Elastography of the uterine cervix in gynecology: normal appearance, cervical intraepithelial neoplasia and cancer. A systematic review

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Abstract

Aims: To revise the current literature about the usefulness of elastography in cervical cancer (CC) and cervical intraepithelial neoplasia (CIN), from methods and technical limitations, to diagnosis, staging and the ability of predicting the response to oncologic treatment. **Methods:** An electronic database search was performed (PubMed, EMBASE, Web of Science) with the data range from January 2000 until May 2020. All studies, fully-available in English, assessing elastography of the uterine cervix in CC and CIN were selected. Studies were reviewed and discussed according to the elastographic technique and to the purpose of the research. **Results:** Twenty-three articles were found: 11 articles regarding strain elastography, 4 articles assessing shear wave elastography and 8 papers with matter-related information. Elastography was used in the study of normal variants of the uterine cervix as well as: the positive diagnosis of CC and CIN, clinical staging and the prediction of therapeutic response in CC. Comparison of the elastographic techniques was also performed. **Conclusions:** Elastography has multiple applications in the gynecological pathology of the cervix. The methods used to assess the cervix are diverse, and none have become universally accepted. With regard to CC and CIN, elastography is still an ongoing research field.

Keywords: strain elastography; shear wave elastography; uterine cervix; cervical cancer

Introduction

Cervical cancer (CC) is among the leading causes of oncologic morbidity and mortality worldwide, accounting for 6% of all cancers in women [1]. The particular feature of CC is the possibility to detect its precursor, cervical intraepithelial neoplasia (CIN). Early intervention prevents the development of invasive forms of cancer. Given the viral etiology and its sexual transmission, CIN develops mainly in young patients, at a reproductive age, who want to preserve their fertility. Current screening programs are represented by clinical examination and

cervical cytology. To these are added, for diagnostic purpose, colposcopy and biopsy, as well as other expensive techniques such as magnetic resonance imaging (MRI) and, more recently, diffusion-weighted MRI, dynamic contrast enhanced MRI and 18 F-fluorodeoxyglucose positron emission tomography (FDG- PET). Although these techniques have superior diagnostic abilities, they are not used in current practice due to high costs, long examination time, large-scale equipment unavailability, radiation exposure, and possible adverse reactions to contrast agents [2]. CC is the only gynecological cancer with clinical staging, according to FIGO [3]. The stage is the key to the choice of treatment [3,4].

Complementary to conventional ultrasound examinations, in recent years, elastography has been the focus of much medical research, as it is a non-invasive, widely available imaging technique. So far, elastography has been intensively studied in thyroid and breast lesions, in liver and lymph node pathology; there are also numerous data on the use of elastography of the cervix in obstetrics, for the prediction of premature birth [5-9].

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According to the physical principle underlying the technique, there are two main types of elastography: strain elastography (SE) and shear wave elastography (SWE).

Years after the employment of elastography in other conditions, both SE and SWE started to be assessed in exploring the premalignant and malignant pathology of the cervix. This phenomenon, which represents the period that needs to pass from the appearance of a breakthrough to its validation in different fields, was called “the sleeping beauty” [10]. As the usefulness of elastography in the gynecological pathology of the cervix is becoming more fully acknowledged, an increasing number of papers have been published [11]. However, the most recent guidelines and recommendations of EFSUMB for the clinical practice of elastography in non-hepatic applications do not even mention the normal and diseased uterine cervix as a possible application [12].

The aim of this paper is to revise the current knowledge regarding the usefulness of elastography in CC and CIN, from methods and technical limitations, to diagnosis, staging and ability of predicting the response to oncologic treatment. To the best of our knowledge, this is the first article to revise the data on the above-mentioned topics.

Methods

An electronic database search was performed (PubMed, EMBASE, Web of Science) with the data range from January 2000 until May 2020. The search terms “elastography” + “uterine” + “cervix” were used. All the studies assessing elastography of the uterine cervix in CC

and CIN were selected. Inclusion criteria were: articles related to SE and SWE of the normal and abnormal uterine cervix in gynecology, including CIN and CC; articles with full text available in English. Exclusion criteria were: articles assessing the biomechanics of the uterine cervix, only an abstract available in English, papers in other language than English.

The selected papers were reviewed and discussed regarding the classification illustrated in figures 1 and 2.

Results and discussion

Following the database search, 23 papers were found: 11 on SE, 4 on SWE, and 8 papers with matter-related information.

Classification according to the elastographic technique

Strain elastography: external or internal mechanic compression

SE assesses tissue elasticity based on the response of the analyzed area to a dislocation force, which is represented by a mechanic compression. Most papers reported using an external compression to induce tissue dislocation; standardization of the applied force was performed in accordance to the indicators provided by the ultrasound machine [2,13-21]. Nonetheless, the intrinsic compression provided by the adjacent arterial pulsation was in some cases considered sufficient by other authors [15,22].

Strain elastography with color scores

As a result of the mechanical compression, a double-image display is offered by the ultrasound machine: one showing the conventional gray scale image and one depicting a color-coded stiffness map of the same area. Regarding the deformability of the analyzed structure, areas with high deformability express high strain and represent soft structures, whereas areas with low deformability and low strain represent hard or rigid structures. The strain is color coded: usually red is chosen to depict soft tissue and blue represents rigid tissue; the values in between are colored in green. However, most manufacturers provide the operator the choice of color significance. The examiner can further select a targeted region on the elastogram, called region of interest (ROI).

Elasticity scoring systems have been used by several authors in order to classify the images on scales ranging from “normal” to “definitely abnormal”. The different scales that were used are summarized in Table I.

In addition to assessing lesions by color scores, one study used a second method, the “computer assisted generation of color spectrum”, which was based on a mor-

Fig 1. Classification according to the elastographic technique

Fig 2. Classification according to the purpose of the study

phometry software that returned the percentage of each of the three basic colors (red, green, blue) in the ROI [20].

Strain elastography with strain ratio

With SE, there was constant concern about the quantification of the visual color-coded information. While some authors considered color scores subjective, there was rising interest in the semi-quantitative assessment of the cervix, by using strain ratio (SR) [17]. The technique implies the selection on the elastographic image of two ROIs, one representing the area to be analyzed (cervical

tissue, cervical lesion = A) and the second being used as reference (B). The machine's software automatically computes SR as the ratio between the strain of the reference and the strain of the cervix (B/A), thus providing numeric results (fig 3). A value of SR >1 signifies that the reference has a greater capacity to be dislocated, therefore it has a larger strain than the cervical tissue, meaning the cervix has a higher stiffness than the reference by x times, where x is the value of SR. The challenge is the choice of the reference, since it is difficult to choose a

Table I. Elasticity scoring systems used in the assessment of normal and abnormal uterine cervix

Author, year/Reference	Type 1	Type 2	Type 3	Type 4	Type 5
Thomas 2007 [20]	definitely normal: typical color distribution (2/3 green and 1/3 red, less blue)	probably normal: typical color distribution (2/3 green and 1/3 red and blue)	inconclusive: typical color distribution (2/3 green and 1/3 red and blue)	probably abnormal: abnormal color distribution (blue > red)	definitely abnormal: abnormal color distribution (blue > red)
Lu 2014 [17]	green in the entire hypoechoic lesion on the elasticity image and deformity of the entire image on elastography	mosaic pattern of green and blue and deformity of most of the lesion	blue in the central part and deformation of surrounding tissue instead of the central part	blue in the entire hypoechoic lesion without entire deformation	blue in the entire hypoechoic lesion and its surrounding area
Bakay 2015 [15]	liquid structures, colored as the three-color artifact	a) very elastic formations, mainly green coloring with addition of red and yellow foci b) medium elasticity objects with small rigid inclusions, green coloring with blue foci c) mosaic structure with inclusions of different colors	stiff formations, with green – blue coloring in almost equal proportions	very stiff formations, with prevailing blue coloring	-
Xie 2018 [19]	soft, predominantly purple, green or yellow with < 10% displaying blue, the node is indistinguishable from surrounding tissues	moderately soft, predominantly yellow or green with blue areas comprising between 10% and 50%, the node is partially delineated from surrounding tissues	moderately stiff, predominantly blue with yellow or green areas comprising between 10% and 50%, the node is partially delineated from surrounding tissues	stiff, predominantly blue with <10% yellow or green, the node is distinguishable from surrounding tissues	-

Color significance: red for soft tissue, green for intermediate structures and blue for hard tissue

Fig 3. Strain elastography with SR measurement: R = reference; T1 = analyzed cervical tissue.

tissue located at the same depth as the cervix, in its immediate proximity, which is not subjected to pathological changes. So far, SR has been computed between: the cervix and surrounding parametrial tissue [2,13,14,18,23]; the cervix and the lowest segment of the uterine corpus [16]; cervical lesions and normal cervical tissue [17]; the cervix and a synthetic reference device [21].

There is evidence that SR is a useful technique in the assessment of the normal and abnormal uterine cervix [17]. However, there is concern regarding the value of the parametrial strain, as reference tissue, since cancer can infiltrate both sides of the pelvic wall. The parametrium can also be subjected to stiffness changes as a result of oncologic therapy [2,13,24]. With regard to the myometrial strain as reference, it should be noted that the myometrium's depth is higher than the cervical one; nonetheless, the myometrial strain can be altered by local pathological processes (leiomyomas, adenomyosis) [21]. In order to bypass this technical difficulty, a study aimed at assessing the cervical stiffness during pregnancy used a custom-made synthetic reference device placed over the transducer tip [25]. The idea was supported by Fuchs et al, who stated that the use of a reference material could help improve quantitative elastography, resulting in a more accurate method [26]. Based on these reports, we conducted a study assessing the non-malignant and malignant cervix, using a custom-made silicone synthetic reference device, placed in the immediate proximity of the uterine cervix, as a reference [21].

Shear wave elastography

2DSWE measures the speed of the shear wave (SW), without the need for any external mechanic compression. The speed of the shear wave is color-coded throughout the image. Most systems also display the image acquisition quality. A ROI can be selected at the level of one

or two examined structures on the same image and the device automatically computes the stiffness in each ROI, independently, as the SW speed, translated into kPa. In addition, if 2 ROIs have been selected, the device can calculate a stiffness ratio between them, based on the kPa values measured in each ROI.

Acoustic Radiation Impulse Force (ARFI) elastography, also known as point elastography, measures the speed of the SW in a single sample in the image. It is not possible to select two structures simultaneously and therefore the computation of a stiffness ratio is impossible. The measurement results are expressed in m/s or kPa.

Transvaginal shear wave elastography

Given the advantage of quantitative results, several researchers have investigated the use of transvaginal SWE in exploring the normal and abnormal cervix [4,27,28]. The results and the technical limitations encountered by them are detailed in the sections below.

Transabdominal shear wave elastography

A single paper reported on the use of transabdominal SWE in CC. While the ability to scan tissues surrounding the cervix, lymph nodes and the involvement of the urinary bladder and rectum are considered advantages of this approach, limitations regarding deep tissue examination and the influence of high adiposity levels in some patients have been recognized [29].

Classification according to the purpose of the study

A) Methodology

Technique optimization for SWE

In spite of the advantage of returning quantitative data, SW are prone to scattering, reflection or refraction and these artifacts can further affect the precision of SWE [28,30]. While the unnecessary of mechanic compression can be regarded as an advantage over SE, transducer pressure on the tissue may result in apparent high SW speed values because of nonlinear tissue responses [30]. Manchanda et al reported that a wider range of compression exerted on the tissue near the transducer as compared to deeper tissue, resulted in falsely high elasticity readings in the proximal tissue [27], presumably due to focal inhomogeneity of propagation. This limitation was overcome by extending the image stabilization time to 3-5 seconds before making the measurements [27].

An important technical constraint is related to the depth of the assessed tissue. While one article reported on the expected depth of 3 cm for the main push pulses to produce SW, other authors found that 4 cm was the maximum depth up to which stiffness values could be evaluated on a transvaginal scan, also depending on the patient's habitus and version-flexion of the uterus [27,28]. Maneuvers such as placing a cushion below the waist or

asking the patient to lift the pelvis were useful in some cases [27].

The cervical position is another important factor, with the vertical position relative to the transducer plane being the most inconvenient for SW examination. Due to this anatomical variant, one study reports the lack of obtaining SW measurements in some cases [28]. SW precision of propagation, which translates in uniformity, can also be affected, resulting in regions of heterogenous color or loss of color on the elastogram [28]. To avoid the mismatch between the acoustic energy focus point and SW detection plane, excitation frequencies less than 7 MHz with full-aperture excitations should be used with an intracavitary probe [31]. The presence of nabothian cysts disrupt SW propagation, therefore the vicinity of these cysts should be avoided [30]. Despite the above-mentioned factors, most papers investigating SWE in the examination of the cervix have concluded that this is a useful method for exploring the cervix [4,27,32]. Some authors recommend the use of the anterior portion of the cervix, to the detriment of the posterior, while others support the use of the middle region of the cervix, to obtain the most reliable results through SWE [28,32].

Normal SW speed values of the uterine cervix range widely according to different authors and are illustrated in Table II.

Reproducibility

The Intraclass Correlation Coefficient (ICC) can be used to compute inter-rater reliability estimates, a low level of agreement being close to 0 and a high level of agreement 1 [28]. ICC values ≥ 0.9 are perfect, 0.70-0.89 good, 0.50-0.69 moderate, 0.30-0.49 mediocre, ≤ 0.29 bad [23]. ICC estimates and their 95% confidence intervals (CI) are usually calculated.

When describing new means of measurement performance on elastography, several authors have assessed the inter- and intraobserver variability, as an indicator of the reproducibility and reliability of the technique.

In SE, a paper reporting on the usefulness of SR measurement between the whole uterine cancer and the surrounding normal parametrial tissue on 36 patients with locally advanced cervical cancer, described that all examinations were performed by the same sonographer, but all SE images were analyzed by 2 ultrasonographers. They noted an interobserver ICC = 0.986 (95%CI, 0.947-0.996; $p < 0.001$) and an intraobserver ICC = 0.991 (95%CI, 0.964-0.998; $p < 0.001$) [2]. The same group extended their research on 45 patients and obtained an intraobserver ICC: 0.969 (95%CI, 0.824-0.996; $p < 0.001$) and an interobserver ICC: 0.944 (95%CI, 0.701-0.992; $p = 0.001$) for the variability of measurements, but highlighted that all patients were evaluated by a single sonographer and that in future studies, inter- and intraoperator variability of SE could be performed [14]. Another paper regarding the use of SR between the uterine cervix and the parametrial tissue in diagnosing the benign and malignant cervix reported the interobserver ICC of 0.931 (95%CI, 0.902-0.952) [23].

A reproducibility study conducted on 112 pregnant patients using SE noted that in most regions of the cervix the ICC ranged from 0.82-0.92 for intraobserver variability and from 0.70-0.80 for interobserver variability; all measurements were performed offline, on stored images from videoclip sequences, with the operators blinded to previous measurements [24]. A multicentric ongoing study on SE with a dedicated program (E cervix) assessing 895 pregnant patients for the intraobserver variability and 43 patients for the interobserver variability reported the following results: ICC intraobserver single measures 0.633-0.723, ICC intraobserver average measures 0.838-0.887, ICC interobserver single measures 0.814-0.977, ICC interobserver average measures 0.901-0.988 [22].

As to SWE, interoperator testing was performed on 15 participants with normal uterine cervix at different sites: the external os anterior and posterior were comparable for all 15 subjects; the interior os anterior was

Table II. Normal stiffness / shear wave speed values of the uterine cervix

Author, year/reference	Normal SW speed value in the uterine cervix	N	Ultrasound machine
Manchanda 2019 [27]	18.90 $\pm$ 4.22 kPa	56	Aixplorer (SuperSonic Imagine, Aix-en-Provence, France)
Liu 2019 [4]	2.86 $\pm$ 0.23 m/s (mean) 3.27 $\pm$ 0.31 m/s (maximum)	68	
O'Hara 2019 [28]			Canon (formerly Toshiba) Aplio 500
*external os, anteriorly	2.52 $\pm$ 0.49 m/s	63	version 6 and 6.5
*external os, posteriorly	2.87 $\pm$ 0.63 m/s	55	(Otawara-shi, Tochigi, Japan)
*internal os, anteriorly	3.29 $\pm$ 0.79 m/s	55	
*internal os, posteriorly	4.10 $\pm$ 1.11 m/s	26	

SW – shear wave, SD – standard deviation, N – number of patients, * – cervical location for SW measurement

comparable in 14 participants and the internal os posterior was comparable in 6 participants; in the remaining cases, shear wave propagation was unobtainable for both operators. The results were: ICC external os anterior = 0.83 (95%CI, 0.45-0.95), ICC external os posterior = 0.69 (95%CI, 0.07-0.90), ICC internal os anterior = 0.92 (95%CI, 0.76-0.97), ICC internal os posterior = 0.90 (95%CI, 0.37-0.98). The authors concluded that there was good level of agreement for external os anterior and internal os anterior and posterior, but with broad CI reducing the reliability of the result [28].

B) Normal variants

Age-related stiffness

Three papers assessed cervical stiffness related to age. The first study used SE with color scores – the scales are described in the above sections [20]. The analysis included 49 premenopausal and 40 postmenopausal patients, age ranging between 17-79 years old. The authors further calculated a tissue quotient (TQ) = %red / %green, to identify subtle differences based on color distribution. ANOVA test was used to correlate TQs with patient age. The proportion of stiff, blue tissue was assessed separately for pre- and postmenopausal patients. The calculated TQ values revealed no significant difference between different age groups. The authors concluded that, elastographically, cervical tissue does not change with age [20]. In the second study SWE was performed in 56 patients, with the age ranging between 20-60 years old. No significant difference was found in the mean elasticity values for different age groups [27]. In contrast, the third

study, also assessing the cervix with SWE, evaluated 69 patients, age ranging between 18-49 years old and concluded that cervical stiffness appeared to overall increase with age [28].

C) Positive diagnosis

(normal - abnormal, benign – malignant)

Color analysis was used for comparing normal with abnormal cervixes [15,20]. In the *computer-assisted analysis*, patients with CC (n=13) had a significantly higher proportion of blue - indicative of hard tissue (34±15%) than patients in the normal group (n=89, blue proportion 26±13%), p=0.025; subjective scores were also markedly higher where assigned to cervical lesions as compared to the normal group (p=0.000) [20]. The second paper assessing the cervix with elastographic *color scores* pointed out that the non-malignant cervix (n=25) was mapped predominantly green, showing elasticity, whereas the malignant cervix (n=62) showed blue coloring, revealing a high rigidity degree. Therefore, the authors concluded that the benign and malignant cervixes were imaged differently on elastography [15].

Strain Ratio. The diagnostic value of SR is summarized in Table III.

All of the studies illustrated in Table III concluded that SR, as a means of assessing the uterine cervix, was a useful technique in differentiating normal from abnormal, benign from malignant and diagnosing cervical cancer, relative to a certain cut-off value.

Despite reporting the SR of the tumors being significantly higher than that of normal tissue (3.8 vs 1.2,

Table III. Diagnostic value of strain ratio (SR)

Author, year/ Reference	Reference for cervical stiffness	Benign mean SR±SD	Malignant mean SR±SD	Cutoff	Se (%)	Sp (%)	PPV (%)	NPV (%)	Acc (%)	AUC
Sun 2012 [23]	Parametrial tissue	2.81±2.24 (n = 29)	8.19±5.66 (n=81)	4.53	89.7	78.8	-	-	-	0.905
Lu 2014 [17]	Normal cervical tissue	Range 0.62-4.50 (n=40)	Range 4.85-8.91 (n=44)	4.525	90.9	90	90.9	90	90.5	0.905
Shady 2015 [13]	Parametrial tissue	*2.46±0.46 for normal cervix and 6.65 for fibroid lesions (n=35)	*11.51 for primary CC and 10.60 for recurrent CC (n=35)	8.7	93.8	100	100	80	95	0.98
		*2.46±0.46 for normal cervix (n=30)	*10.41 ± 2.59 for diseased cervix (n=27 primary CC, n=5 recurrent CC and n=8 fibroids)	3.4	100	100	100	100	100	1
Dudea-Simon 2020 [21]	Synthetic reference device	0.89 (n=39)	2.07 (n=6)	1.42	100	94.9	-	-	-	0.966
		0.89 (n=39)	*1.42 (n=32 for CIN)	1.03	75	74	-	-	-	0.752
		*1.42 (n=32 for CIN)	2.07 (n=6)	1.51	100	65	-	-	-	0.797

SR – strain ratio, SD – standard deviation, Se – sensitivity, Sp – specificity, PPV – positive predictive value, NPV – negative predictive value, Acc – accuracy, AUC – area under the curve, * – other classification, CC – cervical cancer, CIN – cervical intraepithelial neoplasia, n – number of cases

$p < 0.01$), in a single study comparing normal ($n=8$) with malignant cervixes ($n=6$), the authors defined A = reference, B = cervix and SR was computed as B/A , as opposed to the authors listed in Table III, who computed SR as reference/cervix. Therefore, this single paper reported the CC lesions to be significantly softer than normal cervical tissue and explained that the finding was consistent with the clinical experience, showing cervical cancerous lesions to be soft and fragile and to easily bleed [16].

Several authors mentioned that while SR was useful in diagnosing advanced CC, the studied techniques failed to identify *in situ* CC, as well as CIN by using a biological tissue as a reference [15,20]. We have conducted a recent study, assessing SR in diagnosing CC and CIN, using a synthetic experimental device as reference material. Our results, illustrated in Table III, differ from those of other researchers; we estimate that our findings represent the expression of stromal changes associated with CIN, rather than of CIN itself. The use of a plausibly more sensitive and less susceptible to variations technique might have led to this aspect being revealed [21].

The utility of SR has been clearly demonstrated. However, at least one question needs to be addressed: how can such different values of the cut-offs, for the differentiation between benign and malignant, be explained?

Differences could be generated by: the choice of study groups; the size of study groups; the choice of the reference for cervical tissue comparison, taking into account that SR is the value of cervical stiffness relative to a reference; and the type of the ultrasound machine and settings used by the investigators. Indeed, it has been noted that the same cervix, examined with different equipment, produces different results [33]. Therefore, although the technique provides useful information, at present, it is not possible to define a universally valid cut-off value for diagnosing malignant lesions of the cervix.

SWE has also been assessed for the positive diagnosis of cervical disease. The results of transvaginal SWE results are presented in Table IV. It should be noted that the benign group included both cervical fibroids and polyps, therefore, the technique seems useful in differentiat-

ing both normal from abnormal and benign from malignant lesions. As with transabdominal elastography, both qualitative and quantitative technologies (Virtual Touch tissue imaging and Virtual Touch tissue quantification) had good diagnostic value in CC [29].

D) Staging

The prognosis of CC is closely correlated with the spread of the disease at the time of diagnosis. Particularly, staging in CC is clinical. Imaging investigations, such as computed tomography or MRI, can provide additional information, but are not included in the staging protocol.

Elastography could bring a benefit in the precision of staging, which is of major importance in choosing the therapeutic option and in determining the prognosis. Both SE and SWE were used to assess the CC invasion. The tumor contour was well visualized on elastograms, allowing the accurate description of the tumor location, as well as tumor measurement [4,15,18]. According to changes in stiffness, hard areas spreading outside the cervix to the uterine body, with clear delimitation from the elastic myometrium, were indicative for uterine body invasion. Evaluation of vaginal invasion involves differential diagnosis with a cervical tumor with exophytic growth. However, areas of soft structures around the external cervical orifice, represented by vaginal mucus, should normally be observed; parametrial invasion was described as the interruption or disappearance of a normally-seen soft pericervical strip [15,23]. In addition, several studies have compared the effectiveness of elastography compared to conventional ultrasound in describing invasion [15,18,23]; the results are presented in the corresponding section.

E) Prediction of response following oncologic treatment

Factors for early prediction of response to treatment are a particular research field in oncology. Elastography has been investigated in this regard as an imaging biomarker. The potential of SR as an early predictor of radiotherapy response in patients with advanced CC has been studied. Cervix to lowest segment of the uterine body SR was determined one month after radiotherapy and the results were reported to the cytological and histological re-

Table IV. Diagnostic value of transvaginal shear wave elastography

Author, year/ Reference	Normal cervix (n=68)		Benign cervix (n=40)		Malignant cervix (n=138)		Cutoff (m/s)	Se (%)	Sp (%)	AUC
	Maximum	Mean	Maximum	Mean	Maximum	Mean				
	SWS±SD (m/s)	SWS±SD (m/s)	SWS±SD (m/s)	SWS±SD (m/s)	SWS±SD (m/s)	SWS±SD (m/s)				
Liu 2019 [4]	3.27±0.31	-	3.93±0.39	-	-	-	3.45	87.5	75	0.909
	-	2.86±0.23	-	3.53±0.52	-	-	3.25	60	94.1	0.878
	-	-	3.93±0.39	-	5.24±1.11	-	4.15	89.1	72.5	0.909
	-	-	-	3.53±0.52	-	4.91±1.12	3.95	79	75	0.895

SWS – shear wave speed, SD – standard deviation, Se – sensitivity, Sp – specificity, AUC – area under the curve, n – number of cases

sults. Although this study included a small number of patients (n=6), the results seem encouraging: SR decreased to values comparable to those of the normal cervix in patients who showed a complete oncological response, and did not significantly decrease in those with residual disease [16]. Subsequently, another research group conducted two studies, which showed that cervix to parameter SR can be used as an early predictor of outcome in patients with concurrent chemoradiotherapy. Performing 3 examinations, pre-therapeutic, one and 2 weeks after the treatment initiation, both tumor diameter and SR were measured; differences in tumor diameter and SR were calculated, cutoffs were established (change in tumor diameter by 32.7% and SR by 27.2%) and 88.9% sensitivity and 88.9% specificity for SR as a predictive factor were obtained, using MRI and clinical examination as a reference [2,14].

Interestingly, in all cases it was found that the SR changed before the change in tumor volume, assessed by conventional ultrasound. One possible explanation would be that the biomechanical properties of tumor tissue change before morphological changes occur, as a result of chemoradiotherapy. This idea is supported by the fact that the sensitivity and specificity of elastographic SR in the evaluation of treatment response are higher than those of conventional ultrasound [18]. The suggestion emerges that the use of SR as an imaging biomarker might allow early, individualized adaptation of oncological treatment.

F) Prediction of pregnancy following conization

An interesting approach is the study of elastography in the evaluation of the reproductive potential following a conization. It is known that patients who undergo conization for CIN are often young, and have a desire for a future pregnancy. It was demonstrated that SE with color scores could identify, by evaluating the stiffness of the cervix before and 6 months after conization, the group of patients with increased chances of obtaining a pregnancy [19]. This paper opens new perspectives both in the study of cervical regeneration and in patient's counselling related to pregnancy achievement after conization, a topic that would be worth expanding through more extensive studies.

Comparison of elastographic techniques

A) SE and SWE compared to conventional ultrasound

SE with color scores was assessed compared to conventional ultrasound in the evaluation of uterine, vaginal and parametrial cancer invasion and it produced an overall increase in sensitivity and specificity [15]. While conventional ultrasound generally shows an enlarged cervix associated with malignancy, with blurring between the cervical contour and the surrounding structures and possibly increased flow on Doppler, SWE is able to show

the contour and tumor size, as well as an extension of the invasion, by revealing increased local stiffness measured in kPa [4]. Therefore, the inclusion of elastography in the ultrasonographic examination protocol is presumed to improve the quality of the method.

B) SE with color scores compared to SR

Both methods have been used in CC diagnosis, with good results. However, the examiner's experience and interpretation can significantly influence the accuracy of color scores. In a study evaluating both techniques in the differential diagnosis of cervical lesions, sensitivity, specificity, accuracy, positive predictive value and negative predictive value were globally improved when using SR (90.9%, 90%, 90.5%, 90.9% and 90%, respectively) as compared to color scores (81.8%, 85%, 83.3%, 85.7% and 81%, respectively) [17]. It must be emphasized again that the SR is a semiquantitative evaluation technique, which provides numerical results of cervical stiffness, compared to a reference.

C) SE compared to SWE

It is known that SE provides qualitative and semi-quantitative results, while SWE provides quantitative results, expressed in m/s or kPa. However, both methods are hampered by technical limitations in cervical exploration.

There is currently no available study focused on the comparative assessment of SE and SWE in the analysis of cervical cancer. Such a type of research was performed in breast disease: it was found that both methods had a similar area under the curve (AUROC), but the sensitivity and specificity varied depending on the thickness of the mammary gland and the histological type of tumor [34]. Therefore, future studies that will contribute to the development of protocols for the elastographic examination of the cervix are awaited.

Conclusion

Elastography has multiple applications in the gynecological pathology of the cervix. The methods used to assess the cervix are diverse, and none have become universally accepted. There are still unanswered questions and directions for future research.

Conflict of interest: none

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