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Multimodal endocavitary ultrasound versus MRI and clinical findings in pre- and post-treatment advanced cervical cancer. Preliminary report.

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Abstract

Aims: The aim of this study was to evaluate the use of pre and post-therapy transrectal and transvaginal ultrasonography (TRUS, TVUS) with contrast enhancement and strain elastography compared with clinical examination and magnetic resonance imaging (MRI) in the assessment of advanced stage cervical cancer. **Material and methods:** This was a prospective study, carried out over a period of nine months on subjects with advanced-stage cervical cancer (stage ≥IIB). All included patients were examined clinically and underwent abdomino-pelvic contrast enhanced MRI and multimodal US examinations (TRUS with strain elastography and contrast enhanced TVUS) at the time of diagnosis and after radiochemotherapy. Tumor size and staging at TRUS and TVUS was compared with the same data obtained by clinical examination and MRI. Pathology was the golden standard. **Results:** Eight patients accomplished the inclusion criteria. In five cases the tumor stage was identical on clinical and MRI examinations. In all cases parametrial infiltration was diagnosed by all pre-treatment examinations. No significant differences were observed in tumor size between clinical, US and MRI exams either at baseline or post-therapy, in native or post-contrast examinations. The size of the tumor evaluated pre-treatment proved to be significantly smaller post-contrast in both US and MRI examinations compared with the native images. Post-therapy, no significant differences were observed on US measured tumor dimensions when comparing native with post-contrast images. Oppositely, significant smaller dimensions were observed on post-contrast MRI compared with native scans. **Conclusions:** TRUS is accurate in the estimation of pre-therapy cervical cancer dimension. The post therapy tumor evaluation is better performed with MRI. The use of intravenous contrast agents on both examinations did not improved the accuracy of tumor evaluation pre- or post-therapy.

Keywords: cervical cancer, MRI, ultrasonography, contrast, elastography

Introduction

Cervical cancer is the second most common gynecological malignancy [1]. It is the only gynecological malignancy staged clinically, according to the FIGO (International Federation of Gynecology and Obstetrics) criteria [2]. This includes physical examination, colposcopy, biopsy, chest X-ray, barium enema, intravenous urography, sigmoidoscopy, and cystoscopy [3]. Imaging modalities are used for detection of parametrial, pelvic wall invasion, and adenopathies, but they do not change the clinical staging [4]. The majority of newly diagnosed cases are in locally advanced stages (parametrial invasion FIGO ≥ IIB) [2].

The disease prognosis depends on factors not included in the FIGO criteria, such as tumor volume and the presence of adenopathy. Clinical staging, especially in the assessment of pelvic sidewall invasion, has been shown to be inaccurate [5]. Accurate staging is essential for subsequent therapy planning and parametrial invasion is the key decision factor: surgery in early stages (FIGO ≤ IIA) [6] and radiochemotherapy in advanced stages [7]. The optimal

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therapy for a tumor >4 cm is radiochemotherapy, even in the absence of parametrial invasion [8].

Magnetic resonance imaging (MRI) is accepted as the most reliable imaging modality for staging cervical cancer and performs better than clinical examination in advanced disease in the detection of parametrial invasion and adenopathies [9].

Transrectal ultrasonography (TRUS) for the evaluation of tumor size and parametrial involvement in cervical cancer was first applied by Zaritzky et al [10]. In recent years TRUS has been rarely used for the evaluation of cervical cancer despite the fact that it performs better than the FIGO evaluation [11]. Transvaginal US (TVUS) is not recommended for the assessment of the parametria as the ultrasound probe is located too close to the parametrium [12]. However, TVUS has been used for the assessment of cervical cancer vascularisation using contrast enhanced US (CETVUS) [13]. Strain elastography (SE) is a rather new US technique and its usefulness in the assessment of cervical cancer has been scarcely reported [14]. The association of gray scale, Doppler, CEUS, and SE represents a multiparametric US approach to cervical cancer that may add complementary information to MRI at a lower cost and with greater accessibility for non radiologists.

The aim of this preliminary study was to assess the feasibility and potential usefulness of multiparametric US as compared to MRI in the assessment of advanced stage cervical cancer pre- and post therapy. The findings of the study should allow the setting up of examination protocols for a larger scale study.

Material and methods

A prospective study was carried out over a period of nine months on subjects with advanced-stage cervical cancer (stage ≥IIB) confirmed by pathology. Ethical approval of the study was obtained from the Institutional Ethics Committee. Informed consent was obtained from all patients.

The study was designed for two assessment sessions of the same patients: initial and at 3-4 months after radio-chemotheraphy. All clinical examinations were performed by a radiotherapist (C.O.) specialized in gynecologic oncology, with the aim to establish the tumor stage according to FIGO criteria [3]. Tumor size (lateral and anteroposterior dimensions) was recorded.

After clinical examination the patients underwent abdominal and pelvic MRI with intravenous contrast agent, followed by TRUS and TVUS. TRUS was performed first. During TVUS, intravenous contrast enhancement with SonoVue® (Bracco, Milan) was used, thus obtaining CETVUS. The MRI examinations were carried out within three days of the clinical examination; ultrasound examinations were performed within three days of the MRI examination. All ultrasound techniques were performed on the same day. The ultrasound and the MRI examiners assessed the following: presence of cervical tumor, tumor stage (MRI examination), tumor size in three dimensions (lateral, anteroposterior, and craniocaudal dimension) measured pre- and post contrast, the presence of parametrial and vaginal infiltration, lymph node involvement, and vesical and rectal invasion.

MRI protocol

MRI scanning was performed using a 1.5 T scanner (General Electric Sigma Excite®, GE Medical Systems, Milwaukee WI, USA). For pelvic imaging a phased-array coil was used and the following sequences were performed: axial T1 FSE, sagittal T2 FRFSE, oblique axial T2, axial T2 FRFSE, axial DWI with b values of 800/1000 mm^2/s. For abdominal examination, a phased-

Table I. Image analysis criteria of MRI images with stage correspondence. Cervical cancer appears as a hyperintense mass on T2-weighted images [adapted after 15-17].

FIGO CLASSIFICATION	MRI IMAGING FINDING
IIB – the tumor invaded the parametrium	Oblique axial T2WI: disruption in the hypointense ring of cervical stroma.
IIIA – the tumor invades the lower third of the vagina	Sagittal T2WI: hyperintense mass protruding into the lower vagina, the hypointense vaginal wall being disrupted.
IIIB – the tumor extends to the pelvic wall and may produce hydronephrosis	Oblique axial T2WI: hyperintense mass invading the parametrium and pelvic wall. Pelvic sidewall invasion if the tumor extends to a distance of <3 mm from the pelvic wall.
IVA – the tumor invades the bladder or rectal mucosa	Axial, oblique axial, and sagittal T2WI: disruption or segmental thickening of the hypointense bladder or rectal wall. Axial T1WI: CE in the involved bladder or rectal wall.
IVB – distant metastases	CE examination: the presence of abdominal metastasis and lymph nodes (short axis measurement > 1cm).

CE – contrast enhancement

array coil was used and : axial 2D FIESTA, coronal 2D FIESTA, axial T2 FRFSE with FAT SAT, axial T1 FSPGR FAT SAT were performed. At 18–20 s following intravenous injection of gadolinium dimeglumine (Magnevist®, Berlex, Wayne NJ, USA) 0.1 mol/L per kg body weight, a LAVA 3D sequence, and an axial T1 FSPGR with fat sequence was performed in the abdomen. Pelvic post-contrast imaging was acquired 5 minutes after intravenous injection with axial T1 FSE images. The MR image analysis criteria are presented in table I.

US protocols

All US studies were performed on a Siemens Acuson S 2000™ machine (Siemens, Erlangen) with 4-9 MHz multi-frequency endocavitary convex linear array probe. The patients were placed in gynecological position (the pelvis raised 30°) with medium bladder distention. The endocavitary probe was covered with a single use barrier and was closely positioned to the tumor. The sagittal scan was used as the reference plane. The transverse plane of the cervix was obtained with rotation of the probe with 90°.

TRUS was used for morphologic and Doppler analysis of the tumor, including parametrial infiltration. On TRUS, the cervical tumor appeared as a solid mass, hypoechoic compared to the neighboring normal miometrum. Parametrial infiltration was suggested by the asymmetric extension of the hypoechoic tumor in the parametrial fat. Abnormal vascularization of one parametrium was diagnosed when the hypoechoic parametrial tumor extension presented the same vascular pattern and density as the cervical tumor, or when one parametrium presented vessels with higher density than the opposite. Tumoral infiltration of the rectal wall and/or posterior wall of the bladder was diagnosed when a breach of continuity of the layers was seen with direct continuation of the cervical cancer at least as deep as the muscular layer of the rectum or bladder [11,18]. Also, tumoral infiltration of rectal and/or bladder wall was diagnosed when immobility of the vaginal fornix against these structures was seen on real time examination [19]. The tumor size was measured in three orthogonal diameters.

CETVUS was obtained primarily for assessing tumor response to treatment. The secondary goal of CETVUS was the assessment of tumor extent as depicted by vascular enhancement, compared with tumor size measured on the gray scale US.

For CETVUS, a 2.5 ml dose of SonoVue® (Bracco, Milan) followed by intravenous flush of 10 ml saline was used. Sixty second clips were recorded and reassessment of the appearance was performed at 90, 120 and 240 sec. CE was estimated in the arterial phase – fast homogeneous contrast uptake or no contrast uptake, compared to surrounding tissues and in the venous phase – persistent enhancement or wash out at the level of the tumor compared with the surrounding tissues. Tumor size of the contrast enhancing tissue was measured both for comparison with the gray scale image and for assessment of tumor response to treatment.

The purpose of SE was twofold, similar to CEUS: to assess tumor response to treatment by comparing the evolution of the stiff area size and to compare the stiff area with the apparent size of the tumor in the gray scale image. SE of the uterine cervix on TVUS was performed during the same US session. The sample box size of the elastogram was adjusted according to the size of the analyzed mass, to encompass as much peritumoral tissue as possible; the used color scale was red (soft), green (medium hard) and blue (hard).

After cross-sectional imaging the patients underwent radiochemotherapy.

At 3-4 months after radiochemotherapy the patients underwent complete re-assessment, by repeating all the above mentioned steps: clinical evaluation, MRI and multimodality US.

All US exams were performed by the same highly experienced examiner (R.B. – more than 35 years experience in pelvic sonography). All MRI examinations were assessed by the same radiologist (Cs.Cs. – with 5 years of experience in pelvic oncologic imaging). The MRI and US assessors were blinded to the results of each other.

After reassessment the patients underwent surgical treatment. Histopathological examination considered microscopic relapse in case of tumors limited to the cervix with size between 10-15 mm and macroscopic relapse for tumors with size larger than 15 mm.

Inclusion criteria consisted of the presence of complete assessment of a patient (clinical, MRI, and US) both pre- and post treatment, with pathologic proof of the tumor and assessment of the operative material. Exclusion criteria were: lack of consent to participate, incomplete data, unavailability of images and/or conclusive pathology report.

Statistical analysis

Mean and standard deviation were used as summary statistic for quantitative variables that proved normal distribution; otherwise median and interquartile range (as (Q1−Q3), where Q1 = first quartile, Q3 = third quartile) were used. Qualitative data were summarized as absolute frequency expressed as number of subjects that accomplished the criterion and relative frequency with associated 95% confidence interval calculated using an exact method [20]. ANOVA test was used to compare qualitative normal distributed data between three groups (as gynecological examination – Gyn, ultrasound examination – US,

and magnetic resonance imaging – MRI). Student t-test for independent samples was used to compare quantitative normally distributed data on two groups. Paired t-test was used to compare values on native examination with post-contrast examination. Z-test was used to compare qualitative data between two groups. Statistica software (v. 8, StatSoft) was used for statistical analysis. A p-value lower than 0.05 was considered statistically significant.

Results

A number of 26 patients were investigated in the study period. All patients met the pre-treatment inclusion criteria. Among them 8 patients were lost at the follow-up. A number of 18 patients had complete MRI examination, but only 8 patients had both MRI and ultrasound complete examinations. Finally eight subjects accomplished the study inclusion criteria and were analyzed. The age of the patients ranged from 32 to 59 years (49±9.38 years). The histopathological diagnosis identified the presence of squamous carcinoma in 7 patients and undifferentiated carcinoma in 1 patient.

All patients were classified as IIB or IIIA, with a significantly higher percentage of patients classified as IIB (75%:25%, p=0.0011). In five out of eight cases (62.50%, 95%CI [26.56−85.94]) the classification of tumor was identical in both clinical and MRI examination.

The usefulness of parametrial invasion detection on clinical, TRUS and MRI examinations was estimated on the pre-therapeutic examinations. In all eight cases parametrial infiltration was diagnosed by all pre-treatment examinations.

No significant differences were recorded in regard of tumor size between clinical, US and MRI exams, either at baseline determination or post-therapy, in native or in post-contrast examinations (Table II).

The pre-treatment tumor size proved to be significantly smaller on post-contrast scanning both in US and MRI examinations, as compared to the native images (p<0,001).

Post therapy, there were no significant differences between native and post-contrast tumor dimensions measured with US; oppositely, significant smaller dimensions were observed on post-contrast MRI as compared to native MRI (Table III).

CETVUS pre-treatment examinations detected increased contrast uptake in all eight cases (fig 1). In the post-treatment examination contrast uptake was present in two cases with no tumoral relapse on histology (fig 2).

Pre-treatment intravaginal SE detected increased hardness – pattern 3 – in all eight cases. In the post-treatment examination elastography detected increased hardness in one case, with macroscopic tumoral relapse on histology.

Macroscopic relapse was proven by pathology in two out of eight patients. Both clinical and MRI examinations recognized the macroscopic relapse while TRUS missed one of the two macroscopic relapses. In this case the in-

Table II. Comparison of diameters between techniques and respectively between native and post-contrast enhancement examinations

Diameter	**Baseline**		**Post-therapy**	
	native	**post-contrast**	**native**	**post-contrast**
AP [mm]				
Gyn	36.88±15.57		6.50±4.41	
US	37.31±10.40	33.38±10.39	7.41±5.54	5.88±4.36
MRI	34.25±14.06	30.63±14.07	9.63±10.46	6.63±9.24
p-value	0.8874[a]	0.3538[b]	0.6829[a]	0.8411[b]
LL [mm]				
Gyn	41.31±13.58		8.75±6.94	
US	36.81±11.59	32.88±10.11	8.00±6.07	6.25±4.71
MRI	41.00±15.94	37.00±14.92	9.50±10.53	6.88±9.99
p-value	0.7701[a]	0.2595[b]	0.9336[a]	0.8360[b]

Gyn = clinical examination; US = ultrasound examination; MRI = magnetic resonance examination; AP = antero-posterior; LL = latero-lateral; [a] ANOVA test; [b] Student t-test

Table III. Post-therapy tumor dimensions comparison: native versus post-contrast.

Diameter	**US**			**MRI**		
	native	**post-contrast**	**p-value**	**native**	**post-contrast**	**p-value**
AP [mm]	7.41±5.54	5.88±4.36	0.0676	9.63±10.46	6.63±9.24	0.0003
LL [mm]	8.00±6.07	6.25±4.71	0.0524	9.50±10.53	6.88±9.99	0.0002

AP = antero-posterior diameter; LL = latero-lateral diameter

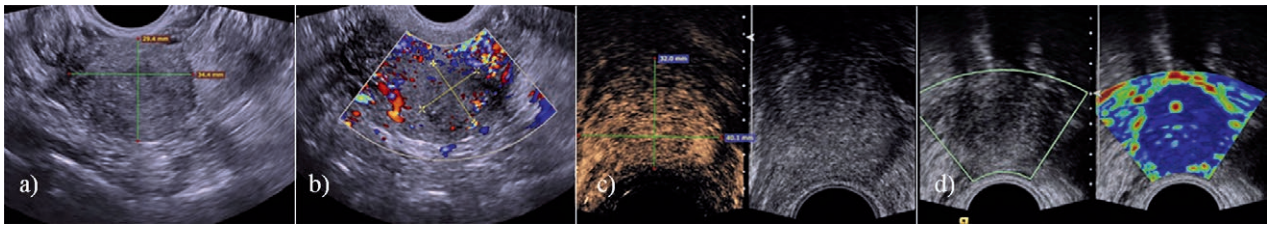


Fig 1. A 48-year-old woman with cervical carcinoma clinically staged as IIIA. Pre- treatment TRUS shows a hypoechogenic tumor with irregular extension in the lateral parametrium (a); color Doppler (b) shows at the level of parametrium the same vascular pattern and density as in the cervical tumor. The rich tumoral vascularization is depicted with CETVUS (c). Increased hardness at the level of the tumor (type 3) is seen on SE (d).

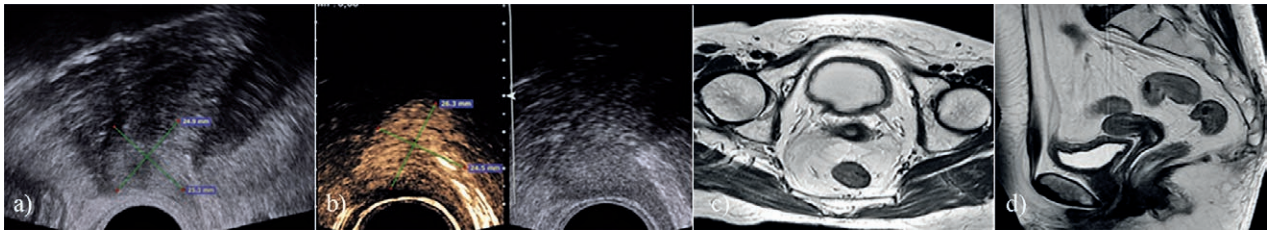


Fig 2. Same patient as in figure 1 after radiochemotherapy. TRUS (a) and CETVUS (b) show a hypoechogenic structure, respectively focal contrast uptake at the level of irradiated cervix. The oblique axial (c) and sagittal T2-weighted MR images (d) show restoration of cervical stroma in hyposignal which is an indicator for tumor free cervix. There was no tumor relapse on pathology.

travaginal elastography described a lesion with increased hardness, but the intravaginal post contrast sonography showed no contrast uptake at the level of the irradiated cervix. Microscopic relapse was proved by pathology in two patients out of eight with perfect match on both gynecological and MRI examinations. TRUS missed one case of microscopical relapse. In this case neither intravaginal SE, nor CETVUS were able to depict any changes. For patients without microscopic relapse on pathology, false positive results were obtained for two patients on gynecological examination, two patients on TRUS and one patient on MRI. Histopathology data confirmed iliac adenopathies in one patient, described by pretherapy and post-therapy MRI.

Discussions

Published data focused on staging cervical cancer by comparing MRI with clinical examination described an accuracy of 47% for clinical examination and 86% for MRI in the study of Ozsarlak et al [21] on 29 patients, and 61.3% for clinical examination and 89.3% for MRI as reported by Dhoot et al [22].

In our study MRI underestimated one case and overestimated another case involving the lower vagina. These staging errors did not influence subsequent therapy. In one case, clinical examination underestimated the stage and did not detect pelvic wall invasion. In this clinically underestimated case, MR staging led to a change of therapy.

Literature data described that TRUS is useful to assess parametrial invasion. In the study of Innocenti et al [11] on 124 patients, sensitivity was 78%, specificity 89%, and diagnostic accuracy was 87%. Similar results were reported by Aoki et al [23] in a study including 30 patients. Published data show that the best modality for detection of parametrial invasion is MRI with an accuracy of 92% reported by Kim et al [24] and 88% reported by Hrickak et al [25].

In our study parametrial infiltration detected on pretherapy gynecologic, MRI, and TRUS (with color Doppler) examinations was corrected indentified in all cases. It has to be mentioned that pretherapeutic TRUS underestimated pelvic side wall invasion, in the same case with the clinical examination.

The tumor size at the time of diagnosis is also essential for subsequent therapy. Mc Carthy et al demonstrated that in tumor larger than 4 cm the optimal choice is radiochemotherapy over surgery, even in the absence of parametrial invasion [26].

In our study on clinical examination in three patients one diameter was over 4 cm and in two patients the tumor dimensions were at the limit of 4 cm. Six of eight patients had endophytic development of the tumor. Extension at the level of the endometrium cannot be assessed clinically. The cranio-caudal dimension and the tumor volume were determined by MRI and TRUS as the techniques are multiplanar. For an accurate comparison of tumor dimension assessment between clinical examination, US and MRI in this study we used only the latero-lateral and antero-posterior tumor size.

Only a few studies have compared clinical examination, TRUS, and MRI pre- and post-therapy in cervical cancer. One of the largest studies so far including 95 patients with early stage cervical cancer, was published by Fischerova et al and it showed comparable accuracy of TRUS and MRI in pre-therapy patients and a superior accuracy of TRUS over to MRI in the post-therapy stage [27]. Pinkavova et al demonstrated that the accuracy of residual tumor detection in advanced stage cervical cancer after therapy is 77% for MRI and TRUS, and the sensitivity is 83% for TRUS and 96% for MRI [28]. Magee et al showed in a study on 81 patients that there is a significant correlation between the tumor size and the stage of the disease [29].

There were no significant differences in regard of tumor dimensions measured with the three examinations used in our study (comparing clinical examination with US and MRI) neither in native and post contrast, nor in pre and post-therapy examinations.

The administration of intravenous contrast medium for cervical cancer assessment is not necessary, as it does not lead to a more accurate staging [30]. The nonenhancing parts from the measured tumor may be related to tumor edema, hypovascular, hypoxic or necrotic tissue.

However, the administration of contrast media pretherapeutically may be useful as an early assessor of the therapeutic response. High contrast uptake indicates high cellularity and oxygenation which, in its turn, may be considered a favorable factor for radio- and chemotherapy. All eight patients included in the study showed contrast media uptake at the level of the tumor on the pre-therapeutic examinations (MRI and US). On the post-therapeutic examinations the lesion size decreased significantly, result which is similar with other published studies [31,32].

The post contrast evaluation of the irradiated cervix is non-specific. Contrast uptake may occur in residual tumor or in post-radiation changes, as well. Helen et al reported that in the first 6 months after radiotherapy, differentiation of recurrent tumor from posttreatment normal appearance of the female pelvis can be difficult [33].

The decrease of tumor size at 2-3 months post-radiotherapy indicates a good therapeutic response. All the patients in the study showed partial or complete response to radiochemotherapy and underwent surgery (radical hysterectomy and pelvic lymphadenectomy). On postoperative pathological examination two patients showed macroscopic relapse, two patients had microscopic relapse and four patients had total therapeutic response without tumor relapse. A microscopic tumor relapse is almost impossible to detect on the clinical, US or MRI examination. In our study most of the false-positive and false-negative results were found in patients with microscopic tumor relapse, with the mention of only one false negative case, on the TRUS examination. In this case the post contrast intravaginal sonography and SE did not detect the tumor relapse. These results are of no clinical importance because in case of microscopic relapse or in tumor free cervix post-therapy, the management is surgery [14].

The use of CETVUS did not lead to a more accurate evaluation of the irradiated cervix. Contrast uptake was present in two cases with no tumor relapse on histology. There was one case of macroscopic relapse missed by the TRUS examination. In this case SE described a lesion with increased hardness, but CETVUS showed no contrast uptake at the level of the cervix.

An important prognostic factor for uterine cervical cancer is the involvement of the lymph nodes. They are not included in the FIGO staging, therefore presence of adenopathies does not change the staging of the disease. In this study iliac adenopathies were detected in one patient, by pretherapy and post-therapy MRI, and were confirmed by histopathology. The size of the adenopathies significantly decreased post-therapy. Both clinical examination and endocavitary US did not detect the adenopathies.

Some limitations of the study must be acknowledged: the limited number of cases was due to difficulties in fulfilling the inclusion criteria and also to the declared feasibility aimed purpose of the study. No intra- and interobserver agreement data are available to the date.

Conclusions

The advantages of TRUS may reside in availability and lower costs. TRUS was accurate for the estimation of pre-therapy tumor dimension, MRI was accurate both in the estimation of pre-therapy tumor dimension and in staging. The post-therapy tumor evaluation was better performed with MRI. The use of intravenous contrast agents on both examinations did not appear to improve the accuracy of tumor diagnostic neither on pre-therapeutic, nor on post-therapeutic examinations. More data are required to assess the usefulness of elastography.

Conflict of interest: none

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