PRACE POGLĄDOWE
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Usefulness of magnetic resonance in evaluation of cervical cancer progression

Rola rezonansu magnetycznego w ocenie stopnia zaawansowania raka szyjki macicy

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Abstract

Magnetic resonance belongs to a group of modern diagnostic methods which, together with classic gynecological, transvaginal ultrasound and histopathological examinations, should be routinely used in patients with suspicion or diagnosed cervical malignancies. The procedure allows precise localization and staging of the tumor, as well as evaluation of the volume of the local lymph nodes. Obtained data are useful in selection of optimal therapy and evaluation of cancer progression.

Intravenous injection of the paramagnetic contrast media significantly increases diagnosis accuracy, especially of small lesions. It is also helpful in differentiation of post-radiotherapy changes and malignant infiltration. The new applications, such as diffusion weighted imaging, magnetic resonance spectroscopy and fat or water saturation are also widely used to improve final diagnosis.

The endovaginal receiver coil allows high spatial resolution imaging of the cervix, which is particularly useful in very small, controversial lesions.

Key words: **cervical cancer** / **magnetic resonance** / **staging** / **diagnosis** /

Streszczenie

Tomografia rezonansu magnetycznego należy do nowoczesnych metod obrazowania ciała, która wraz z podmiotowym badaniem ginekologicznym, ultrasonografią przezpochowową i oceną histopatologiczną powinna być rutynowo stosowana w diagnostyce pacjentek z podejrzeniem lub potwierdzonym złośliwym rozrostem w obrębie szyjki macicy.

Metoda umożliwia dokładną ocenę lokalizacji i zaawansowania nowotworu oraz objętości okolicznych węzłów chłonnych. Uzyskane dane pozwalają na wybór najlepszego sposobu leczenia oraz są istotne przy ocenie postępu choroby. Podanie paramagnetycznych środków kontrastowych znacząco poprawia diagnostykę małych zmian.

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Jest również pomocne w różnicowaniu zmian popromiennych od naciekowych.
Diagnostykę poszerza się również o ocenę dyfuzji, obrazowanie w opcji saturacji tłuszczu i wody oraz spektroskopię rezonansu magnetycznego.
W małych zmianach zalecane jest również wykonanie badania dodatkową sondą pochwową.

Słowa kluczowe: **rak szyjki macicy** / **rezonans magnetyczny** / / **zaawansowanie nowotworu** / **diagnostyka** /

Cervical cancer is the second most common malignancy in women worldwide, with incidence peak between 45-50 years of age [1]. In Poland is sixth on the list of morbidity and seventh of mortality rates [2,3]. In highly developed countries, where prophylaxis, treatment funds and social awareness are higher, a considerable reduction in both cervical cancer morbidity and mortality has been observed [4].

Success of the treatment lies mainly in diagnosing the lesion at the earliest possible stage. In order to achieve that, prophylactic tests are carried out, including pelvic organs assessment on the basis of classic gynecological, cytological and ultrasonographic examination [2,4].

In recent years the combined therapy has become the treatment of choice (chemo- and radiotherapy) and has significantly improved treatment results of patients in advanced stages. It considerably reduces the risk of late-onset complications which further indicates the importance of disease staging in order to select the best method of treatment [5]. Due to the lack of specific markers for cervical cancer, it is the clinical examination and modern methods of imaging, particularly magnetic resonance (MR), that play the most important role in the process of diagnosis [4-7].

Cervical cancer imaging in magnetic resonance

Magnetic resonance is a test based on proton magnetic properties which, according to the current state of knowledge, is harmless for human body. The test is useful in an early detection of focal lesions. It is also believed to be the best method of assessing the stage of cervical cancer as it provides good spatial and contrast resolution and the possibility of multi-dimensional imaging. It is estimated that MR sensitivity and specificity for changes in lesser pelvis are 75–80% and 94–96%, respectively [6]. In patients with diagnosed cervical cancer the obtained images allow to precisely determine the location and size of the tumor, which is clearly separated and visible, as well as the range of neoplastic infiltration of the adjacent structures. The examination is the method of choice for treatment planning, monitoring and check-up [7, 8]. MR imaging is more precise than clinical examination and computed tomography (CT). MR precision has been estimated to be 92%, whereas it is 78% for clinical examination and 70% for CT [9].

Prior to undergoing an MRI examination, a patient should be fasting and have a moderately filled urinary bladder. 1 mg of glucagon is administered intramuscularly to minimize peristalsis-related artifacts. In routine imaging the enteral contrast media are not administered. However, Gd-DTPA – a complex of gadolinium with diethylenetriamine chelating agent pentaacetic acid – may be administered if there is a suspicion of lesions originating from the bowel or the ovary [7, 10].

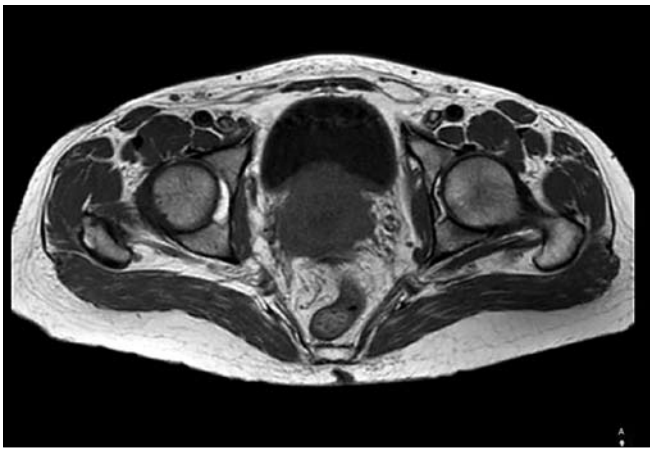

Figure 1. Low differentiation of the cervical cancer from unaffected part of the uterine cervix in the T1-weighted image.

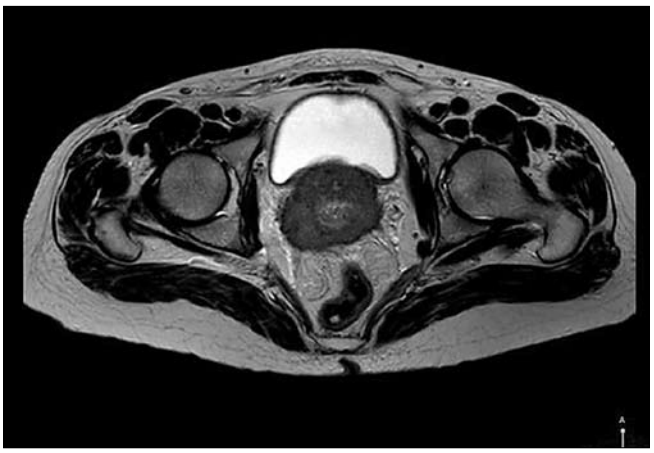

Figure 2. Oval-shaped, poorly-demarcated tumor on the right part of the uterine cervix in the T2-weighted image.

Similarly to other parts of the body, MR of the pelvis is performed using spin-echo sequence, T1 and T2-weighted images, in multi-dimensions (sagittal, coronal, axial), with a section thickness of 5-6 mm and a 1,5 mm gap [6, 7, 9].

On T1-weighted images tumor lesions have low signal intensity (Figure 1), heterogenic structure and appear isointensive in comparison with a normal cervical canal structure [7]. T2-weighted images are used for assessment of organ morphology, particularly three primary layers of the uterus.

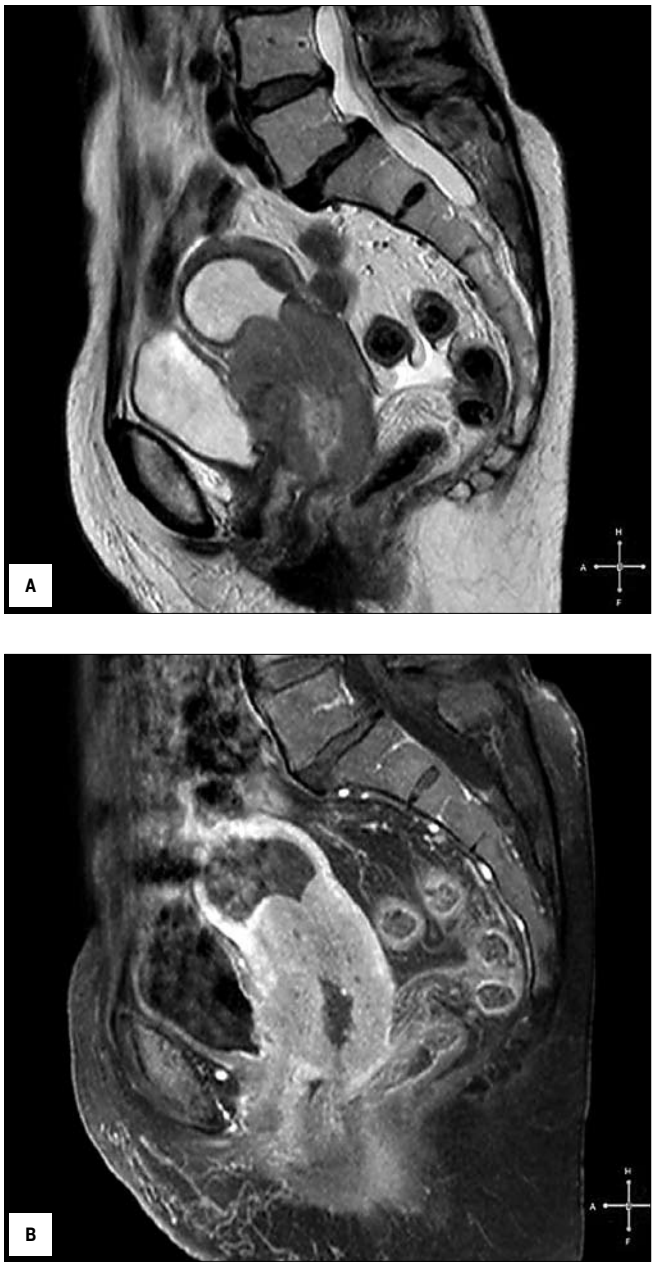

Figure 3. Poorly-seen margin between the cervical tumor and the bladder and the rectum suggesting their infiltration in the T2-weighted (**A**) and in fat saturation images (**B**).

Cervical cancer in T2-weighted images has high signal intensity in the cervical stroma. T2-weighted images are the most significant in the assessment of parametrium, and the discontinuity of the hypointensive rims is a signal of the invasion. The same rule (presence of hypointensive rims on T2-weighted images) is also valid when assessing an invasion of the rectum and/or urinary bladder. (Figure 2, 3A).

Additional sequences are used for better assessment of tumor morphology, especially features such as hypoxia or angiogenesis [11], and it is achieved by water or fat saturation imaging. (Figure. 3B).

They allow to differentiate regions containing the fatty tissue fatty tissue, free lipids and blood. A gel-filled tampon (the same gel as the one used for ultrasonographic examination) may be placed to determine the extent of the invasion in the vagina. After administering paramagnetic contrast medium (gadolinium chelate), the structures in the tumor are clearly enhanced in most cases. This allows to better determine the rim of the lesion as well as the adjacent structures infiltration. (Figure 5).

Contrast-agent is particularly useful in monitoring of patients after radiotherapy in order to differentiate between post-radiation and scar changes with the disease recurrence [9].

The cervical cancer staging, currently used in a radiological assessment, is similar to the clinical-surgical and pathomorphological classification of the International Federation of Gynecology and Obstetrics (FIGO).

In accordance with the latest recommendations, both the volume of the tumor and adjacent lymph nodes are assessed on the basis of the obtained images and later reconstructions [12, 13]. Both parameters have a decisive influence on the choice of treatment method and constitute an important prognostic factor [14]. As mentioned before, the routinely used diagnostic methods – clinical examination, CT and ultrasonography – have lower precision when compared to MR, which also allows to measure water diffusion. (Figure 4.).

In certain cases, MR spectroscopy and endovaginal receiver coil are employed since they allow for more detailed diagnosis.

Measurement of tumor and lymph node volume

On the basis of a retrospective study of 106 patients with diagnosed advanced stage cervical cancer, Hunjung et al. [15] observed the usefulness of tumor volume measurement before commencing treatment. Patients classified as a high-volume tumor are more likely to have a recurrence than low-volume ones. Such findings were confirmed by Dae et al. [16].

Kamimori et al. [14], when assessing 125 IB1-patients, concluded that tumor diameter - measured before commencing treatment - has a positive correlation with numerous prognostic factors, particularly with the infiltration of the parametrium. Research proves that tumor diameter is an important predictor which may be used when choosing the method of treatment, especially in case of patients qualified for less radical surgery, without the necessity to perform biopsy. Pointreau et al., [12] added the lymph node volume to the group of prognostic factors. However, Goudy et al., [17] after examining 219 patients with advanced stage cervical carcinoma (Ib1-IIb) observed that lymph nodes infiltration is of tremendous importance in a risk-assessment of metastases and response to treatment. Liyanage et al., [7] emphasize that, despite the fact that lymph nodes imaging has not been included into the FIGO classification, their morphology should always be assessed since 5-year survival for patients with lymph nodes infiltration is estimated to be about 39-54%. In case of patients with non-infiltrated lymph nodes it is up to 67-92%. The role of MR is further underlined by the fact that despite early tumor detection, the presence of lymph node metastases excludes surgical treatment and these patients should be qualified for the chemoradiotherapy. In more advanced stages, lymph nodes assessment is also helpful in planning the extent of radiation areas.

According to Camisão et al., [9] a metastatic lymph node is at least 10 mm in short axis. Nevertheless, lower values of 7.0-10 mm are also mentioned, depending on the location. For common,

internal and external iliac lymph nodes, the value is 9.0, 7.0 and 10 mm, respectively.

It is worth to underline that the imaging after administration of paramagnetic contrast agent is very useful for assessing the location and morphology of the nodes.

In order to optimize treatment planning, the nomenclature of lymph nodes has been based on the classic anatomical classification by Takafumi et al. [18]. Pelvic lymph nodes were divided into five major groups: common iliac, external iliac, internal iliac, obturator and parametrial. Liyanage et al., [7] also noticed that cervical cancer metastases are usually primarily located in parametrial nodes, followed by common iliac and obturator ones. Due to potentially spread process of cancer metastases, the authors recommend 3D-nodes measurement in three dimensions: antero-posterior, cranio-caudal and transverse.

Diffusion weighted imaging

Diffusion weighted imaging (DWI) may be applied to assess the pelvic organs. The image contrast is achieved by the assessment of the random movement of water molecules in tissues. Data on concentration and density of the cells, as well as microcirculation and cell membrane permeability are used [19, 20]. Changes of the apparent diffusion coefficient (ADC[1]) have been proven to be connected with the cellular density in case of neoplastic lesions. During the examination, the area which takes the largest part of the neoplastic lesion in T2-weighted images is marked. The rim of the lesion is determined by comparison with T1- and T2-weighted images, and then after administering paramagnetic contrast agent. The marked area is then copied onto the ADC map and the values are compared with parameters obtained within the normal healthy tissue. Diffusion weighted imaging has many advantages, chief among them the relatively short time of scanning, without the necessity of intravenous administration of paramagnetic contrast agent, what is particularly important in case of patients with renal failure. It needs to be emphasized, that the sequence is complementary to the standard examination protocol.

Liu et al. [21, 22], after examining 42 women with cervical cancer and 15 patients with uterine myomas, are of the opinion that MR with diffusion sequence allows to determine the histopathologic type of the tumor on the basis of healthy cells and tumor cells density. Messiou et al., [23] presented similar conclusions regarding the usefulness of diffusion in the assessment of uterine morphology and the possibility of an early detection of the neoplastic infiltration. Liu et al., [21, 22] and Zhang et al., [24] reported similar observations. Moreover, the authors state that MR supplemented with the diffusion sequence allows to predict tumor response to treatment. Nevertheless, these results come from research carried out on a relatively small number of patients (17 and 14, respectively) and require verification. Lin et al. [25], after conducting diffusion technique test in 50 patients diagnosed with cervical cancer, concluded that the method allows to identify metastatic lymph nodes (micro-metastases) of even 5 mm. Apparent diffusion coefficient values within the tumor and metastatic lymph nodes were significantly

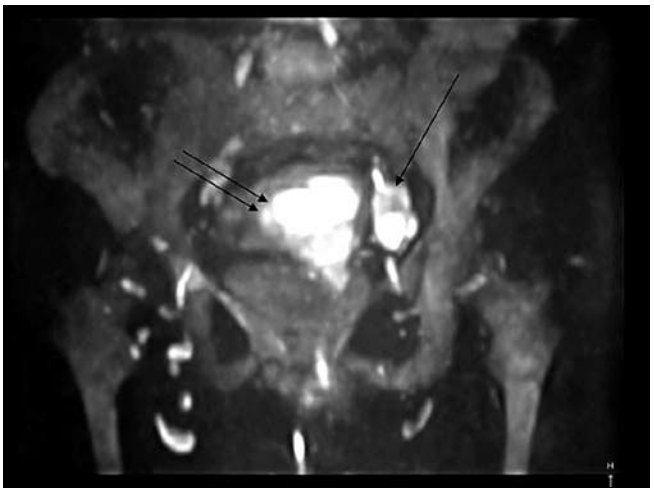

Figure 4. The tumor of the lesser pelvis (double arrow) and metastases in the lymph nodes (single arrow) in the diffusion weighted imaging (DWI).

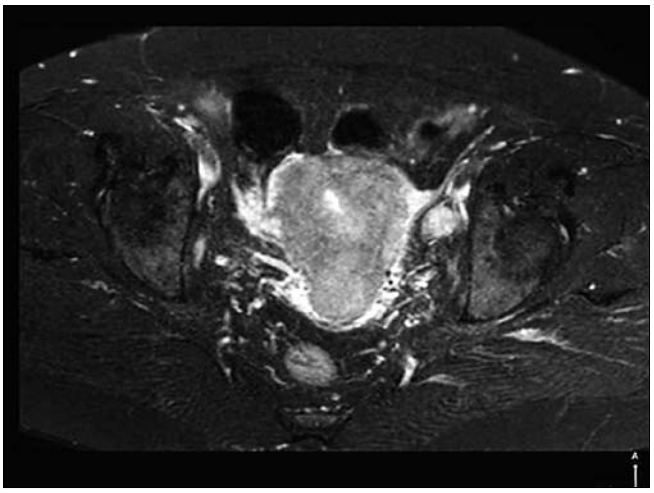

Figure 5. Contrast-enhanced tumor and surrounding structures suggesting infiltration of the parametrium.).

lower than in analogical normal healthy structures, which results from morphological differences, especially tumor necrosis. In comparison to conventional MR, the relative value of ADC increases sensitivity from 25 to 83%, with no significant difference of the test specificity, which was 98 and 99%, respectively.

Balleyguier et al., [13] in the guidelines of the European Society of Urogenital Radiology also recommend to incorporate the diffusion sequence into the optimized protocol of pelvic MR

Dynamic imaging after administration of paramagnetic contrast agent.

Opinions on intravenous administration of paramagnetic contrast agent in patients with cervical cancer vary considerably. According to Sala et al., [6], it is not necessary to administer paramagnetic contrast agent as it does not improve the test precision in comparison to the classic imaging in T2-wieghted sequence. However, the authors point to the fact that dynamic imaging may be of use when differentiating between infiltrative and post-surgical changes. Camisão et al., [9], confirm these

1 Apparent Diffusion Coefficient

observations and note that dynamic sequences often do not allow to measure the volume of the main lesion and the depth of the cervical stromal infiltration precisely. Therefore, they should not be performed routinely.

Nevertheless, the contrast medium administration may be useful in locating fistula in an advanced stage of the disease or during check-up after treatment completion.

Donaldson et al., [26], on the basis of MR documentation analysis performed before and after completion of radiotherapy in 50 patients with cervical cancer, established that the dynamic imaging is complementary to clinical and classic MR examination. Thus, it may be used to assess microcirculation within the tumor, including tissue vascularization and capillary permeability, what may in fact contribute to the treatment prognosis. Spensley et al., [5] and Ellingsen et al., [27] had reached similar conclusions and Liyanage et al., [7] add that dynamic imaging may increase the efficacy of detecting very small tumors, between 3.1-5.0 mm infiltration. The sensitivity of the method has been estimated at 92%, in comparison with 23% in case of T2-weighted images without contrast enhancement. Small-volume lesions have significant enhancement at the early phase of the examination, when compared to slight enhancement of the normal cervical epithelium. The authors also noted, in accordance with earlier observations, that administration of contrast medium may help to differentiate between post-radiation and infiltrative changes.

Yuh et al., [28], after analyzing 101 examinations with the use of diffusion sequence and dynamic imaging, demonstrated their usefulness in predicting tumor response to chemotherapy on the basis of tumor vascularization and differences in lesion volume during treatment. The authors also underline the importance of the discussed methods in the imaging of the residual tumor after treatment completion – progression of tumor assessment and local recurrence.

Table I. Staging of cervical cancer according to FIGO classification in relation to the magnetic resonance imaging.

FIGO		MR
I	pre-invasive cancer	normal image
IA	invasive cancer identified only microscopically.	
IA1	measured invasion of the stroma ≤ 3 mm in depth and ≤ 7 mm in diameter	
IA2	measured invasion of the stroma > 3 mm but < 5mm in depth and ≤ 7 mm in diameter	
IB	clinically visible lesion, infiltration confined to the cervix or preclinical lesion greater than Stage IA.	lesion with medium intensity signal on a low-intensity signal of the cervical stroma
IB1	clinically visible lesion ≤ 40 mm	
IB2	clinically visible lesion > 40 mm	
II	carcinoma extends beyond the cervix, but does not extend into the pelvic wall; it involves the vagina, but not as far as the lower third.	
IIA	without parametrial invasion	loss of normal low-intensity signal of the vaginal fornix or the wall in the cervical cancer tumor
IIA1	clinically visible lesion ≤ 40 mm	
IIA2	clinically visible lesion > 40 mm	
IIB	with obvious parametrial invasion with no extension to the pelvic wall with/without involvement of the vagina	discontinuity of the hypointense rim of the cervix
III	tumor extends to the pelvic wall and/or involves lower third of the vagina	
IIIA	tumor involves lower third of the vagina, with no extension to the pelvic wall	loss of normal low-intensity signal of the lower third of the vaginal wall
IIIB	extension to the pelvic wall and/or hydronephrosis or non-functioning kidney	infiltration of internal obturator, levator ani, piriformis and iliac muscles and adjacent iliac vessels; additional symptoms, i.e. enhanced signal of the pelvic floor intensity, hydronephrosis, ureteral extasia due to occlusion (primary tumor) or metastases to lymph nodes
IV	carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum	The carcinoma has involved the mucosa of the bladder and/or rectum, Spread of the growth to adjacent organs, spread to paraaortic and inguinal lymph nodes
IVA	carcinoma has involved the mucosa of the bladder or rectum	
IVB	spread to distant organs	

Fat and water saturation sequences

Fat saturation MR sequence allows to differentiate focal lesions containing blood or lipids. It also enables to identify teratoma and endometriosis, as well as allows to assess perirectal fat tissue and its infiltration in patients with advanced cervical cancer [29].

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy technique (MRS) may be a useful tool both in preliminary diagnosis and in subsequent check-up tests after radiotherapy completion, especially when other standard diagnostic methods are ambiguous [30]. MRS is applied in the assessment of tumor metabolic profile. The proton spectrum of cervical cancer is characterized by the presence of a high signal typical for triglyceride, that may be used as marker of neoplastic process. According to Da Silva et al., [31] the method allows to recognize hyperplasia but it remains impossible to determine the exact nature of the neoplastic change, that is to differentiate between primary and metastatic lesion.

Endovaginal coil

Magnetic resonance with the use of endovaginal coil has high sensitivity in preoperative imaging of the cervical cancer, especially for lesions in diameter below 1cm^3. The obtained results are important for treatment planning, particularly for patients who wish to preserve their fertility, as well as for planning radical surgical treatment at an early stage of the disease. The coil allows to assess water behavior in nontumor and tumor structures [32]. Charles-Edwards et al. [33], after analyzing 113 patients in diffusion sequence concluded that the endovaginal coil increases the precision of infiltration assessment at early stages of the cancer.

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