Original Research

MEDICAL IMAGING

The value of contrast-enhanced ultrasound in cervical cancer assessed in comparison with magnetic resonance imaging

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Abstract

Introduction. Currently, magnetic resonance imaging (MRI) is the most commonly used imaging method in the assessment of the loco-regional extension in cervical cancer. Contrast-enhanced ultrasound (abbreviated CEUS) is being investigated as an alternative or complement to the MRI investigation.

Objectives. To evaluate the performance of CEUS in identifying loco-regional invasion of cervical cancer compared to MRI, considered the accepted reference standard.

Methods. Sixty-one patients with histopathologically confirmed cervical cancer were investigated as part of the pre-treatment workup by CEUS and MRI. We calculated the accuracy and concordance of CEUS versus MRI for tumor invasion in the vagina, bladder, rectum, parametrium, and uterus. For the time-intensity curve associated parameters analyzed (TTPK, AUC, peak intensity, wash in and wash out gradient) we calculated sensitivity, specificity and threshold value of positivity, for tumor invasion at the above-mentioned sites, with graphical representation of the ROC (receiver operating characteristic) curve.

Results. CEUS was highly accurate in detecting bladder (93.4%, 95% CI: 87.2-99.6) and uterine invasion (88.5%, 95% CI: 80.5-96.5). Substantial agreement between CEUS and MRI was observed for invasion in the uterine body (k=0.77, 95% CI: 0.56-0.98) and bladder (k=0.56, 95% CI: 0.35-0.77). ROC curve analysis for loco-regional invasions showed that the wash in gradient at a cut-off value of 2.23 had a sensitivity of 76% and a specificity of 67% in predicting uterine invasion.

Conclusions. Our results demonstrate high accuracy and good agreement between CEUS and MRI regarding especially uterine and bladder invasion. This imaging method could help select patients in early stages for fertility sparing surgery, and also be of use in cases in which early bladder invasion is suspected.

Keywords: contrast-enhanced ultrasonography, cervical cancer, magnetic resonance imaging

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Introduction

Cervical cancer is currently the fourth leading cause of cancer mortality in women worldwide [1].

Accurate staging of the case is essential for choosing the appropriate therapeutic procedure and for estimating prognosis [2-4]. The new staging of cervical cancer is more accurate and allows initiation of appropriate oncological treatment [5-8]. MRI is the examination that can provide a good analysis of local invasion and helps staging [3,9]. A systematic review has shown superiority of MRI over clinical examination with respect to parametrial invasion, with a sensitivity of 84% vs. 40%, but also in the assessment of locally advanced disease (sensitivity of 79% vs. 53%) [10].

Updated European guidelines emphasize the use of ultrasound and magnetic resonance imaging in the initial evaluation of patients with a diagnosis of cervical cancer [11]. Also, by means of sectional imaging, the primary tumour can be assessed in terms of invasion into neighbouring organs - bladder, ureters and rectum. In a European multicenter study, Epstein et al. demonstrated good agreement between ultrasound and MRI in terms of tumors smaller than 2 centimeters as well as invasion in the parametrium [12,13]. Magnetic resonance imaging has until recently been considered the method of choice in evaluating tumor size, primary tumor and loco-regional nodes, with very good resolution [14-16] .

When performed, contrast-enhanced intravenous ultrasound (CEUS) is always used as an extension of gray-scale and Doppler ultrasonography [17]. Testa et al. have shown the usefulness of CEUS in the exploration of gynecological pathology since 2005 [18]. CEUS has the potential to provide the clinician with information regarding the extent of tumor vascularity as well as delineation of cervical cancer from surrounding anatomic planes and organs. To date there are few studies comparing the contribution of CEUS in relation to MRI in the evaluation of cervical cancer [19].

We conducted a study using CEUS in patients diagnosed with cervical cancer and compared the results obtained with those from MRI examination, considered as the reference standard, to evaluate the accuracy of CEUS exploration.

The aim of the study was to assess the performance of CEUS versus MRI in the evaluation of local invasion in patients diagnosed with cervical cancer, as well as to establish the threshold of CEUS positivity for parameters expressed by continuous variables, in order to find the best compromise between CEUS sensitivity and specificity.

Objectives

- To calculate the accuracy of the new test, for the evaluation of CEUS performance, compared to MRI;
- The validity analysis of the test by measuring the sensitivity and specificity of CEUS;
- To evaluate the concordance between CEUS and MRI in the assessment of local invasion;
- To analyze the prediction of CEUS by calculating positive and negative predictive values (PPV, NPV);
- Identification of the positivity threshold that guarantees the highest level of sensitivity and specificity of the CEUS parameters, using the ROC curve.

Methods

Study participants

We conducted a prospective study including 70 patients diagnosed with cervical cancer from January 2018 to May 2021.

Inclusion criteria

- biopsy-confirmed diagnosis of cervical cancer, regar dless of stage,
- Recent history (no more than 7-10 days) of pelvic MRI examination performed as part of the pretherapeutic imaging workup,
- Patients who have not undergone any oncological or surgical treatment prior to the CEUS examination.

Exclusion criteria

- known drug allergies, known hypersensitivity to sulphur hexafluoride,
- severe lung disease,
- recent acute coronary syndrome or unstable ischemic heart disease,
- acute heart failure.

Out of the total of 70 patients examined by CEUS, we excluded 4 patients who did not undergo pelvic MRI with contrast agent (claustrophobia), 4 patients for whom we did not have access to the MRI examination and one case of anaphylactic shock when SonoVue contrast agent was administered, with discontinuation of CEUS examination. A total of 61 (87%) patients were included in the final analysis.

For this study we obtained the consent of the Ethics Committee of the Iuliu Haţieganu University of Medicine and Pharmacy and the Ethics Committee of the "Prof. Dr. I. Chiricuţă" Oncological Institute, thus being in common agreement with their ethical rules, as well as with those provided by the Helsinki Declaration of 1975, revised in 2000.

Ultrasound examination technique and patient preparation

All patients were examined with the ultrasound machine General Electric Logiq E9, XDclear 2, with 3D transvaginal probe with frequency of 3-10 MHz, in supine position. Prior to the examination patients signed the informed consent regarding the type of procedure, the role of the procedure and potential risks. Patients were fitted with a peripheral venous catheter (20G). We set the mechanical index of the ultrasound machine to 0.1 (MI) in order not to damage the SonoVue microbubbles.

Native, grey-scale examination

Under these conditions, we examined each patient in grey scale by transvaginal ultrasound, obtaining transverse and longitudinal sections. Mini videos were saved in gray scale examination.

CEUS examination

We chose the sagittal or anterior-posterior (AP) plane of section in which the cervical tumor had the largest size, with integration of the cervical canal into the plane for reproducibility of examinations. In the GE Logiq contrast-enhanced examination software, the ultrasound image was divided into two halves - one in gray scale and one in CEUS examination mode. Cross-sections were also acquired and recorded in the cross-sectional plane in the area of maximum cervical size. We used SonoVue contrast medium (Bracco, Milan, Italy), which has a good safety profile [20]. This substance consists of microbubbles stabilized by a phospholipid membrane and contains sulfur hexafluoride. The section plane once obtained, it was centered in the gray scale examination window, the transvaginal probe never being repositioned.

At the chosen time point (T0), a bolus of 2.5 ml of prepared solution was administered, followed by a bolus of 5 ml of saline. Videos of 180 seconds were recorded (T0-T180). We established two time-reported vascular phases namely an arterial phase - from T10-T15 and beyond, and a venous phase from T45 and beyond. These time periods have been described in the literature and there is a consensus on this for similarly vascularized organs [21]. All videos obtained from the examination of all patients included in the study were saved.

After completion of the examination, the patient was monitored for an additional 30 minutes to ensure the absence of possible adverse reactions. Post-procedural blood pressure values were measured, heart rate and oxygen saturation at the nail bed were assessed using a pulse oximeter.

We analyzed the contrast loading ("wash in") and contrast depletion ("wash out") phenomena during each examination.

Analysis of CEUS parameters

The chosen ultrasound machine had its own software for the graphical representation by time intensity curve (TIC) (Figure 1) and quantitative representation of the CEUS parameters chosen for analysis. Contrast kinetics is characterized by quantitative parameters associated with the TIC curve, which are expressed in arbitrary intensity units (AIU) over a time interval. We chose to analyze peak intensity (PI) (measured in AIU), time to peak (TTPK) measured in seconds, area under the curve (AUC) measured in AIU x seconds, wash in gradient and wash out gradient measured in seconds. We arbitrarily chose regions of interest (ROI) in obviously tumor-modified tissue with increased intensity and in apparently healthy cervical tissue with normal intensity.

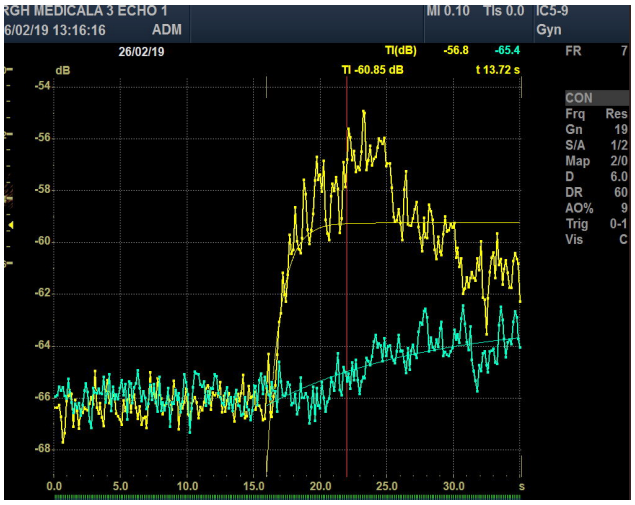

Figure 1. CEUS. Graphical representation of TIC in the arterial phase in a 70-year-old ME patient diagnosed with stage IIIB squamous carcinoma of the cervix. Yellow is the TIC curve in the tumor area of maximum intensity. Green shows the TIC curve in apparently tumour-free tissue.

MRI examination

Patients included in the study received full contrast-enhanced MRI examination of the pelvis.

Bladder invasion was assessed by analysing the tissue in the cervico-vesical space with respect to its continuity in relation to the bladder wall in T2 sequence. Loss of this interface with contrast enhancement showed bladder invasion. The same was interpreted for the recto-vaginal space - discontinuity with loss of interface between organs demonstrated rectal invasion. Invasion of the uterine body was diagnosed in patients in whom tumour tissue was objectified superior to the isthmic portion of the uterus, with contrast enhancement at this level. Parameter invasion was diagnosed in T2 sequence and in combination with DWI when the edges of the cervix had an irregular, infiltrative and discontinuous outline.

We recorded in the database information regarding: bladder invasion (yes/no), vaginal invasion (yes/no), extension into the uterus (yes/no), parametrial invasion (yes/no) and extension to the rectum (yes/no).

Analysis of the data obtained

In order to assess the accuracy and parameters of CEUS, we compared the results obtained from the CEUS test with those obtained by performing the reference standard, i.e. the MRI examination. First we analyzed the qualitative variables (invasion in vagina, uterus, parametrium, bladder and rectum) by including them in 2×2 contingency tables and comparing the results obtained: number of tests in agreement and disagreement with the reference standard.

We calculated the test accuracy, sensitivity (SE), specificity (SPE) and positive (PPV) and negative predictive values (NPV) with 95% confidence intervals [22].

For CEUS parameters expressed by a quantitative

variable (TTPK, PI, AUC, wash in and wash out gradient), to assess validity we plotted the ROC (receiver operating characteristic) curve, using the sensitivity on the ordinate and the 1-specificity value on the abscissa, for different values of the cut-off. We selected the optimal cut-off value, corresponding to the point closest to the upper left corner, which provides the highest values of sensitivity and specificity simultaneously [23].

The degree of agreement between CEUS and MRI in assessing local invasion was assessed by Cohen's k coefficient [23]. Values of $k \leq 0.40$ represent low concordance; 0.41-0.60 moderate concordance; 0.61-0.80 substantial concordance; 0.81-1.00 near perfect (excellent) concordance.

Comparison of means was performed using the Student's test and the Chi test^2 was used to compare percentages.

We used SPSS (Version 2023, Statistical Package for Social Sciences Inc, Chicago) to perform the statistical calculations.

Results

The age of the patients ranged from 33 to 78 years, with an average age of 55.4 years. Most patients, 95.1% (58 patients) had squamous cell histology, 3.3% (2 patients) had adenocarcinoma and 1 patient (1.6%) had adenosquamous carcinoma (Table I).

The majority of cases (86.88%) were stages IIB and higher, with therapeutic indication of radio-chemotherapy (Table I).

Table I. General and tumor characteristics of patients.

	N=61
	M± DS
Age (years)	55.4 (33-78) ± 11.62
FIGO staging	
IB1	4 (6.6%)
IB2	3 (4.9%)
IIA	1(1.6%)
IIB	33 (54.1%)
IIIA	3 (4.9%)
IIIB	16 (26.3)
IVA	1 (1.6%)
Histological type	
squamous cell carcinoma	58 (95.1%)
adenocarcinoma	2 (3.3%)
adenosquamous carcinoma	1 (1.6%)

M - mean; SD - standard deviation

Accuracy calculation, sensitivity and specificity measurement and prediction analysis of the CEUS test

The presence of vaginal invasion was detected by both CEUS and MRI in 50 patients. In total there were 52 concordant results with an accuracy of 85.25% ($CI_{95\%}$ 76.34% - 94.15%) (Table II). Nine cases (14.8%) were identified by MRI but not by CEUS (false negative results). Sensitivity was 84.75% ($CI_{95\%}$ 75.57%-93.92%) and NPV was 18.18% ($CI_{95\%}$ -4.62% - 40.98%). The overall concordance was k = 0.27.

Table II. Presence of vaginal invasion detected on CEUS vs. MRI examination.

		MRI		
		Yes	No	Total
CEUS	Yes	50	0	50
	No	9	2	11
Total		59	2	61

Concordant CEUS vs. MRI results for parametrial invasion were identified in 53 out of 61 patients (86.9%, $CI_{95\%}$ 78.41%-95.36%), while CEUS did not detect invasion in 8 cases (13.1%, false negative results) (Table III). Sensitivity was 86.4% ($CI_{95\%}$ 77.7%-95.18%), NPV 20% ($CI_{95\%}$ -4.80%-44.8%), and k- coefficient = 0.29 ($CI_{95\%}$ 0.15-0.44).

Table III. Presence of parametrial invasion detected on CEUS vs. MRI examination.

		MRI		
		Yes	No	Total
CEUS	Yes	51	0	51
	No	8	2	10
Total		59	2	61

Regarding invasion of the uterine body both examination techniques identified 30 cases, with 24 negative cases, at an accuracy of 88.5% ($CI_{95\%}$ 80.52%-96.52%), sensitivity of 88.24% ($CI_{95\%}$ 77.4%-99.07%), specificity 88.9% ($CI_{95\%}$ 77.03%-100.7%), PPV of 90.9% ($CI_{95\%}$ 81.1%-100.7%), and NPV of 85.7% ($CI_{95\%}$ 72.75%-98.68%). The k-coefficient was 0.77 ($CI_{95\%}$ 0.56-0.98) (Table IV).

Table IV. Presence of uterine body invasion detected on CEUS vs. MRI examination.

		MRI		
		Yes	No	Total
CEUS	Yes	30	3	33
	No	4	24	28
Total		34	27	61

Fifty-seven cases out of 61, corresponding to an accuracy of 93.44% ($CI_{95\%}$ 87.23%-99.66%) had concordant bladder invasion results. Sensitivity and PPV were 60% ($CI_{95\%}$ 17%-102.9%), and specificity and NPV had values of 96.43% ($CI_{95\%}$ 91.57%-101.29%). The k-coefficient was 0.56 ($CI_{95\%}$ 0.35-0.77) (Table V).

Table V. Presence of bladder invasion detected on CEUS vs. MRI examination.

		MRI		
		Yes	No	Total
CEUS	Yes	3	2	5
	No	2	54	56
Total		5	56	61

Table VI. Presence of rectal invasion detected on CEUS vs. MRI examination.

		MRI		
		Yes	No	Total
CEUS	Yes	1	0	1
	No	0	60	60
Total		1	60	61

Only one case was identified with rectal invasion on CEUS and MRI examination, making it impossible to calculate the test parameters as well as the k-coefficient (Table VI).

Identifying the positivity threshold and obtaining the ROC curve

All CEUS parameters were included to obtain the ROC curve for uterine invasion. The other locations of loco-regional invasion could not be included in the ROC curve analysis due to the small number of cases. Sensitivity and specificity of CEUS parameters according to the positivity threshold value are shown in table VII. The cut-off value for the wash in gradient was 2.231 with a sensitivity of 76% and a specificity of 67% for the identification of uterine invasion ($p<0.01$) (Figure 3).

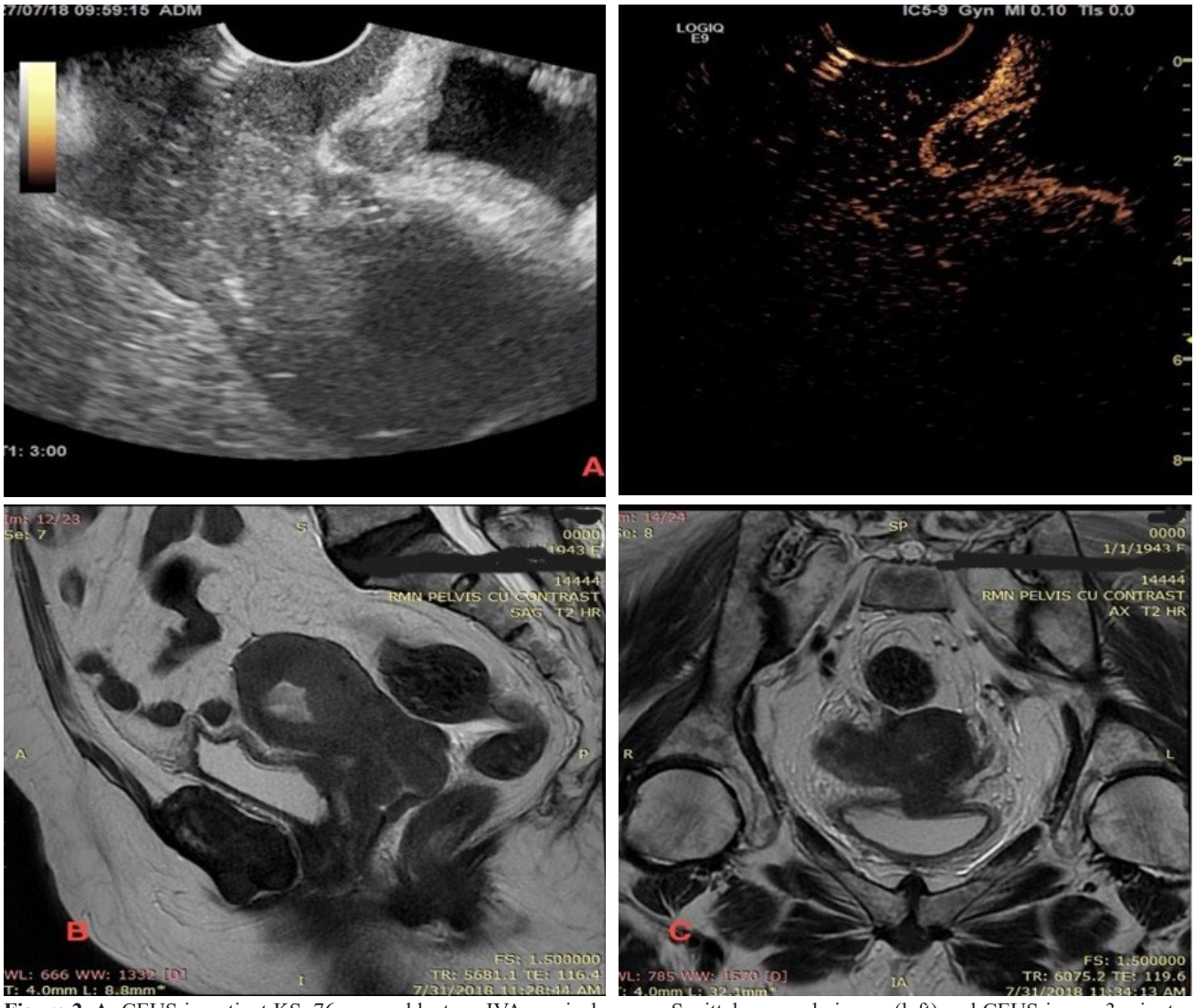

Figure 2. A. CEUS in patient KS, 76 years old, stage IVA cervical cancer. Sagittal grayscale image (left) and CEUS image 3 minutes after SonoVue injection. Loss of bladder-cervical and cervico-uterine space contour with tumor infiltration of the entire bladder wall is seen. **B.** Sagittal MRI image in T2 sequence - tumour invasion into the vesico-uterine space with loss of bladder wall contour is observed. **C.** Axial T2-slice MRI image showing full bladder wall invasion.

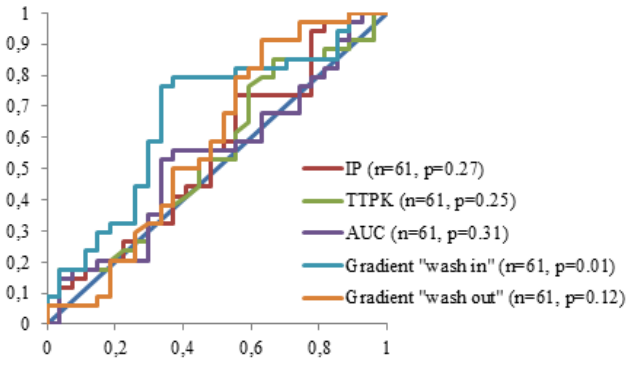

Figure 3. ROC curve of CEUS parameters for uterine invasion (IP - intensity peak, TTPK - time to peak, AUC - area under the curve, Gradient - wash in gradient, wash out gradient).

Table VII. Sensitivity and specificity of CEUS parameters for detection of uterine invasion.

	Se%	Sp %	p	Value of the positivity threshold
IP	74	44	0.27	20.17
TTPK	76	41	0.25	8.85
AUC	56	63	0.31	289.56
Gradient "wash in"	76	67	0.01*	2.23
Gradient "wash out"	79	44	0.12	0.51

Table VIII. Sensitivity and specificity values as a function of the positivity threshold for the wash in gradient.

Positivity threshold (seconds)	Sensitivity	Specificity
4,507	3%	100%
2,889	35%	74%
2,231	**76%**	**67%**
1,852	85%	30%
1,171	100%	4%

Table VIII shows the opposite evolution of sensitivity and specificity according to the positivity threshold chosen for the wash in gradient for which statistical significance was obtained. At a threshold value of 2.23, the sensitivity was 76% and the specificity was 67%, which are the highest possible values recorded simultaneously (Figure 3).

Discussion

This study aimed to evaluate the performance of CEUS in patients with a diagnosis of cervical cancer compared to MRI scanning, which is considered the reference standard. There are few published studies addressing the role of CEUS in the evaluation of cervical cancer, and to our knowledge this is the only study in Romania.

Clinical and imaging assessment in the pre-treatment workup of cervical cancer is essential for initiating the therapeutic decision. The latest changes to the FIGO staging system for cervical cancer in 2018 include ultrasonography, computed tomography, magnetic resonance imaging, and positron emission tomography in the group of imaging investigations that may be necessary for more precise staging [2,11,12]. These investigations are necessary to identify with better accuracy the size of tumors, local or distant lymph node invasion and allow the identification of additional prognostic factors that determine a particular therapeutic approach for each individual case [2,24].

Earlier studies, such as the one conducted in 1998 by Hawnaur et al. showed the advantages of ultrasonography over MRI exploration in the evaluation of bulky tumors in patients with reserved prognosis [24]. In 2013 Epstein et al. reported a good correlation between ultrasonography and MRI with respect to tumor detection and measurement in early stages of cervical cancer, relating the information obtained to the gold standard - histopathological examination [13].

Transvaginal ultrasonography has higher accuracy, specificity and sensitivity than transabdominal ultrasonography in the evaluation of cervical malignancy [25], which is why we opted for the transvaginal approach in the present study.

In our study vaginal invasion was identified in 50 patients of the total 61 included, with an accuracy of 85.25%, corresponding to a sensitivity of 84.75%. However, in addition to CEUS, 9 cases (14.7%) were reported as positive for vaginal invasion by MRI (k = 0.27). Byun et al. obtained an accuracy of 83.3% for ultrasound compared to 87.5% for MRI with a sensitivity of 44.4% for gray-scale and Doppler ultrasound and 55.6% for MRI [26]. The major difference in sensitivity (84.75% versus 44.4%), can be explained by the ability of CEUS versus gray-scale and/or Doppler ultrasound to highlight tumor tissue by characterizing tumor vasculature [27].

The ability to detect parametrial invasion by CEUS was poorly concordant with MRI examination. In the present study, 8 cases (13%) of parametrial invasion were not identified by CEUS, with a low k-coefficient= 0.29. Other authors obtained moderate concordance (k = 0.46) between CEUS and MRI in a study of 108 patients [19]. On the other hand Epstein et al. reported better concordance between endovaginal gray-scale and Doppler ultrasound and histopathological examination (k = 0.75) taken as the gold standard, than with MRI (k = 0.45) regarding parametrial invasion [13].

Uterine extension in early cervical cancers should be well documented, when considering surgical treatment to preserve fertility [12]. Fertility sparing surgery is an option for tumors of 2 cm or less [28]. In our study we obtained substantial agreement (k-0.77) between the two examination techniques with respect to uterine invasion. It is important to assess the distance between the cranial edge of the tumour and the internal cervical os, if opting for a

fertility sparing treatment [12,14]. Xiao et al. published a meta-analysis showing a sensitivity of 87% and a specificity of 91% for MRI assessment of the distance between the cranial edge of the tumour and the internal cervical os [29]. Sensitivity and specificity with respect to uterine invasion in our study were 88.24% and 88.9%, respectively, by CEUS versus MRI, values close to the aforementioned meta-analysis, and the PPV of 90.9% guides the clinician with respect to the prediction of uterine invasion detected by CEUS in case of a positive result. Woo et al., in a meta-analysis published in 2020, identified a sensitivity of 84% and specificity of 96% for MRI scanning versus gray-scale ultrasound in the detection of invasion beyond the internal cervical os [30].

In our study CEUS identified bladder invasion with increased accuracy (93.44%), with a coefficient k = 0.56, similar to Zheng et al. (k = 0.61) [19]. The high accuracy may be useful to correctly identify stage IVA cancers. Furthermore the NPV value of 96.43% could justify the use of CEUS to exclude bladder invasion in medical centres without MRI examination facilities.

For tumour extension in the parametrium, vagina and rectum, the small number of patients included in the study did not allow calculation of positive and negative predictive values.

The existence of a single case of rectal invasion resulted in 100% accuracy between CEUS and MRI, thus requiring a larger number of patients to obtain valid information.

There are few studies in the literature that have investigated the semi-quantitative parameters of CEUS [27], with validity analysis and cut-off point investigation to ensure the highest values of their sensitivity and specificity. In our study we evaluated CEUS parameters (TIC, PI, AUC, wash-in gradient and wash-out gradient) in order to identify local tumor invasion. Furthermore, we obtained a statistically significant value for the CEUS parameter, namely the wash in gradient of the contrast agent used in the exploration of invasion of the uterine body analysed by ROC curve analysis (Table VII and VIII).

In addition, our study obtained a threshold value of positivity for the wash-in gradient, which could be used to individualise surgical treatment in stages IA - IB1 cervical cancer in patients who opt for fertility preservation.

One of the limitations of the study is related to the small number of patients, who were included by consecutive submission based on inclusion criteria and patient compliance for CEUS examination, representing a convenience series, with predominance of advanced stages. For this reason, we cannot consider the sample representative of the entire population of patients with histopathologically confirmed cervical cancer.

The advantage of ultrasound examination, including CEUS, is based on real-time evaluation of the tumor, with the possibility of identifying reduced tissue mobility in relation to the surrounding anatomical planes (bladder-uterine fold, peritoneal reflection on the anterior rectal wall, adnexa, iliac vascular bundles). The recording of images and videos allows subsequent evaluation of patients after oncological treatment (surgical or radio-chemotherapy) and offers the possibility of dynamic follow-up of each individual case.

An advantage of the present study was the interpretation of the MRI results by a specialist with experience in the field, thus avoiding interobserver differences as potential sources of error. Also, the acquisition and interpretation of CEUS images was performed by a single specialist, unaware of the MRI results, in a “blind” manner, thus limiting potential errors.

Conclusions

In conclusion, CEUS has good agreement with MRI in terms of assessing local invasion of cervical cancer (uterus and bladder). This imaging method could help select patients with early stages for fertility sparing surgery, and also be of use in particular cases in which early bladder invasion is suspected. CEUS can be effectively used in the assessment of loco-regional extension in cervical cancer patients, facilitating a complete pre-treatment work-up.

These preliminary results require further investigations on a larger number of patients in all stages of cervical cancer to compare CEUS accuracy with MRI and to suggest cut-off values for differentiation of normal from abnormal tissue.

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