Magnetic resonance imaging in the diagnosis of malignant gynaecological tumours

Oslikavanje magnetskom rezonancijom u dijagnostici ginekoloških tumora

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Abstract. Magnetic resonance imaging (MRI) is a widely used imaging modality that depicts detailed information regarding morphological and functional characteristics of the human body. It is routinely used in gynaecologic oncology for female pelvis imaging because of the high spatial and soft-tissue contrast resolution. Furthermore, MRI is an important diagnostic tool for the assessment of common gynaecological malignancies – endometrial carcinoma, cervical carcinoma and malignant ovarian tumours. Novel technical developments enabled the multiparametric MRI approach in the diagnosis of respective tumours combining T1-weighted (T1W) sequences, T2-weighted (T2W) sequences, diffusion-weighted (DW) sequences with apparent diffusion coefficient (ADC) values and dynamic contrast-enhanced (DCE) sequences. With highlighted novelties, MRI importance ranges from tumour detection to treatment response monitoring and early recurrent disease evaluation. This review discusses the value of MRI in the diagnostic assessment of the common gynaecological malignancies with an emphasis on tumour staging.

Key words: endometrial neoplasms; magnetic resonance imaging; ovarian neoplasms; uterine cervical neoplasms


Ključne riječi: magnetska rezonancija; novotvorine endometrija; novotvorine jajnika; novotvorine vrata maternice
INTRODUCTION

Magnetic resonance imaging (MRI) is an imaging modality that recreates detailed images of the tissues and organs of the human body. It employs powerful magnets as sources of strong homogeneous magnetic field to affect the proton spin, their energy state and their field alignment with the intent to obtain a magnetic resonance signal and create an image of the human body. The use of MRI is increasing at a great rate in gynaecologic oncology and it is becoming an essential imaging technique in the diagnosis, treatment planning and follow-up of malignant gynaecological tumours. MRI has a high spatial and soft-tissue contrast resolution which allows an accurate anatomic characterization of the pelvis, female reproductive system and related tumours – endometrial carcinoma, cervical carcinoma and malignant ovarian tumours. In this review, we aimed to illustrate the capabilities of MRI sequences in the diagnosis of the most common gynaecological malignancies with an emphasis on tumour staging.

ENDOMETRIAL CARCINOMA

MRI is widely recommended as a preferable technique for the preoperative assessment and treatment evaluation of endometrial carcinoma (EC). According to the American College of Radiology (ACR) appropriateness criteria, MRI is recognized as the preferred imaging modality for treatment planning whenever is possible. One of the main objectives when imaging EC is accurate assessment of depth of myometrial invasion (MI) due to its correlation with lymph node (LN) metastases and patient survival. For instance, the prevalence of LN metastases in the superficial MI is 3% whereas the percentage in the deep MI increases to 46%. Also, Ytre-Hauge et al. report that tumour size is strong prognostic factor in patients with EC (AP tumour diameter >2 cm predicts deep MI whereas CC diameter >4 cm predicts LN metastases). In updated European Society of Urogenital Radiology (ESUR) guidelines for MRI staging of EC, T2-weighted (T2W) sequences are essential for the evaluation of primary tumours since they accurately demonstrate disruption or irregularity of normal uterine anatomy. Moreover, they demonstrate characteristic mild hyperintense tumour signal compared to adjacent junctional zone and myometrium and intermediate to hypointense tumour signal in contrast to endometrium. Use of diffusion-weighted (DW) sequences is also advised. Recommended ESUR slice thickness is ≤4 mm with a field of view (FOV) of 20-25 cm. The optimal evaluation of myometrial invasion is achievable in sagittal and axial planes using T1-weighted (T1W) contrast enhanced images (or as a part of dynamic-contrast enhanced (DCE) sequences). For the assessment of lymphadenopathy, axial T2W sequences with large FOV are obligatory while the use of DW images is dependent on tumour grade. Compared to DW imaging, recent study from Yue et al. concluded that diffusion kurtosis imaging (DKI) can detect EC and differentiate histological tumour grades more efficiently.

FIGO classification (2009) is used for the staging of EC and it divides tumour spread into four stages. Stage I of FIGO classification is characterized by the absence of MI or MI <50% (IA) and >50% (IB). MRI staging accuracy for MI is displayed in Table 1. One study reported MRI diagnostic precision equivalent to intraoperative frozen sectioning whereas some studies are contradictory, demonstrating MRI inferiority to frozen sections. Highly effective assessment of MI is enabled with DCE-MRI. Furthermore, Du et al. suggest that use of fast low-angle shot (FLASH) 3D DCE-MRI imaging may be valuable for evaluating MI (sensitivity 84%, specificity 90%, accuracy 88%). Two studies compared reduced FOV DW-MRI with 3D DCE-MRI in the detection of MI. Both research groups concluded that the addition of DW imaging technique improves staging accuracy of depth of MI and it can be an adequate diagnostic alternative to 3D DCE-MRI, especially when the use of
Table 1. Accuracy of MRI in staging of endometrial cancer – overall myometrial involvement

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Table 2. Accuracy of MRI in staging of endometrial cancer – overall cervical involvement

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Table 3. Accuracy of MRI in staging of endometrial cancer – overall lymph node involvement

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contrast agents is contraindicated\textsuperscript{17,18}. Furthermore, meta-analysis from Deng et al.\textsuperscript{19} found T2W+DW-MRI superiority over DCE-MRI and DW-MRI alone in detection of MI. Stage II is characterized by cervical stromal invasion and it does not include extraterine spread. However, it is associated with greater risk of LN metastases and it is one of the prognostic factors for determining high-risk disease\textsuperscript{20}. MRI staging accuracy for cervical involvement is displayed in Table 2. Sagittal and axial oblique T2W imaging is preferable in detection of cervical involvement.
because of the high contrast resolution. In comparison to DCE-MRI, Lin et al. reported that DW-MRI demonstrated higher accuracy in evaluation of cervical stromal invasion which yields improvement in imaging of EC. ADC values were similar in patients with or without cervical invasion and canal widening did not produce false negative findings on DW imaging. Overall, in DW imaging cervical stromal invasion is suspected by the presence of high signal intensity on high b values and low signal intensity on ADC maps.

Stage III is composed of three subdivisions: IIIA, IIIB, and IICC. Characteristic findings of disruption of serosal T2W hypointensity or loss of enhancement of myometrial outer margin on DCE-MRI imply serosal invasion, therefore stage IIIA. Also, for small cervical and vaginal implants in stage IIIB, DW and DCE imaging are beneficial.

MRI staging accuracy in the evaluation of lymphadenopathy is displayed in Table 3. The middle and lower uterine segments drain into parametrial, paracervical and obturator LNs whereas the upper segments drain into common iliac and paraaortic LNs. The main limitation of MRI in size-based LN assessment is that a considerable proportion of metastatic LNs are smaller than the commonly applied threshold size of 10 mm (short-axis diameter). Compared to conventional MRI, the combination of LN size with relative ADC values on DW imaging shows promising results in detecting malignant pelvic LNs and decreasing the short-axis threshold to 5 mm.

Meissnitzer and Forstner also reported that LNs are easiest to display on DW imaging and they recommend the threshold of 8 mm for pelvic LNs and 10 mm for abdominal LNs.

Stage IV of EC represents tumour invasion into bladder or bowel mucosa (IVA) and/or the existence of distant metastasis (IVB). Rectal or bladder wall invasion is best evaluated in the sagittal plane. Peritoneal deposits are best shown on delayed DCE-MRI. The majority of recurrences occur within lymph nodes (46%), vagina (42%), peritoneum (28%) and lungs (24%).

**CERVICAL CARCINOMA**

MRI is widely regarded as the favourable imaging modality for the pretreatment evaluation of cervical carcinoma (CC) due to its ability to assess stromal and parametrial invasion. The revised FIGO classification (2019) recommends MRI as the method of choice for pretreatment evaluation of local tumour extent in patients with FIGO stage IB or greater. In ESUR guidelines for MRI staging of CC, T2W images are the mainstay for tumour detection because they demonstrate characteristic moderate hyperintense tumour signal compared to normal hypointense cervical stoma. Axial oblique T2W sequences with 3-4 mm slice thickness, small FOV (24 cm) and plane perpendicular to the long axis of the cervix provide more accurate assessment of stromal and parametrial invasion (PI). ESUR recommends fat-suppressed T2W sequences for the evaluation of PI (especially in younger patients) whereas axial T1W sequences are used for the assessment of pelvic and abdominal lymphadenopathy. DCE-MRI is used for detection of small lesions (<2 cm), depiction of bladder and rectal wall involvement and for post-treatment follow-up. Novel technical developments enabled the use of tracer kinetic models and DCE-MRI for the evaluation of microcirculation and microenvironment of CC tissue, which can be helpful in individual treatment planning and precise prognosis. DW-MRI is often helpful for tumour detection, definition of tumour extent, residual lesion detection and the assessment of the enlarged LNs. Qian et al. conducted a study where 61 patients with CC underwent DW-MRI based on single-shot echo planar imaging (SS-EPI) and readout-segmented echo-planar imaging (RESOLVE). Authors concluded that RESOLVE performed with greater consistency than SS-EPI. Another study has shown that reduced FOV DW-MRI has potential advantages in comparison to conventional DW-MRI in terms of better image quality and fewer artefacts. Recent additional studies are needed to improve MRI assessment in individuals with LN metastases and complex ovarian masses. With continuous technical developments, MRI has potential to improve patient’s outcome and overall survival rates.
study from Arteaga de Castro et al.\textsuperscript{39} obtained lipid profiles in CC with \textsuperscript{1}H magnetic resonance spectroscopy (MRS) at 7T and concluded that specific fatty acid ratio might be related to tumour grade in CC. Song et al.\textsuperscript{40} conducted preliminary tentative research on MRI with specific molecular probe – superparamagnetic iron oxide (SPIO)-antitenascin-C. Based on the highest tenascin-C expression in CC tissues with LN metastasis, in contrast to low expression in normal cervix, authors concluded that functional protein targeted MRI can be an useful technique for depiction of CC with node metastasis. When distinguishing squamous cell carcinoma from adenocarcinoma, a study carried out by Becker et al.\textsuperscript{41} suggests the use of intravoxel incoherent motion imaging (IVIM) due to the promising potential in histopathological tumour differentiation and correlation with tumour grades of CC. Revised FIGO classification (2019) is used for the staging of CC and it divides tumour spread into four stages. Stage I is composed of two subdivisions: IA and IB. The tumour is confined to the cervix and characterized by the presence of microinvasion into surrounding tissue (Figure 1). In the early stage of CC, the patient prognosis is associated with tumour size, histological subtype, degree of differentiation, depth of tumour invasion, LN status and lymphovascular space invasion\textsuperscript{23-25}. Tumour size is a strong prognostic factor and larger tumours are associated with extravesical spread, LN metastases and overall patient survival\textsuperscript{32,44-46}. Furthermore, the risk of LN involvement increases with increasing tumour size from 6% (max. diameter <2 cm) to 36% (max. diameter >4 cm)\textsuperscript{24}. Although conventional MRI techniques play no role in the evaluation of stage IA, the use of DW- and DCE-MRI provides detection of lesions smaller than 2 cm\textsuperscript{21,27,30}. For FIGO stages IA/IB1, Downey et al.\textsuperscript{47} report that the use of endovaginal coil T2W imaging technique produces higher sensitivity and lower specificity compared to external array coil technique. However, the addition of DW-MRI to existing endovaginal technique produced a small reduction in sensitivity, but substantial improvement in specificity. In stage IB, CC is detectable on T2W images as a solid mass with a moderate hyperintensity relative to surrounding hypointense cervical stroma. At this stage, one of the major determinants of surgical treatment is the presence of PI. An intact hypointense cervical stroma and thickness of “hypointense rim sign” greater than 3 mm are very significant for the exclusion of PI (specificity of 96-99%, NPV of 94-100%)\textsuperscript{27,44}. Lakhman et al.\textsuperscript{48} reported that patients with FIGO stage IB1, tumour size ≥2 cm, deep cervical stromal invasion and distance ≤5 cm between tumour and internal cervical os (ICO) were associated with increased possibility of radical hysterectomy. In contrast, Yamazaki et al.\textsuperscript{49} suggest that patients with FIGO stage IB1, MRI-based tumour diameter <2.5 cm, MRI-based volume index <5 cm\textsuperscript{3} and negative serum tumour markers (SCC-Ag or CA-125) should require less invasive surgery as an alternative therapy. Stage II of FIGO classification is characterized by tumour invasion beyond the cervix but with no extension onto the lower third of the vagina or the pelvic wall (Figure 2). Vaginal infiltration is detected on T2W images as a hyperintense tumour disrupting normal hypointense vaginal wall (Figure 3). Vaginal opacification is optional for the staging of CC. However, for improved assessment of vaginal extension and local recurrence, some authors advise the use of gel-based endovaginal distension\textsuperscript{50}. In stage IIB, CC is displayed as a hyperintense solid mass on T2W images with irregular margins, disrupting the cervical stroma and invading the parametrium (Figure 4). Woo et al.\textsuperscript{51} compared diagnostic performances of oblique axial and true axial T2W images in the evaluation of PI and reported that oblique axial images yield improved diagnostic performance compared to true axial images, especially for tumours greater than 2.5 cm. However, one of the major pitfalls of T2W-MRI staging is overestimation of PI in large lesions, especially when MRI tumour size is over 2.9 cm\textsuperscript{23,52}. In this situation, DW-MRI and DCE-MRI can be helpful\textsuperscript{23}. Stage III is composed of three subdivisions: IIIA, IIIB and IIC. IIIA is characterized by the involvement of the lower third of the vagina with no pelvic wall extension (Figure 5). In this stage, sagittal and axial oblique T2W images are the most suitable for tumour evaluation. IIIB includes the ex-
Figure 1. T1W image in sagittal plane – cervical carcinoma (FIGO IB)

Figure 2. T1W image in sagittal plane – cervical carcinoma (FIGO IIA1)

Figure 3. T2W image in sagittal plane – cervical carcinoma (FIGO IIA2)

Figure 4. T2W image in transversal plane – cervical carcinoma (FIGO IIB)
tension to the pelvic wall and/or hydronephrosis or non-functioning kidney (Figure 6). Stage IIIC is specified by the involvement of pelvic and/or paraaortic LNs. The majority of lymphatic drainage from the cervix is directed through the lateral pelvic and hypogastric pathways\(^24\). Positive LN distribution is primarily along the obturator region (91%), external iliac region (27%), common iliac region (19%), internal iliac region (14%) and presacral region (5%)\(^53\). In contradiction to standard pelvic metastatic LN assessment, Choi et al.\(^54\) demonstrated more accurate prediction of LN status when the threshold size in short-axis diameter was 9 mm. Furthermore, authors also concluded that lobulated or spiculated contour is a helpful indicator of LN metastasis. Cut-off value for round pelvic LNs is often set at 8 mm\(^44\) while the threshold for parametrial nodes is 5 mm\(^22\). Furthermore, Hong et al.\(^55\) demonstrated in small sample size (28 patients) that interstitial MR lymphography may overcome deficiencies of conventional MRI in detection of LN metastases with accuracy, sensitivity and specificity of 92.9%, 80% and 95.7%, respectively. In two meta-analyses, authors reported that DW-MRI was beneficial for differentiation between metastatic and benign LNs whereas the ADC values in CC tissues with positive LNs were considerably lower compared to those with normal LNs\(^56,57\).

Stage IV represents tumour infiltration of the bladder or bowel mucosa (IVA) and/or the existence of distant metastases (IVB) (Figures 7-9). Bladder or rectal invasion is best seen on sagittal and axial T2W images. Stage IVB is characterized by lymphatic and hematogenous dissemination, most frequently in the paraaortic or inguinal LNs, liver, lungs, adrenals and/or bones\(^23,32\). The majority of relapses occur within the pelvis (74%) and the most common sites are vaginal cuff, cervix, parametrium and pelvic sidewall\(^58\).

**MALIGNANT OVARIAN TUMOURS**

ESUR and ACR guidelines for the preoperative staging of ovarian tumours selected contrast-enhanced CT as the modality of choice\(^59,60\). Thus, MRI is used as a valuable complementary problem-solving method for the differentiation between benign and malignant tumours. ESUR published updated recommendations for MRI of the sonographically intermediate adnexal mass-

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**Figure 5.** T1W image in sagittal plane – cervical carcinoma (FIGO IIIA)

**Figure 6.** T2W image in axial plane – cervical carcinoma (FIGO IIIB)
The imaging protocol consists of basic and problem-solving MRI sequences. Conventional sequences include T2W sagittal sequence of the pelvis and combination of T1W and T2W sequences covering the ovarian mass and its relationship to the adjacent uterus. Problem-solving sequences are based upon tumour characteristics acquired during conventional imaging. Therefore, T1W hyperintense tumour should be evaluated with fat-suppressed T1W sequence; T2W hypointense solid mass with oblique T2W and DW-MRI; T2W solid mass with DW-MRI and contrast-enhanced T1W sequences (preferably DCE-MRI); and cystic-solid mass with DW-MRI and contrast-enhanced T1W sequences (preferably DCE-MRI). Imaging features often indicative of malignancy include mass larger than 4 cm in size, thickness of the wall or septa greater than 3 mm, papillary projections, necrosis and presence of solid and cystic architecture. The usual MRI appearance of selected malignant ovarian tumours is displayed in Table 4. Yuan et al. performed a study on 46 female rat epithelial ovarian carcinoma (EOC) models to evaluate DCE-
MRI in the assessment of EOC features. TIC type analysis, derived from DCE-MRI, demonstrated more frequently type 3 than type 2 \((p<0.001)\) which appears to be specific for malignant tumours. Malek et al.\(^{64}\) conducted a study on 47 patients with 56 adnexal lesions and found that mean ADC value differed between benign and malignant lesions \((1.36\pm0.5\times10^{-3}\text{ mm}^2/\text{s} \text{ and } 1.05\pm0.91\times10^{-3}\text{ mm}^2/\text{s}, \text{ respectively}; p<0.001)\), all of 27 malignant lesions displayed high intensity signal on DW-MRI and that type 3 TIC yields substantial improvement, contrary to DW-MRI and mean ADC value, in distinguishing benign from malignant tumours (74% sensitivity, 66% specificity). In another study (total of 85 ovarian lesions), authors noticed that the b value of 1000 \text{ s/mm}^2 provides statistically significant difference in ADC and exponent apparent diffusion coefficient (EADC) values between benign and malignant ovarian masses \((p<0.05)\).\(^{65}\) Recent study evaluated DW-MRI and ADC values for categorizing EOC. Patients were divided into type 1 (low-grade serous carcinoma (LGSC), endometrioid carcinoma (EMC), clear cell carcinomas (CCC), borderline serous/mucinous cystadenomas)) and type 2 (high-grade serous carcinoma (HGSC)) cancer groups\(^{66}\). In contrast to type 1, authors found that type 2 cancer occurs more frequently in older patients and those in advanced FIGO stage. Type 2 cancer had a lower mean ADC value \((p<0.01)\), smaller size and lower probability of presenting with septa and hyperintensity on T1W images. Type 1 cancer was present in the younger population and the subsequent ADC value was inversely related to Ki-67 expression \((p<0.05)\). Morioka et al.\(^{67}\) evaluated MRI findings for discrimination between CCC and EMC. Authors concluded that growth pattern of mural nodules and height-to-width ratio are independent discriminating factors \((p<0.0004, p<0.036, \text{ respectively})\). In terms of differentiating EMC from HGSC, one study unveiled four features (cystic tumour with mural nodules or papillary projections, homogeneously iso- or hyperintense cystic component on T1W imaging, higher ADC values and synchronous primary cancer) that provided sensitivity, specificity, positive predictive value and accuracy for defining EMC of 87.0%, 93.5%, 76.9%, 96.7% and 92.2%, respectively\(^{68}\). A retrospective study from Xu et al.\(^{69}\) included 11 patients with metastatic ovarian tumours and 26 patients with primary malignant EOC. In contrast to patients with EOC, patients with metastatic tumour were younger \((p=0.015)\), maximum lesion diameter was smaller \((p=0.005)\), locules were more uniform \((p=0.024)\) and the enhancement of solid portions was more moderate \((p=0.037)\). Furthermore, Lindgren et al.\(^{70}\) detected a notable association between low ADC values and poorly differentiated ovarian cancers \((p=0.035)\) and lower 3-year overall survival rate in patients with low ADCs \((p=0.023)\). Also, in primary tumours, low ADC values were in correlation with high Ki-67 expression \((p=0.001)\).

FIGO classification (2014) is used for staging of malignant ovarian tumours and it divides tumour

| Table 4. The usual MRI appearance of selected malignant ovarian tumours |
|--------------------------|--------------------------------------------------------------------------------------------------|
| MRI appearance\(^{8,22,83,84}\) | SC=Cystic or multilocular tumour with solid components, thick septa, mural nodules and papillary projections |
| EMC=Solid or cystic tumour with smooth margins |
| MC=Multilocular cystic tumour with thick septa and honey-comb like locules |
| IT=Large, complex solid tumour with cystic areas, soft tissue components, calcifications and fat |
| DY=Multiloculated solid tumour with fibrovascular septa, necrosis and haemorrhage |
| AGCT=Unilateral, solid tumour; multilocular cystic tumour with solid components; solid tumour with sponge-like appearance; often haemorrhage foci |
| JGCT=Large, unilateral, multiloculated cystic tumour with a solid portion, irregular septa and intracystic haemorrhage |

SC= serous carcinoma; EMC=endometrioid carcinoma; MC=mucinous carcinoma; IT=immature teratoma; DY=dysgerminoma; AGCT=adult granulosa-cell tumour; JGCT=juvenile granulosa-cell tumour
spread into four stages. Stage I tumour is confined to one ovary or the fallopian tube (IA) or both ovaries or fallopian tubes (IB). The tumour capsule is intact and there is no presence of malignant cells in ascites or peritoneal washings. Stage IC is suspected with intraoperative spill (IC1), ruptured capsule or tumour on ovarian or fallopian tube surface (IC2), findings of tumour cells in ascites or peritoneal washings (IC3). In the review, Javadi et al. emphasize the fact that stage I presence of unilateral dominant mass and contralateral multiple or small masses may represent metastatic disease. Findings of tumour extension or implants on uterus or fallopian tube are suggestive for stage IIA whereas the involvement of other pelvic tissues represents stage IIB.

The majority of ovarian malignancies present as stage III (84% are stage IIIC) with HGSC as the main representative. Stage III of the disease involves one or both ovaries or fallopian tubes with extrapelvic peritoneal implants and/or retroperitoneal LN involvement. Ovarian carcinoma mainly spreads through the paraortic and pelvic lymphatic pathways. The diagnosis of lymphadenopathy is based on a short-axis diameter of LN ≥ 10 mm. The threshold LN size of 2 cm in the distinction between stages IIIB and IIIC is purely subjective and not evidence-based. In addition, stage IIIC includes perihepatic metastases but without the parenchymal invasion. Lesions usually display elliptic or biconvex shape and smooth contours along the liver surface. However, the invasion of the surface may occur in less than 5% of cases. In addition, ascites may be one of the imaging pitfalls because it can obscure peritoneal implants in delayed contrast-enhanced MRI. Stage IV of the disease is present at 12-21% of patients. The main characteristic of the stage IVA is presence of pleural metastasis with subsequent radiological display (pleural effusion, pleural nodularity, focal pleural thickening). Stage IVB is composed of parenchymal and extraabdominal metastases, mainly into liver, spleen, inguinal and supraclavicular LNs. Recurrence in malignant ovarian tumours most commonly appear in vaginal vault, rectouterine excavation and as abdominal peritoneal implants. In 18-33%, LN metastases are detected in paraaortic region.

CONCLUSION

MRI provides excellent soft-tissue contrast resolution and is widely accepted as the first choice or problem solving imaging modality for the diagnosis, staging, treatment planning and follow-up of selected gynaecological malignancies. The addition of multiparametric MRI protocols enabled more precise assessment of tumour invasion and improved staging accuracy altogether. Further investigations are needed to improve limited diagnostic performance of MRI in patients with LN metastases and complex ovarian tumours. With constant development of new imaging techniques and emerging importance of tracer kinetic models, MRI has potential to improve patient’s outcome and overall survival rates.

Conflicts of Interest: Authors declare no conflicts of interest.

REFERENCES


