

COMPARISON OF ULTRASOUND AND MRI INFORMATIVENESS FOR DETECTION AND TREATMENT MONITORING OF CERVICAL CANCER METASTASES IN THE VAGINA

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Aim: To assess ultrasound (US) method informativeness in the recurrence detection and treatment monitoring of patients with cervical cancer metastases in the vagina via comparing the US and magnetic resonance imaging (MRI) data. **Materials and Methods:** 42 patients with recurrence of cervical cancer were examined by transvaginal US and MRI. Data on radiation diagnostics of cervical cancer metastasis in the vagina were compared with pathomorphological data. US and MRI data on the metastatic tumors size were compared. **Results:** The diagnostic efficiency of US and MRI for recurrence detection was determined. The sensitivity, specificity and accuracy of US were 92.8; 93.3 and 93.3%, respectively, and of MRI — 95.2; 96.6 and 95.8%, respectively. The informativeness of MRI was higher than US in cervical cancer recurrences detection, but the difference was not significant ($p > 0.05$). US can provide data as informative as MRI for estimation of metastases sizes in the vagina. The mean difference between MRI measurements and US measurements of the metastases volume was 0.79 mm (95% CI 0.62–0.95 cm³). **Conclusions:** US as a cheaper and simpler method could be an alternative for metastases detecting and treatment monitoring, especially if there are contraindications to MRI. **Key Words:** recurrence of cervical cancer in the vagina, ultrasound, MRI.

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Cervical cancer (CC) is the fourth most common cancer in women, ranking after breast cancer, colorectal cancer and lung cancer. The estimated age-standardized incidence of CC is 13.1 per 100,000 women globally. With almost 0.6 million cases and 0.3 million deaths per year, CC continues to constitute a major public health problem [1].

Although radical surgery and radiotherapy represent effective treatment modalities, up to one third of patients will develop progressive or recurrent tumors, the pelvis being the most common site of failure [2]. The relapse rate of CC ranges between 11% and 22% in International Federation of Gynaecology and Obstetrics (FIGO) stages Ib–IIa and between 28% and 64% in FIGO stages IIb–IVa [3]. The treatment of recurrent CC remains challenging, and the prognosis of patients with recurrent CC remains poor, with a 5-year overall survival rate of less than 5%, despite intensive therapy [4].

The main task of long-term patients dynamic monitoring after treatment is timely detection of the recurrence. The aim of surveillance is to detect relapse at a stage when salvage treatment has the best chance of being effective and to monitor and minimize treatment-related toxicity after the last primary treatment, since approximately 50% and 75% of CC recurrence cases occur within the first one and two years after primary treatment, respectively [5, 6]. Recurrent CC can be present as a local recurrence or as metastatic disease. Metastatic disease will de-

velop in 15% to 61% women with CC, usually within the first two years after completing treatment [7]. Mostly, the recurrences occur in the pelvic cavity, primarily on the vagina cult.

In addition to clinical, gynecological examination, colposcopy, histological examination, radiological diagnostic methods are used to detect disease progression, assess the process spread and accurately determine the metastatic tumors sizes [8]. Magnetic resonance imaging (MRI) is considered the most informative for CC study [9–11]. It has a higher sensitivity for the assessment of soft tissue and at present is considered the most informative method for the vaginal pathology evaluation. High soft tissue contrast in MRI allows examining in detail the vagina and the degree of its involvement in the tumor process, forming the basis for chemotherapy planning and objective assessment of tumor regression due to the treatment. However, the high cost of the examination, the need to use contrast agents, the impossibility of examining patients with excessive weight, claustrophobia, artificial heart rate drivers, metal implants, etc., limit the use of MRI. It has been shown that ultrasound (US) method provides information comparable to MRI in CC assessment in the hands of experienced diagnosticians [12–14]. But its effectiveness for the vaginal tumors diagnosis is considered as low. However, due to the development of diagnostic equipment it becomes possible to qualitatively visualize not only the uterus with appendages, but also the vagina, detect the tumors, determine their size and extent.

The aim of present study was to determine the informativeness of US method in the recurrence detection and patients with metastases of CC in the vagina and treatment monitoring by comparing the US and MRI data.

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Abbreviations used: ADC — apparent diffusion coefficient; CC — cervical cancer; CDI — color Doppler images, CE — contrast enhancement; FIGO — International Federation of Gynaecology and Obstetrics; MRI — magnetic resonance imaging; PDI — power Doppler images; T2WI — T2-weighted imaging; US — ultrasound.

MATERIALS AND METHODS

The study included 42 patients with recurrence of CC examined and treated at the National Cancer Institute, between April 2018 and April 2021. The distribution by stages of CC by FIGO (2018) was: IB3 — 10, IIA — 14, IIB — 6, IIIC — 12 patients by stages of CC by TMN (2006): T1b3N0M0 — 10, T1b3N1M0 — 6, T2aN0M0 — 14, T2aN1M0 — 4, T2bN0M0 — 6, T2bN1M0 — 2 patients. Morphological structure of CC: 34 — squamous cell carcinoma, 6 — adenocarcinoma, 2 — adeno-squamous cell carcinoma. The control group consisted of 30 patients with surgically treated CC stages IV–IIIC without signs of disease progression. The diagnosis of CC localized forms IB3–IIA was considered as the indication for surgical treatment. In patients with IIB–IIIC, the treatment was started with an adjuvant course of chemotherapy, and after reduction of the volume of tumors, surgery was performed according to radical program.

After treatment, follow-up examinations, including gynecological examination, US and MRI, were performed in the following terms: the first and second years — every 3 months, the third year — every 6 months, then — annually. Vaginal metastases in patients enrolled in this study were detected during gynecological and radiological examinations. In all cases, a biopsy of the tumor in the vagina was performed and the presence of a metastatic tumor was confirmed histologically.

Chemoradiation treatment of metastases was provided according to the approved protocols. Patients received radiotherapy on a Clinac-2100 CD linear electron accelerator (total focal dose of 40 Gy). For high dose rate brachytherapy, ^{192}Ir sources (apparatus “GammaMed plus IX”) were applied. During the course of radiotherapy, patients of all groups received chemotherapy — Ftorafur orally 400 mg · 2/day and cisplatin 50 mg · 1/week intravenously No 4–6, total dose 200–300 mg. No surgery for removing vaginal metastases was performed.

Prior to treatment, all patients underwent US and MRI examinations to determine the size and volume of the tumors. A similar study was performed 2 weeks after the end of each course of combined radiation therapy on the background of the chemoradiomodifiers use to re-determine tumors parameters for assessment of the treatment effectiveness.

All patients underwent a complex radiological examination: transvaginal US (standard methods) — on diagnostic US devices Esaote-30 and GE Voluson S6 with a transvaginal transducer, and MRI — on a Philips (Intera) tomograph with a magnetic field voltage of 1.5T, with contrast enhancement (CE) by gadolinium preparations in the standard dosage (0.2 ml/kg body weight). The MRI protocol consisted of turbo spin-echo T2-weighted image (T2-WI) in the sagittal, coronal and axial oblique sequence; turbo spin-echo T1-weighted image (T1-WI) in the axial oblique; transversal CE T1-WI and diffusion-weighted imaging in the axial plane with b-values of 0, 400 and 800 s/

mm² and pre-contrast apparent diffusion coefficient (ADC) maps. The maximum term between US and MRI was 2 week. The written informed consent for participation in the study was obtained from all the patients at enrollment.

As a whole, 236 control examinations were performed during these observations (all patients underwent a control examination several times). However, this ultrasound color (CDI) and power (PDI) Doppler images study included only 72 examinations (42 of them — when the presence of metastases in the vagina was confirmed by histological examination, and 30 examinations of patients in the control group, when the absence of recurrence in the vagina was confirmed morphologically).

MRI and US allows us to determine the presence of the tumor, its size, the spread of the tumor into the vagina surrounding tissues and changes in the metastatic tumor parameters due to chemoradiation.

The volumes of metastatic vaginal tumors were calculated by the formula:

$$V = 0.52 \cdot a \cdot b \cdot c$$

where V is the volume of the metastatic tumor;

a, b, c — the maximum orthogonal sizes of the metastatic tumor.

US and MRI data on the metastatic tumors size were compared with each other and with the clinical course of the disease and morphological data. As there was no surgical removal of the metastases, the results of metastatic tumor volumes determination by radiological methods could not be compared with histological data. Doctors performing US and MRI examinations have more than 15 years of experience in this area. The researchers did not know the results of each other's studies at the time of the survey.

To estimate the correlation between the results of various diagnostic modality, McNemar test was used, $p \leq 0.05$ was considered statistically significant. To assess the agreement between the sonographic and MRI measurements of metastatic tumor volumes, the mean difference between the two measurements and the confidence limits were calculated as described by Bland and Altman [15]. Cases, when the imaging method showed no tumor at all were excluded from this analysis. To assess systematic bias, the 95% CI for the mean difference between the two methods was calculated. Statistical calculations was performed using Software STATISTICA, Version 13.0. Two-sided $p < 0.05$ was considered statistically significant.

RESULTS

In the absence of disease progression after CC therapy, the vagina on US and MRI images was homogeneous in structure, with clear and smooth contours. The walls of the vagina were uniformly thick up to 8–10 mm. On MR scans, the vagina had an average intensity of MR signal on T2-WI. On postcontrast T1-WI scans the walls of the vagina moderately accumulated contrast agent. In the absence of the disease continuation in the vagina, there were registered mod-

erate number of vessels, which were oriented in parallel to the vaginal walls and had smooth course. Spectrography of the vessels of the vagina, established that the maximum systolic blood flow velocity (V_{max}) was 5–10 cm/s, the resistance index (RI) 0.5–0.7.

Vaginal metastases were detected during the first two years after treatment. Mostly recurrent tumors were localized in the upper vagina (36 patients), less often — in the lower third of the vagina (8 patients).

The high contrast of soft tissues makes it possible in MRI to study in detail the vagina and the degree of its involvement in the tumor process. Metastatic tumors on MRI were visualized as hyperintensive formations in comparison to the hypointense undamaged part of the vagina on T2-WI, with violations of the contours (72.7%), and the vagina structure (81.8%), vaginal wall local thickening (85.4%), with intensive accumulation of contrast agent on postcontrast images (87.0%) and diffusion restriction on ADC maps. The presence of hemorrhages within the lesion was determined by the presence of areas with increased signal on T1-WI. The tumor spread into the paracolpos was determined by the appearance of irregular wedge-shaped zones, which had a reduced signal compared to a high signal from fat (Fig. 1). The maximum orthogonal size of the tumor was determined on the T2-WI in the sagittal and axial planes for its volume calculation [16, 17].

On US images, metastases appears as solid lesions, predominantly hypoechoic structures, with

uneven contours. US, in contrast to MRI, can detect not only tumor vascularization increase, but also a change in angioarchitectonics in the affected part of the vagina. In these lesions, there is a new growth of pathological vessels with the changed walls. The latter cannot be considered complete due to incomplete differentiation, but they provide a sufficient blood supply for further tumor development [18]. A characteristic feature of neoplasms on US images is not only an increase in the intensity of their vascularization, but also a change in vascular architecture, the presence of multiple atypical, chaotically located microvessels and arteriovenous shunts. Such vessels have very low peripheral resistance, and (spectrographically registered) low-resistance blood flow and high systolic velocity V_{max} 30.0 ± 9.1 cm/s, RI 0.5 ± 0.1 (Fig. 2). The maximum sizes of tumors were measured on US images: cranial-caudal and antero-posterior in the sagittal longitudinal section of the vagina, transverse in the axial cross-section of the vagina.

Based on the results of the US and MR-criteria, CC was detected or not detected. Cases of correct CC recurrence detection were considered as truly positive conclusions, and cases of correctly defined disease absence of progression was considered as truly negative conclusions. False cancer recurrence detection was considered as false-positive conclusions, and cases with absence of disease progression visualization were considered as false-negative conclusions (Table 1).

As can be seen from Table 1, recurrence (true positive conclusions) was correctly detected by US in 39 patients and by MRI — in 40 patients (Fig. 3).

Missed cases of cancer recurrence happened with the use of both methods in two patients with superficial lesions of the vaginal mucosa. In another patient, a metastasis in the lower third of the vagina was missed on US but detected on MRI.

In 2 patients, it was necessary to differentiate tumor recurrences from inflammatory changes, which are also characterized by an increase in organ size, heterogeneity of structure and increased vascularization. US revealed a false positive conclusion about the

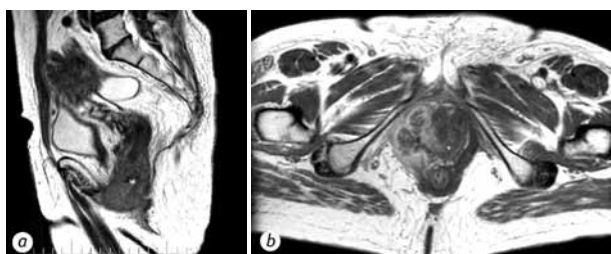


Fig. 1. MR scans of cervical metastases T3b in the vagina: metastatic tumor at the vagina entrance in the form of hyperintensive formation on T2-WI with vagina contours violations (a), with intensive accumulation of contrast agent on the postcontrast images (b)



Fig. 2. Cervical cancer T2b, sonograms of metastatic tumor near vaginal dome, expanding to the posterior wall of the bladder (a), with CDI — atypical blood flow in the tumor (b)

Table 1. Performance of US and MRI examination in correctly detecting CC recurrence, confirmed by histology

Method	Surveys number n	Results of the methods, n				Diagnostic efficiency, %		
		Truly positive	False negative	False-positive	Truly negative	sensitivity	specificity	accuracy
US	72	39	3	2	28	92.8	93.3	93.0
MRI	72	40	2	1	29	95.2	96.6	95.8

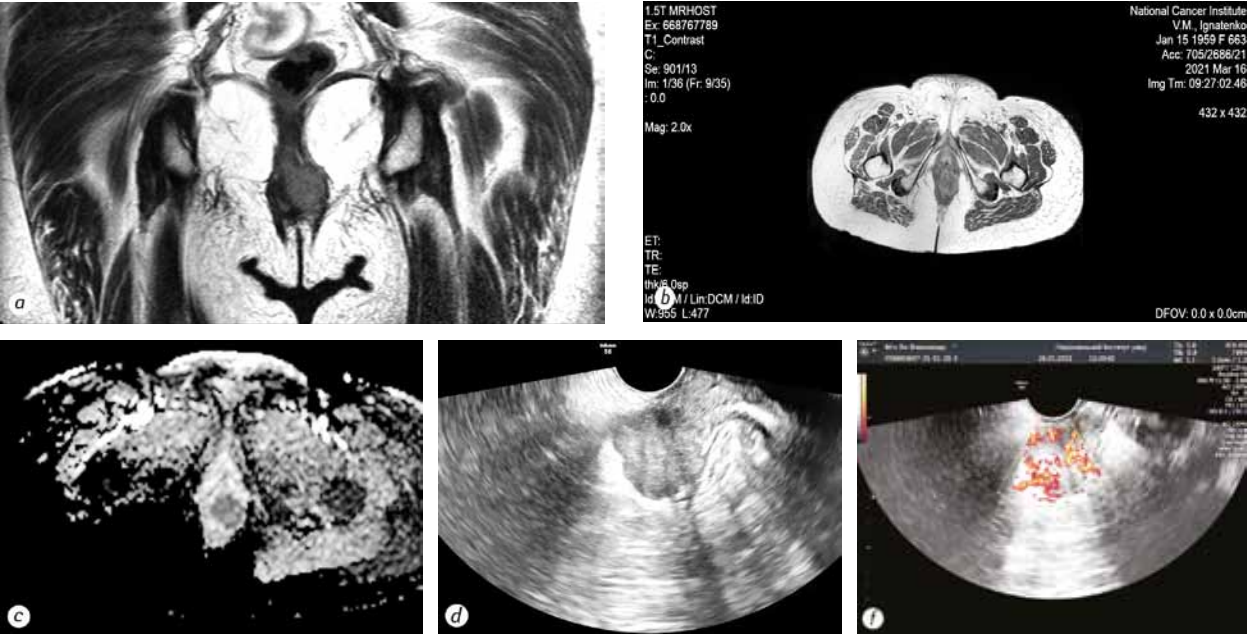


Fig. 3. Metastatic tumor in the vagina in the form of hyperintensive formation on the coronary T2-WI (a), which accumulates a contrast agent on postcontrast scans (b) and demonstrates a restriction of diffusion on the ADC map (c). On the sonogram, metastasis is visualized in the form of a solid formation with bumpy contours (d) with intense vascularization (e)

presence of cancer recurrence, which was simulated by inflammatory changes. MRI in one of these cases ruled out recurrence.

Based on the analysis of the diagnostic efficiency indicators of US and MRI in the detection of CC recurrence were determined. Thus, the sensitivity, specificity and accuracy of US were 92.8; 93.3 and 93.3%, respectively, and for MRI — 95.2; 96.6 and 95.8%, respectively.

We performed a statistical significance analysis of the informativeness discrepancies between the US and MRI CC recurrence detection by McNemar tests. The obtained results are shown in Table 2.

Based on the statistical analysis, it was determined that the MRI informativeness is higher than US in the CC recurrence detection, but the difference was not significant. No statistically significant differences were between the two diagnostic techniques, for CC recurrence correct detection (McNemar’s test).

One of the tasks of our study was determination of the US and MRI possibilities in radiological moni-

toring of conservative treatment effectiveness. For this aim, patients with recurrence during and after conservative therapy were examined.

Studies during conservative treatment are extremely important because accurate assessment of the tumor response to conservative therapy is a necessary condition for timely correction of the treatment. The treatment effectiveness is assessed by tumor size changes. According to the Response Evaluation Criteria in Solid Tumors complete regression was recorded with tumor disappearance, partial regression — with tumor reduction of at least 30%, disease progression — with tumor growth of at least 20%, stabilization of the process — when the disease dynamics does not meet the above criteria.

In our study, positive dynamics of treatment was noted in 33 cases from 42, of which complete regression of the disease was registered in 20 patients, and partial regression in 13 patients. In cases of complete regression, the tumors were not detected, while in cases with partial regression — persisted residual tumor infiltration, which was gradually replaced by fibrosis within one or two months after the end of treatment (radiation therapy effect delayed realization). On the contrary, in 9 patients the treatment response was not obtained: in 7 patients the stabilization of the neoplastic process was registered, in 2 patients the tumor growth was detected at the background of the treatment.

We compared the radiological methods data at different terms: before, during and after conservative

Table 2. Statistical significance analysis of the informativeness discrepancies between the US and MRI in the detection of CC recurrence by McNemar’s test

False/true results of US and MRI		0	1
1		3	2
	(cases of false results of both US and MRI)	0	67
0		(cases of true results of US, but false of MRI)	(cases of true results of both US and MRI)
Statistical analysis	McNemar’s test = 2.0; $p = 0.158$		



Fig. 4. MR-monitoring of treatment response of vaginal metastasis therapy: *a* — before treatment — hyperintensive formation (54 mm in diameter) with bumpy fuzzy contours is visualized in the vagina; *b* — after therapy stage 1 — tumor size reduction up to 26 mm in diameter; *c* — after whole treatment course — vagina with smooth walls, tumor is not detected

treatment of patients with metastatic tumors in the vagina.

Analyzing the US and MR images, we found that effective treatment, in addition to reducing the volume of the tumor, also normalizes the structure and contours of the vagina. In case of tumor regression, MRI registered tumor tissue MR signal intensity decrease on T2-WI, vagina normal zonal anatomy restoration, contrast agent accumulation intensity decrease on postcontrast T1-WI. A decrease in tumor invasion into the paracolpos, a decrease in the intensity of the MR signal from tumor tissue on T2-WI, a decrease in the intensity of contrast accumulation on postcontrast T1-WI were also MR signs of tumor regression (Fig. 4).

US data on recurrent tumors regression due to conservative treatment, in addition to tumor volume reduction, were clearer, smooth contours, more homogeneous structure of the vagina, normalization of blood flow. During treatment monitoring, blood flow parameters changes were observed: vascular loci number decrease, normalization of vascular bed architecture, decrease in Vmax, and increase in RI. At tumor regression, single vessels with low systolic velocity Vmax 6.0 ± 1.1 cm/s and RI 0.69 ± 0.1 were registered (Fig. 5).

Tumor volume was determined at each US and MR examination. To compare the US and MRI informativeness for treatment monitoring of CC metastases, only the data of those 39 patients in whom metastatic tumor was visualized by both methods were taken into account. A total of 78 examinations were performed on these patients during conservative treatment (each patient was examined twice: before and after treatment). But 18 examinations, when the tumor completely regressed and was not detected by US and MRI, were excluded from the study, so this study included 60 examinations, when the volume of metastatic tumor was measured by both methods (Fig. 6).

Before treatment, the average formation size according to US was $24. \pm 1.2$ cm³ (5.3–70.1 cm³), and according to MRI — 25.7 ± 1.4 cm³ (6.1–71.6 cm³). After partial regression, the average formation size according to US was 12.3 ± 1.2 cm³ (4.2–28.9 cm³), and according to MRI data — 12.7 ± 1.3 cm³ (4.5–28.0 cm³). With the tumor process progression, the average for-

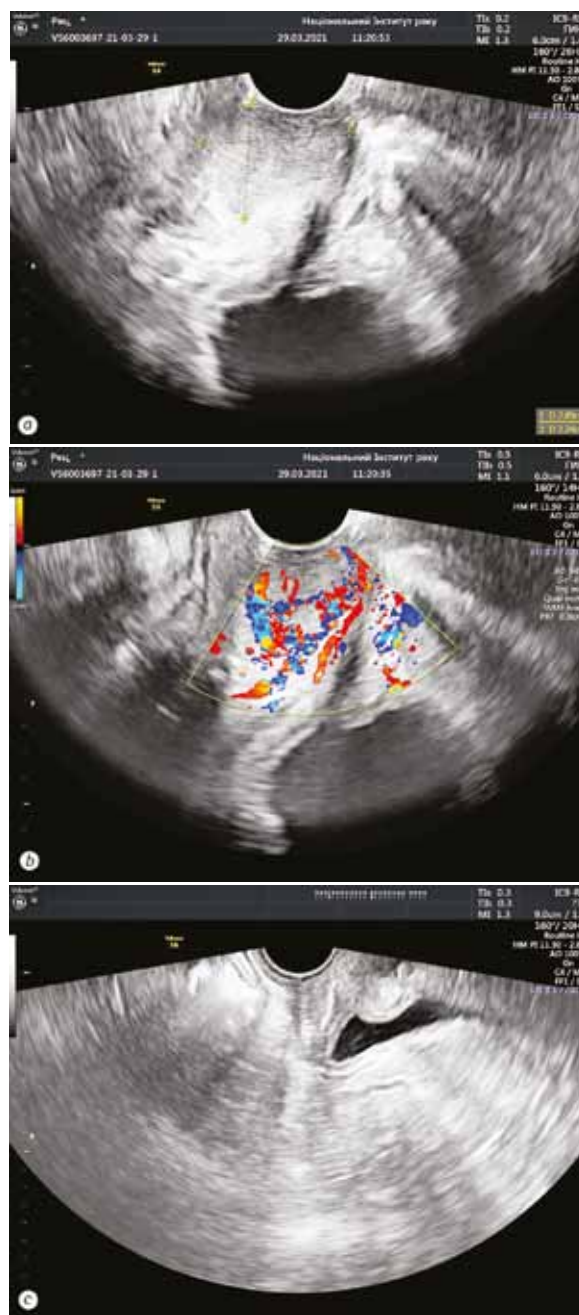


Fig. 5. Sonograms of monitoring of vaginal metastases after chemotherapy: *a* — before treatment, in the vagina a formation with bumpy fuzzy contours is visualized; *b* — with atypical blood flow on the CDI; *c* — after treatment — vagina with smooth non-thickened walls, the tumor is not defined, the vagina vascularization is not changed

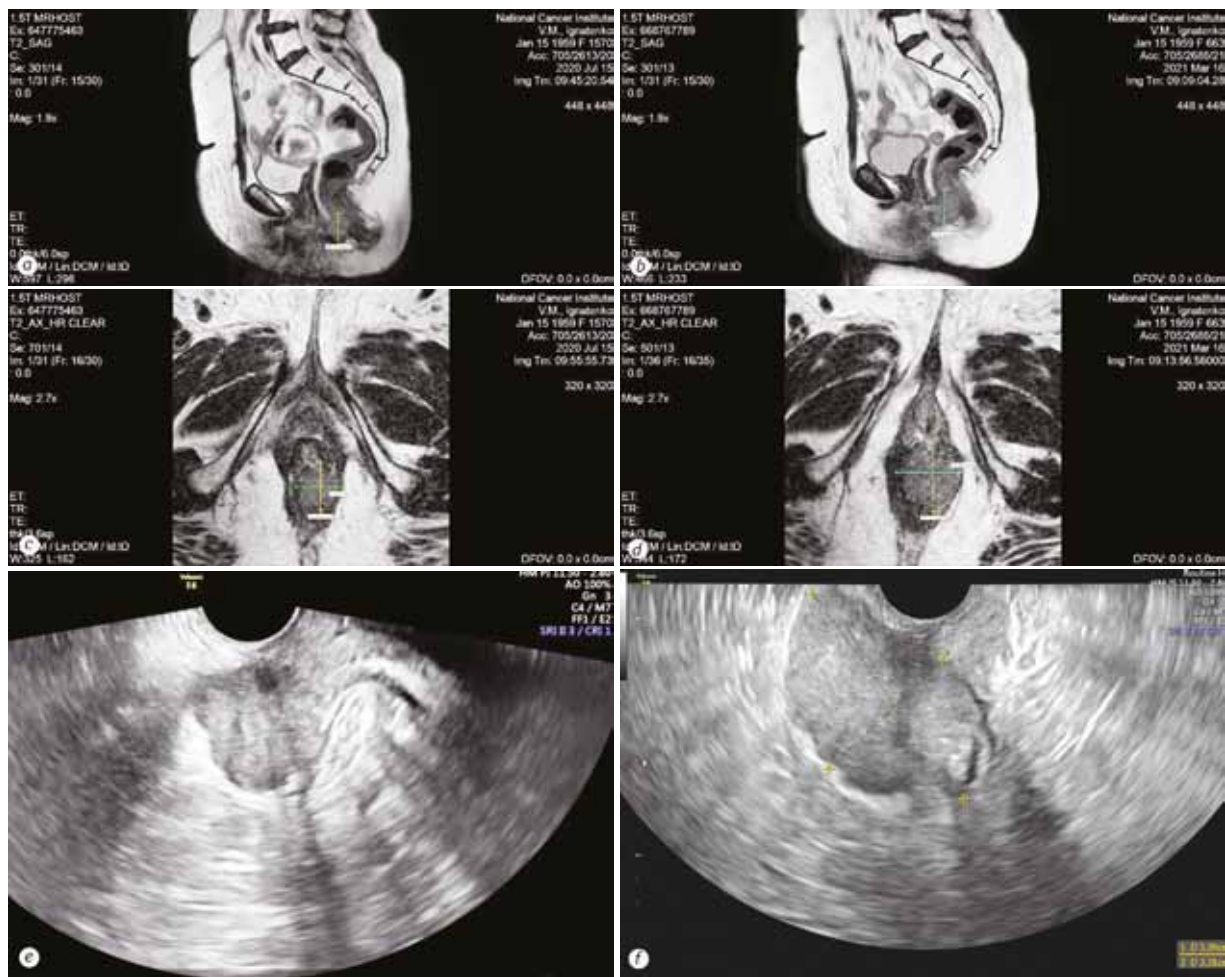


Fig. 6. MR scans and sonograms for monitoring of vaginal metastatic tumors after chemotherapy. Tumor progression: before treatment — vaginal metastasis, which grows to the rectum on the sagittal (a), axial (c) T2-WI MR scans and sonogram (e); after treatment — vaginal metastasis size increasing on the sagittal (b), axial (d) T2-WI MR scans and sonogram (f)

mation size according to US was 56.9–87.4 cm³, and according to MRI — 58.5–88.2 cm³.

The differences between the results of tumor volumes measurements by US and MRI were analyzed by the method of Bland and Altman. The Bland — Altman plot of US and MRI measurements of tumor volume, including only those patients in whom both MRI and US examination showed a tumor (n = 60),

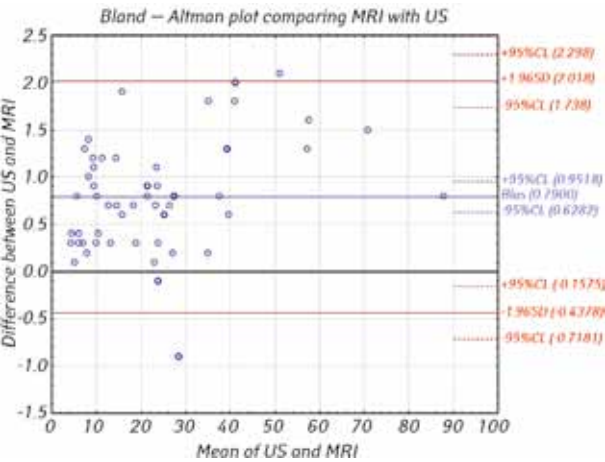


Fig. 7. Bland — Altman plot of tumor volume measurements obtained using MRI and US

is shown in Fig. 7. The mean difference between MRI and US measurements of the tumor volume was 0.79 mm (95% CI from 0.62 to 0.95 cm³).

DISCUSSION

Numerous studies have examined the role of different methods in the diagnosis of recurrent CC. Mostly, to detect the disease continuation MRI, computed tomography and positron emission tomography/computed tomography are recommended among radiation methods. According to National Comprehensive Cancer Network Guidelines Version 1/2021 Cervical Cancer, US method is not recommended for postoperative patients monitoring [19].

At the same time, US is an inexpensive, simple and accessible method of primary imaging. In multiple studies, US has been shown to be as good as MRI and other radiation techniques in assessing primary cervical tumors [20]. It was demonstrated that in hands of experienced specialist US informativeness could be comparable with MRI [12, 13, 21].

In subsequent observations, Csutak *et al.* [22] compared the accuracy of US and MRI in assessing the size of a cervical tumor and concluded that “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”.

Perniola *et al.* [23] investigated the informativeness of US for CC parametrial invasion assessment and concluded that 2D/3D TV-US can be considered accurate in the evaluation of parametrial infiltration while assessing the response to neoadjuvant chemotherapy. The accordance between US and MRI was 94%. The sensitivity of US for parametrial status was 93.8%, with a positive predictive value of 97.8%, using MRI as the standard. The correlation between US and MRI was statistically significant.

Yi Zhu *et al.* [24] compared 360° 3-D transvaginal US and MRI for assessment of vaginal invasion in CC and showed that these methods are in good accordance in CC vaginal invasion assessment (97.2%, kappa 0.873).

However, there are few studies comparing the research opportunities of different radiation techniques for assessing CC recurrence.

Thus, Chao *et al.* [25] compared the informativeness of US, MRI, computed tomography and positron emission tomography/computed tomography in screening postoperative patients. In their study, although primary and secondary imaging detected the same number of recurrences, they did not show any advantages of US compared with other radiation methods.

We did not find any studies on comparative evaluation of US and MRI methods informative values for measuring CC recurrences sizes in the vagina during treatment monitoring.

Previously, it was shown that MRI is the most informative method for detecting vaginal pathology. High contrast resolution and multiplanar capabilities have made MRI the modality of first choice in the diagnosis of vaginal metastases [26].

According to the studies of Soo *et al.* [27], although US and MRI often play complimentary roles, MRI is now the predominant imaging modality. It is often superior to both US and computed tomography because of its ability to produce nondegraded multi-planar images and superior contrast resolution.

In our study, we evaluated the informativeness of two diagnostic methods, i.e. US and MRI, in aspect of CC recurrence correct detection, using histology as the gold standard. Our results showed that US and MRI have a comparable level of diagnostic efficiency in assessment of disease continuation. When detecting CC recurrence, the informativeness of MRI was higher than that of US, but the difference was not significant. When measuring the volume of metastatic tumors, the average differences between US and MRI data were small. These results confirm earlier findings that US may be an alternative to MRI for assessing CC vaginal lesions [12, 13, 21–24, 28]. In addition, US is more convenient and less expensive than MRI.

It seems expedient to continue assessing effectiveness of the US method in other vaginal oncopathologies on a larger number of patients.

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ПОРІВНЯННЯ ІНФОРМАТИВНОСТІ МЕТОДІВ УЗД ТА МРТ ДЛЯ ВИЯВЛЕННЯ ТА МОНІТОРИНГУ ЛІКУВАННЯ МЕТАСТАЗІВ РАКУ ШИЙКИ МАТКИ У ПІХВІ

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Основним завданням спостереження за пацієнтами після оперативного лікування раку шийки матки є своєчасне виявлення рецидиву захворювання. **Мета дослідження:** Визначення інформативності ультразвукового дослідження (УЗД) у виявленні рецидивів та моніторингу лікування хворих з метастазами раку шийки матки в піхву шляхом порівняння даних УЗД та магнітно-резонансної томографії (МРТ). **Матеріали та методи:** Обстежено 42 пацієнтки з рецидивом раку шийки матки за допомогою УЗД та МРТ. Дані променевої діагностики порівнювали між собою та з даними патоморфологічного дослідження. **Результати:** Визначено діагностичну ефективність УЗД та МРТ для виявлення рецидивів. Чутливість, специфічність і точність УЗД становили 92,8; 93,3 і 93,3% відповідно, а для МРТ — 95,2; 96,6 і 95,8% відповідно. Інформативність МРТ була вищою за УЗД у виявленні рецидивів раку шийки матки, але різниця не була значущою ($p \geq 0,05$). Було визначено розміри метастатичних утворень за допомогою УЗД та МРТ до, під час та після закінчення променевої терапії. Дані УЗД і МРТ практично однаково інформативні для оцінки розмірів метастатичних пухлин у піхві. Середня різниця між вимірюваннями об'єму пухлини за даними МРТ та УЗД 0,79 см³ (95% довірчий інтервал 0,62–0,95 см³). **Висновки:** УЗД як більш дешевий і простий метод може бути альтернативою виявлення метастазів і моніторингу лікування, особливо за наявності протипоказань до МРТ. **Ключові слова:** рецидив раку шийки матки в піхві, УЗД, МРТ.