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RADIATION RESEARCH TO DETERMINE LOCAL TUMOR INVASION IN PATIENTS WITH CERVICAL CANCER

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The main task of radiation study of verified cervical cancer (CC) is tumor spread assessment because of its profound effect on the treatment tactics choice and prognosis. *The Aim* of the study was radiation study optimizing for tumor local spread assessment in patients with CC via comparing the usefulness of different magnetic resonance imaging (MRI) based approaches. *Materials and Methods*: 62 patients with CC were examined by MRI on tomograph 1.5 T using contrast enhancement and diffusion-weighted imaging (DWI). Pre-operation data on radiation diagnostics of tumor spread were compared with surgical and pathologic data. *Results*: The diagnostic efficiency of different methods of radiation testing for assessment of local tumor spread in patients with CC was determined. The use of contrast enhancement didn't increase an informative value of MRI in assessment of local tumor spread. False overestimation of tumor spread was caused by intense accumulation of contrast substance around the tumor due to inflammation. Use of DWI allowed to reduce the number of false positive results, and significantly increased the efficiency of MRI ($p < 0.05$): the positive predictive value, sensitivity, specificity and accuracy were 83.3; 90.9; 96.0 and 95.1%, respectively. *Conclusions*: The use of DWI increases informativeness of MRI in assessment of local tumor spread.

***Key Words*: cervical cancer, local tumor invasion, radiation diagnostics, ultrasound, MRI, contrast-enhanced images, DWI.**

With verified cervical cancer (CC), the main task of radiation studies is tumor spread evaluation because of its profound effect on the treatment tactics choice and prognosis [1, 2]. Treatment planning depends on the stage of the disease. The presence of tumor invasions in the parametrium and vagina are of primary importance for the CC stage determination [3].

It is known that among diagnostics techniques magnetic resonance imaging (MRI) is the preferred imaging modality in the CC examination, since this method is more sensitive in soft tissues investigation than ultrasound or computed tomography [2, 4].

T2-weighted (T2W) imaging is the reference sequence for CC staging [1, 5]. Since water gives an intense signal on T2W, and there is a lot of free water in the tumors, they show a high signal intensity on the MRI of T2W, contrasting with the cervical stroma with low signal intensity. However, with some pathologic states, for example, inflammation and edema, which are also characterized by an increased water content and have an intense signal on T2W, a high self-contrast image may not be sufficient for the differential diagnosis of pathological changes [4, 6]. In order to enhance the differences between healthy and pathologically altered tissues, contrast agents and diffusion-weighted imaging (DWI) are used [2]. Paramagnetic contrast molecules cause changes in local field strength and, thus, reflect tumors microvascular network [7]. As a rule, signal intensity in cervical tumor are higher in comparison with these in cervical epithelium and stroma, which helps to differentiate tumors [2]. However, the use of gadolinium-based contrast substances is unfavorable in the cases of renal failure, allergy, pregnancy, causes a lot of side effects [8, 9], and increases the cost of the survey. DWI reflects cellular density. Recent studies have suggested that DWI and apparent diffusion coefficient (ADC) maps can be potentially useful for oncologic diagnostics [9, 10]. There is a lot of works on the MRI use in the CC studies. However, there is no consensus on the usefulness of contrasting and DWI for local tumor spread assessment in patients with CC. We found no reports comparing the effectiveness of conventional native MRI sequences with contrast and DWI for detection the CC invasion into the parametrium and vagina.

The aim of the study was an optimization of radiation assessment of local tumor spread in patients with CC via comparing the usefulness of different MRI sequences (conventional native sequences, with contrast and DWI).

MATERIALS AND METHODS

***Patients*.** In the study were enrolled 62 patients with CC, treated at the National Cancer Institute (Kyiv, Ukraine) from January, 2016 to October, 2017. The distribution by CC stages was as follows: Tis — 2 (3.2%), T1a1 — 3 (4.8%), T1a2 — 2 (3.2%), T1b1 — 17 (27.5%), T1b2 — 16 (25.9%), T2a — 19 (30.6%), T2b — 3 (4.8%) patients. By morphological structure of the tumors, 54 (87.1%) cases were squamous cell carcinoma, 6 (9.7%) cases — adenocarcinoma, 2 (3.2%) cases — adeno-squamous cell carcinoma. All patients underwent tumors surgical removal of the tumors: by cone resection — 1 patient, trachelectomy — 3 patients, hysterectomy — 58 patients. 3 patients with T1b2, 18 patients with T2a and 3 patients with T2b were treated by neoadjuvant chemotherapy. All patients provided a writtten consent on the use of their data for scientific research.

***Data acquisition*.** All patients were examined by MRI on tomograph 1.5 T. The MRI protocol consisted of turbo spin-echo T2W sequence (TR/TE 3000 ms/90 ms; matrix size 300 × 261; slice thickness 4.0 mm; gap

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Abbreviations used: ADC – apparent diffusion coefficient; CC – cervical cancer; CE – contrast enhancement; DWI – diffusion-weighted imaging; MRI – magnetic resonance imaging; T2W – T2-weighted imaging; TR/TE – time repetition/time echo.

1.0 mm) in the sagittal, coronal and axial oblique (perpendicular to the cervical canal) sequence; turbo spin-echo T1W sequence (TR/TE 559 ms/10 ms; matrix size 300 × 261; slice thickness 4,0 mm; gap 1.0 mm) in the axial oblique; transversal contrast enhancement (CE) T1W (after an injection of gadoteric acid at a dose of 0.1 mmol/kg of body weight followed, and scanning was conducted at 60 s after the injection), DW-images (TR/TE, 1389 ms / 66 ms; matrix size 124 × 124; slice thickness 6 mm; gap 1.5 mm; R factor 2; flip angle 90°) in the axial plane with b-values of 0, 400 and 800 s/mm^2 and pre-contrast ADC maps were automatically calculated from the b = 0 and b = 800 s/mm^2 DWI series using special software. DWI was analyzed qualitatively according to the signal intensity of uterine CC, as determined by visually comparing the signal intensity with the myometrium signal. ADC maps were also analyzed qualitatively. The period between the completion of the course of chemotherapy and MRI was at least 2 weeks.

Data analysis. The presence of local tumor spread into the parametrium and vagina was assessed. The results of tumor spread evaluation into the lymph nodes were not included in this study. Three separate sets of images were analyzed: only native images (Native MRIs), only CEs and DWI sequences (evaluated together with T2W). Pre-operation radiation diagnostics results of tumor spread were compared with surgical/pathologic result. Data from radiation research were evaluated as follows:

- true-positive — correctly identified and histologically confirmed cases of the CC invasion outside the uterus;
- true-negative — cases of correct determination of the absence of CC invasion;
- false-positive cases, when the invasion of the CC determined during the MR-study was not confirmed by surgical/pathologic result. Also, the cases were included if the invasion was correctly detected in one organ, but excessively in another;
- false-negative cases, when CC invasion was not detected in MR-study, but then was detected histopathologically.

Statistical analysis was performed using Software STATISTICA, Version 10.0 (portable). For estimation of the correlation between the results of diagnostics techniques and the surgical/pathologic results, χ^2 Pearson method was used, while for estimation of significance of the differences between methods nonparametric test (McNemar two-tailed test) was used. $p \leqslant 0.05$ was considered statistically significant.

RESULTS

Among 62 examined patients with CC, the spread of the tumor process was revealed in a histopathological study in 11 cases (in 3 cases — only in the parametrium, in 8 cases — only in the vagina).

With clinically established cervical Tis1a, MRI allowed to exclude the invisible in clinical investigation endophytic form of cancer invasion to avoid the incision passage through the tumor during conization of the cervix and trachealectomy. It is known, that CC stage T1a is not visible on MRI, but exclusion of an advanced invasive tumor is important for assessing the feasibility of uterus-preserving surgery [4, 6].

In 10 from 11 cases, the presence of invasion was correctly diagnosed with all MRI sequences.

Tumor invasion into the parametrium was diagnosed by the violation of the hypointense ring of the peripheral cervical stroma on T2W, the spiked tumor-parametrial boundary, the presence of hypertensive on T2W tumor masses in the parametrium, that could be estimated as rings of the spread of the tumor [1, 6, 11, 12]. Tumor tissue demonstrated contrast increased accumulation on CE. Tumors with high cellularity were characterized by a combination of hyperintensity in images with a high value of b and a corresponding low intensity on ADC maps [2, 9].

In 1 case, the invasion of CC was not detected in any sequence, since there was a superficial "spreading" invasion of the tumor on the vaginal mucosa, ulcerative by nature.

Hyperdiagnosis of CC invasion took place in 6 patients with native MRI: in 4 cases — on the parametrium, in 2 — on the vagina (Fig. 1).

All false positive results obtained on native sequences remained false after paramagnetic administration.

In addition, the use of contrasting added two false positive results: in 1 case — in the parametrium, in 1 — in the vagina (Fig. 2).

Histopathological examination of these patients detected inflammatory changes, necrosis and hyperemia of tumor surrounding tissues. Such conditions obviously simulate tumor infiltration [4, 6, 9, 12].

The false overestimation of the tumor invasion stage in postcontrast scans was due to the intensive accumulation of contrast agent around the tumor due to increased

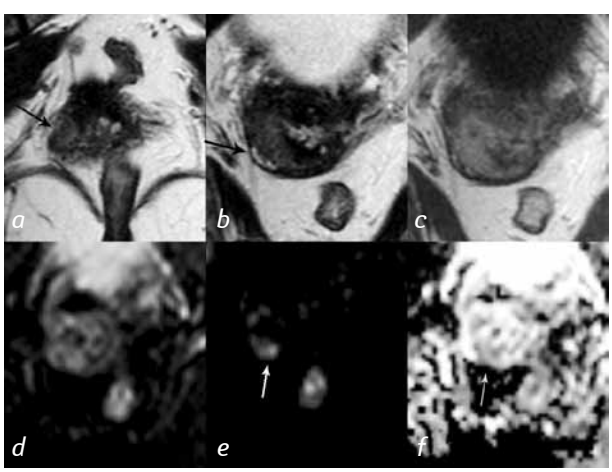

Fig. 1. Pelvic MRI of patient with CC T1b without invasion. On the coronal (*a*) and axial (*b*) T2W images there was a violation of the border between the tumor and right parametrium (black arrows), on CE (*c*) contrast intense accumulation in this zone was detected, which simulated the tumor invasion into the parametrium, but at DWI b = 0 (*d*), b = 800 s/mm^2 (*e*), on the ADC map (*f*) the diffusion restriction zone (white arrows) was located only in the cervix

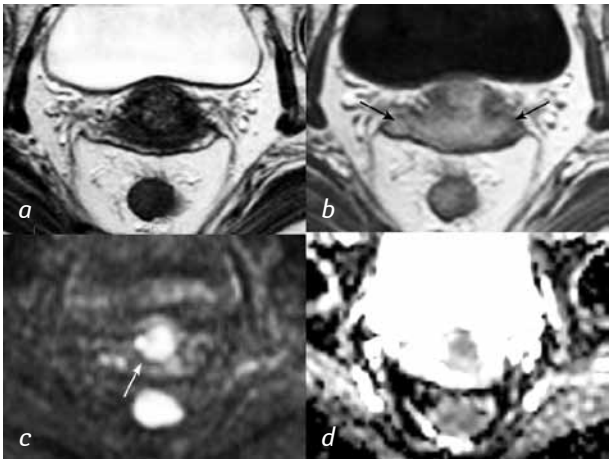

Fig. 2. Pelvic MRI of a patient with CC T2a without invasion into the parametrium. On the axial (*a*) T2W images the interlayer of the hypointensive cervical stroma on the cervix around the tumor was preserved, which excluded the presence of invasion in the parametrium, but CE (*b*) showed intensive contrasting of the parametrium on the right and left (black arrows), which simulated tumor invasion, but at DWI b = 800 s/mm^2 (*c*) and ADC map (*d*) the diffusion restriction zone was located only in the central part of the cervix (white arrow)

vascularization in tissues with reactive inflammation, that obviously make diagnosis more difficult [12–15].

DWI is practically independent on the differences in vascularity. It helps to differentiate high-cellular tumors from areas of inflammation with high water content, which have low cellularity and did not demonstrate a diffusion limitation on DWI [2, 6, 9].

In our studies, the use of DWI allowed to exclude 4 false positive results obtained with native MRI.

In 2 cases, exophytic tumors protruding into the vagina lumen, densely adjoined its walls and stretched them. In the vaginal walls adjacent to the tumor, reactive edema developed, accompanied by the vagina contours vagueness, an increase in signal intensity at T2W, and an increased accumulation of contrast, which simulated invasion, but there was no diffusion limitation on the DWI in the vagina (Fig. 3).

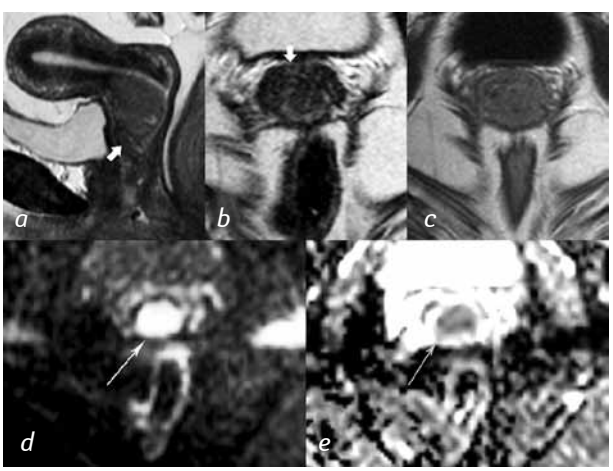

Fig. 3. Pelvic MRI of a patient with CC T1b. Exophytic tumor adhered to vagina walls — presented at sagittal (*a*) T2W. On the axial (*b*) T2W images of the thickened walls of the vagina (short arrows) had contours vagueness, hyperintensive, contrast unevenly accumulation was detected on CE (*c*), but at DWI b = 800 s/mm^2 (d) and ADC map (*e*) the diffusion restriction (long arrows) was detected only in the cervix

In 3 cases among viable tumor tissue, there were areas of reactive inflammation that also gave a hyperintense signal on T2 and demonstrated contrast accumulation in post-contrast scans, which leaded to false results. But the use of DWI allowed to differentiate high-cellular tumor tissue from edema (Fig. 4, 5).

In 2 cases, the hyperdiagnosis of invasion was present with all sequences. In both cases after courses of chemotherapy, inflammatory changes in the cervix were accompanied by necrosis with hemorrhagic areas, which was reflected by increased intensity in native and postcontrast scans, limiting diffusion on DWI (Fig. 6).

DISCUSSION

The informative values for each MRI technique were calculated basing on the obtained results (Table).

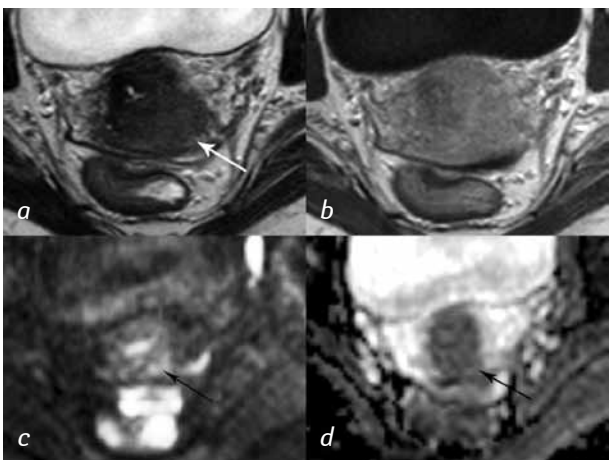

Fig. 4. Pelvic MRI of patient with CC T2b after neoadjuvant chemotherapy. On axial (*a*) T2W images a hyperintensive mass was detected along the left cervix wall (white arrows), which simulated parametrium invasion, on CE (*b*) there was an intensive contrasting of the parametrium on the left, but at DWI b = 800 s/mm^2 (*c*) and on the ADC maps (*d*) only a small area of the diffusion restriction in the cervix posterior-left part (black arrows) was detected. Histopathological examination revealed only inflammatory edema, without parametrium invasion

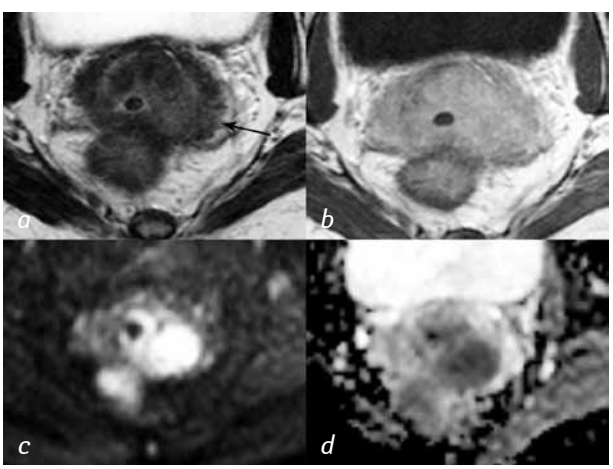

Fig. 5. Pelvic MRI of a patient with CC T2b after neoadjuvant chemotherapy. On axial (*a*) T2W images, increased intensity on the left side of vaginal (arrow) upper third with contrast intense accumulation on the CE (*b*) were determined, which simulated the presence of invasion in the vagina, but at DWI b = 800 s/mm^2 (*c*) signal increase and symmetrical decrease signal on ADC map (*d*) were detected only in the cervix. Histological examination revealed no invasion of the vagina

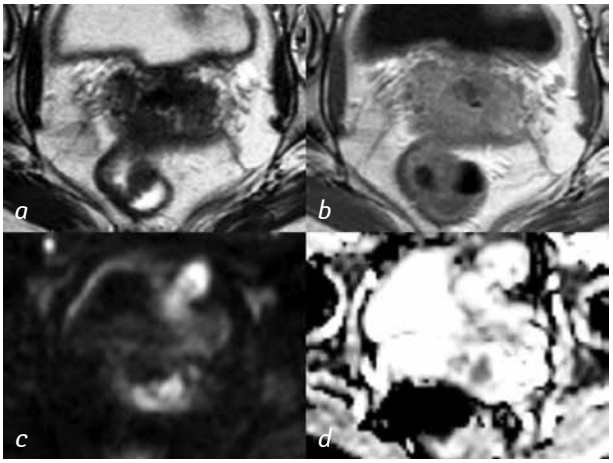

Fig. 6. Pelvic MRI of a patient with CC T2b after neoadjuvant chemotherapy. On axial (*a*) T2W the violations of the cervical borders and hyperintensive masses outside the cervix were detected, accompanied with contrast intensive accumulation on CE (*b*), and signs of diffusion restriction on DWI b = 800 s/mm^2 (*c*) and ADC map (*d*), which simulated the defeat of the parametrium. Histological examination revealed no invasion, but only necrosis with hemorrhagic areas formation

Table. Performance of each MRI technique

	Native MRI	CE	T2W/DWI
n	62	62	62
True-positive	10	10	10
False-positive	6	8	2
True-negative	45	43	49
False-negative	1	1	1
Unable to perform	0	3	0
Positive predictive value, %	62.5	55.5	83.3
Sensitivity, %	90.9	90.9	90.9
Specificity, %	88.2	84.3	96.0
Accuracy, %	88.7	85.4	95.1
χ^2 Pearson value and p	29.6 < 0.001	24.8 < 0.001	43.8 < 0.001
McNemar two-tailed test, p (comparison with native MRI)	–	> 0.05	< 0.05

The greatest correlation between the results of the diagnostic studies and the postoperative data was in a case of T2W/DWI (χ^2 Pearson value 43.8 *vs* 29.6 with native MRI and 24.8 with CE).

The positive predictive value, sensitivity, specificity and accuracy of native MRI in the evaluation of CC invasion were 62.5; 90.9; 88.2 and 88.7%, respectively. The use of CE did not increase the informative value of MRI ($p > 0.05$): the positive predictive value, sensitivity, specificity and accuracy were 55.5; 90.9; 84.3 and 85.4%, respectively. Use of T2W/DWI allowed to reduce the number of false positive results, which significantly increased the efficiency of MRI ($p < 0.05$): the positive predictive value, sensitivity, specificity and accuracy were 83.3; 90.9; 96.0 and 95.1%, respectively.

Limitations of the study were as follows: a small number of observations, the heterogeneity of observations (different stages of the disease and different areas of tumor invasion), the use of only qualitative assessment of the DWI results. Further studies are needed to investigate the usefulness of different MRI sequences for CC diagnosis.

CONCLUSIONS

MRI is an effective technique for assessment of CC spread, being the most informative in a case of combination of native sequences with DWI. The MRI protocol in assessing the presence of local invasion with verified CC, in addition to native sequences, should include DWI, leaving CE as an option.

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