

Apart from identifying the elastographic appearances of the normal cervix, we also investigated whether age-related changes in elasticity can be demonstrated. First investigations during pregnancy showed that the elastic tissue quotient (TQ) changes significantly with the age of the pregnant woman. However, these changes could not be confirmed on the normal cervix. In these cases it was not important whether the women were pre- or post-menopausal. The green part in both groups was about 60%. Thus, it seems that there are pregnancy-specific changes to the cervix which can be seen, if present, to induce labour. However, these changes are not sustained and in the subgroup analyses, changes of the elastic quotients were not significant in women with previous pregnancies, women taking hormones or having had small interventions on the cervix.

5. Conclusion

In conclusion, this is the first description of the normal elastographic appearances of the cervix. Independent of age, the medium firm tissue is represented largely by a green colour in the elastogram. Subjective assessment using a newly developed word and image-based scale to grade the cervical images, was a practicable method for the assessment of focal findings. As with the computer-aided evaluation, it also led to significant differentiation between invasive carcinomas and normal findings. With both analysis methods, patients with a CIN could not be identified.

The investigations concerning pregnant women were likewise simple and practical to implement. In the normal pregnancy group, no changes could be seen. First results point to a "softer" cervix in cases of insufficiency. Whether the method offers potential for monitoring pregnancies at-risk remains to be seen.

References

1) Thomas A, et al. An advanced method of ultrasound Real-time Elastography: First experience on 106 patients with breast lesions. Ultrasound Obstet Gynecol 2006; 28(3):335-340.
2) Thomas A, et al. Real-time Sonoelastography Performed in Addition to B-mode Ultrasound and Mammography: Improved Differentiation of Breast Lesions? Acad Radiol 2006; 13(12):1496-1504.
3) Thomas A, et al. Tissue Doppler and Strain Imaging for Evaluating Tissue Elasticity of Breast Lesions. Acad Radiol 2007; 14(5):522-529.
4) Frauscher F, et al. Prostate ultrasound-for urologists only? Cancer Imaging 2005; 23(5):76-82.
5) Bercoff J, et al. In vivo breast tumor detection using transient elastography. Ultrasound Med Biol 2003; 10(29):1387-1396.
6) Thomas A, et al. Real-time Sonoelastography of the Cervix: Tissue Elasticity of the Normal and Abnormal Cervix. Acad Radiol 2007; 14:193-200.