JBUON 2016; 21(3): 542-548
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

REVIEW ARTICLE

The role of magnetic resonance imaging in the evaluation of endometrial carcinoma

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Summary

Purpose: *Gynecological cancers comprise about 19% of all cancers in women whereas the endometrial cancer is the most common malignant tumor of the female reproductive organs. The application of modern imaging tools plays an important role in the preoperative assessment of disease extent and allows the selection of a proper and adequate therapeutic approach for each patient. The purpose of this review was to show the role of magnetic resonance imaging (MRI) in the evaluation of endometrial carcinoma. MRI enables the display of zonal anatomy of the uterus, detection of the anomalies as well as the detection and characterization of pathological processess. Endometrial cancer is staged with the International Federation of Gynecology and Obstetrics (FIGO) classification, which was significantly revised in 2009. The FIGO classification incorporates two of the important prognostic parameters, the depth of myometrial invasion and histological grade. The depth of myometrial invasion can be accurately assessed by MRI.*

MRI is not officially included in the FIGO staging system. However, it is widely accepted as a suitable imaging technique for preoperative staging, treatment planning and monitoring of patients with endometrial cancer.

Key words: *cervical invasion, endometrial carcinoma, magnetic resonance imaging, myometrial invasion*

Introduction

Gynecological cancers comprise about 19% of all cancers in women whereas endometrial cancer is the most common malignant tumor of the female reproductive organs [1]. The incidence rate of endometrial cancer increases with age [2]. Endometrial cancer is most common in postmenopausal women, and in the premenopausal group it is often associated with obesity, nulliparity, anovulation, diabetes and hypertension [3]. A group at risk for developing endometrial carcinoma includes young women with ovarian cancer, as well as the carriers of autosomal dominant mutations of the DNA mismatch repair (MMR) gene in germ cells [4-6]. The first and the most common symptom of malignant endometrial diseases in about 90% of the patients is an abnormal postmenopausal vaginal bleeding [7].

Endometrial adenocarcinoma is the most common type of endometrial cancer, and is characterized by good prognosis as well as good survival rate [8].

Although a serious approach in symptomatic women leads to early diagnosis and excellent survival rates, there are still no screening tests recommended for asymptomatic women [9].

Treatment planning for each patient depends on the stage of disease and known prognostic factors. The prognostic factors include the histologic

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Received: 16/10/2015; Accepted: 04/11/2015

type, nuclear and histological grade, invasion of the cervix, depth of myometrial invasion, involvement of adjacent organs, regional lymph nodes, presence of distant metastases, patient age, and menopausal status. The application of modern imaging tools (computed tomography-CT, MRI) plays an important role in the preoperative assessment of disease extent and allows the selection of a proper and adequate therapeutic approach for each patient. This way, both the patients requiring a more radical therapeutic approach as well as those who do not require surgery are selected [10,11]. The application of MRI preoperatively reduces the need for an unnecessary nodal dissection [12].

MRI protocol

Pelvic examination is performed in T1W and T2W sequences in at least two planes of scanning. The differentiation of the pathological process can be facilitated by the use of the inversion recovery (IR) sequence as well as T1W fat-suppressed sequences before or after the administration of contrast agent. TW2 sequence in the sagittal plane is the basis of MRI of the female pelvis. MRI enables the display of zonal anatomy of the uterus, detection of the anomalies as well as the detection and characterization of pathological processes.

The sequences enabling the suppression of fat (FAT-SAT) are used for better detection of the processes in structures with excessive fat. Post-contrast studies are used to evaluate endometrium and to assess the local extent of tumor in the uterus. MRI cannot be applied as a screening method, since carcinomas in situ and hyperplasia, as well as polyps cannot be distinguished in an image [13,14].

The most commonly used protocol includes the following sequences: T1 TSE COR, T2 TSE COR, T1 TSE SAG, T2 TSE SAG, T2 SPC NS TRS COR P3 ISO, T1 TRA, T2 TRA, T1 VIBE FS precontrast and T1 VIBE FS TRA, T1 TSE FS SAG, and T1 VIBE FS TRA delayed postcontrast scans.

Normal MRI appearance of the uterus

The position of the uterus varies. Typically, the uterus is located centrally, set on the roof of the bladder. The size and perfusion (an increase of signal intesity (SI) after the contrast administration) vary during the menstrual cycle. After intravenous contrast administration the uterine cavity is visualized as a ring or a T- shaped hypointense structure. On MRI, corpus is characterized by a relatively low SI on both pre and post contrast T1W sequences.

T1W sequences are used to assess the external uterine contour, to evaluate the presence of hematometra and to display lymph nodes. The images include a large field of view to evaluate the entire pelvis and upper abdomen [14].

On T2W sequences, endometrium is distinguished by a high SI from the myometrium which shows an intermediate SI. Two layers of the myometrium can be seen on these sequences. The outer layer is of an intermediate SI whereas an inner one is of lower intensity - junctional zone. This hypointense band known as junctional zone has no clear histomorphological analogue. The appearance of this zone on MR images is probably caused by the reduction of water content, caused by closely packed compact smooth muscle cells with little extracellular matrix, which consequently changes the signal. Endometrium usually shows a high SI on T2W. Endometrial thickness varies from 1-7 mm throughout the menstrual cycle (Figure 1a). The tumor is evaluated on these sequences [14,15].

After intravenous administration of Gd-DTPA contrast agent, the myometrium of a premenopausal woman shows a high SI on postcontrast images, whereas it shows a late moderate enhancement on dynamic sequences. The junctional zone, if it is registered, has a lower SI compared to the rest of the myometrium (Figure 1b). In that case, muscle and cervical tumor invasion can be evaluated on T1W sequences as well , but in a smaller area. Following the contrast administration, the zones also seen on T2W sequences, are shown. In a postmenopausal uterus these three zones are not recognized well. Postmenopausal myometrium is characterized by a homogeneous SI that is lower than in a premenopausal uterus. The maximum thickness of the postmenopausal

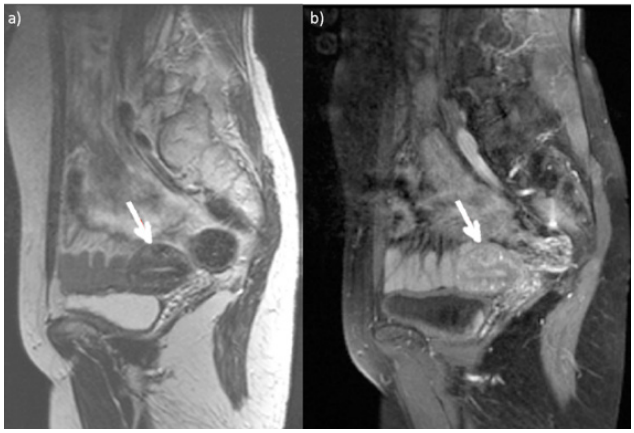

Figure 1. Pelvic MRI: a) T2W image and b) T1W C+ image show a normal uterine anatomy (arrows).

endometrium is between 3 and 5 mm. Cervical stroma does not increase significantly. However, endocervix is better shown [14].

Dynamic MR (DCEMRI) monitors the passage of contrast in time, through the tumor tissue. In the early enhancement phase (0-1 min), subendometrial zone is monitored. It enhances earlier than the bulk of myometrium corresponding to the inner juncional zone. This is particularly significant for postmenopausal women, in whom the junctional zone cannot be seen well. In the next stage of equilibrium (2-3 min) myometrial invasion depth is evaluated. In the late stage a cervical stromal invasion by the tumor (4-5 min) is evaluated [14].

MRI appearance of endometrial carcinoma

Endometrial cancer is assessed with T2W sequences, in at least two planes: the sagittal and the axial plane. It appears as a thickened endometrium and an expanded cavity. The tumor is of intermediate to high SI, but often lower than a typical SI of the endometrium. The abnormal endometrium often appears as heterogeneous SI on T2W. An estimation of the invasion depth is made on T2W sequences. Sometimes application of the contrast is required in order to distinguish the tumor more precisely from the surrounding myometrium as a zone that slowly and to a lesser degree enhances SI compared to an intact myometrium [13,14].

On T1W sequences endometrial carcinoma is isointense as a normal endometrium. On T2W sequences it may be of lower intensity, isointense, of higher intensity or heterogeneous. After intravenous administration of contrast medium, the lower segments of a normal myometrium show earlier enhancement. Endometrial cancer shows earlier enhancement compared to a normal endometrium and a later one compared to the myometrium. The maximum of the contrast between a tumor and the myometrium is achieved in the equilibrium phase. The application of contrast medium has increased the precision of the method and has provided a more precise staging of endometrial cancer [16]. In cases where the junctional zone cannot be detected it is necessary to perform the imaging with the contrast since false-positive results will be reduced [17]. Endometrial cancer shows lower intensity compared to the normal myometrium and it increases slowly on dynamic sequences [18,19]. The diagnosis of myometrial invasion is established by the detection of an interruption of the junctional zone, which appears more hypointese compared with the rest of the myometrium. In postmenopausal women there may be a problem with the identification of the zonal anatomy as well as in patients with a large polypoid tumors located in cavum [17]. Multiple myomas and congenital anomalies, and retroversions can also cause problems with the required identification of the junctional zone [14,17,20]. In patients with adenomyosis (the presence of ectopic endometrial tissue, glands and stroma in the uterine muscle) the sensitivity of MRI is significantly lower. MRI results are more accurate if dynamic MRI is performed. Authors dealing with this type of cancer state that in this case suspicious focal areas of low intensity can be noticed in the early stage of contrast spreading while in the late phase the contrast spreads through the entire endometrium [14,17,19]. Therefore, it is strongly recommended to use dynamic sequences in patients with adenomyosis (8-16% frequency), to achieve a more precise assessment of the depth of the invasion [21].

Staging of endometrial carcinoma; FIGO classification

The staging of cancer is one of the fundamental activities in oncology and is very important in the modern treatment of cancer patients. The staging of the disease helps in treatment planning, prognosis, treatment evaluation, spreading knowledge about the course of the disease and cancer research. Endometrial cancer is staged with the FIGO classification, which was significantly revised in 2009 (Table1) [22, 23].

FIGO classification incorporates two of the important prognostic parameters, the depth of myometrial invasion and the histological grade. It is well known that the depth of invasion is correlated with the occurrence of lymph node metastases. The survival of patients with endometrial cancer decreases with increasing depth of myometrial invasion [24].

The depth of myometrial invasion can be accurately assessed by applying MRI, whereas endometrial sampling enables the determination of the histological grade. MRI findings represent an important predictor of lymph node metastases. In order to determine whether to apply transabdominal, transvaginal, or laparoscopic surgical approach, additional information provided by MR imaging staging examination (eg, the size of the uterus , tumor volume, presence of ascites or adnexal disease) may be very helpful [25].

Table 1. Revised FIGO staging system for endometrial carcinoma

Stage I	Tumor confined to the corpus uteri / involvement of the epithelium and endocervical glands
IA	< 50% myometrial invasion
IB	≥ 50% myometrial invasion
Stage II	Cervical stromal invasion
Stage III	Local and regional spread of the tumor
IIIA	Tumor invades the serosa of the corpus uteri or adnexa
IIIB	Tumor invades the vagina or parametrium
IIIC	Pelvic or retroperitoneal lymphadenopathy
$IIIC_1$	Involvement of pelvic lymph nodes
$IIIC_2$	Paraaortic lymph nodes involvement
Stage IV	Tumor invades bladder and bowel mucosa / distant metastases
IVA	Tumor invades the bladder or bowel mucosa
IVB	Distant metastases

Due to reported similar prognosis in some of the FIGO substages (stage Ia and IIa) in 2009, the staging system was updated introducing certain precise changes [22,26]. The former staging system had three stage I substages; IA confined to the endometrium, IB<50% myometrial invasion and IC ≥50% myometrial invasion, whereas in the new staging system there are two substages for stage I : IA (<50% myometrial invasion) and IB (≥50% myometrial invasion) [27]. In the new system, stage II has no substages and it considers only cervical stromal involvement (which was stage IIB in the former system), whereas the new system diagnoses endocervical glandular invasion (which was stage IIA in the old system) as a stage I endometrial cancer. In the former staging system both the glandular involvement of the cervix and the differentiation between stage IA and IB had certain challenges. The new 2009 FIGO staging is believed to provide a better accuracy in MRI staging. There are still three subdivisions in stage III : IIIA, IIIB, and IIIC.

Stage IIIA are the tumors that invade the serosa or adnexa, and stage IIIB the tumors invading the vagina or parametrium. In the former system, any lymphadenopathy (pelvic or retroperitoneal) was considered a stage IIIC. However, in the new FIGO system there is a division of stage IIIC into the following stages: stage IIIC1 the characteristic of which is the involvement of a pelvic lymph node and stage IIIC2 which is characterized by paraaortic lymph node involvement [28].

These revisions were introduced owing to the prognostic data that suggest a worse outcome in patients in whom paraaortic nodes are involved compared to those with only involvement of the pelvic nodes. There have been no changes in stage IV: Stage IVA tumors are those extended into the adjacent bladder or bowel, and stage IVB tumors with distant metastases (eg, to the lungs or liver) [28-30].

MRI classification is based on imaging. Therefore, it may be useful, but not sufficient for a definite staging. The sensitivity and specificity of the detection of the depth of myometrial invasion according to the results of different studies ranges from 69% to 94% [16,17,31-34]. The routine use of MRI in patients with endometrial cancer may optimize a surgical procedure by providing information on myometrial and cervical invasion, and the presence of lymph node metastases [35]. Errors in the assessment of myometrial invasion can occur in large polypoid tumors, leiomyomas, congenital anomalies and very small atrophic uterus [14]. MRI is not suitable for the detection of superficial lesions affecting the entire endometrium, as well as for the identification of lymphadenopathy [36].

The depth of the myometrial invasion is the most important prognostic factor and is correlated with tumor grade, cervical invasion by tumor and prevalence of cervical lymph node metastases [37].

Lymph node metastases, as well as the depth of myometrial invasion represent significant prognostic parameters. So far, MRI has not provided precise results in the detection of lymph node metastases [33].

Infiltration of the cervix is an independent prognostic factor, which significantly changes the prognosis, survival and the therapeutic approach [17,31].

Staging

Stage I: Tumor confined to the corpus uteri with possible involvement of the epithelium and endocervical glands.

Stage Ia: the tumor has not penetrated the uterine muscle (intramucosal lesions). An image obtained by MRI may show a thickened or normal endometrium, a well-defined junctional zone along the entire circumference of the uterus and

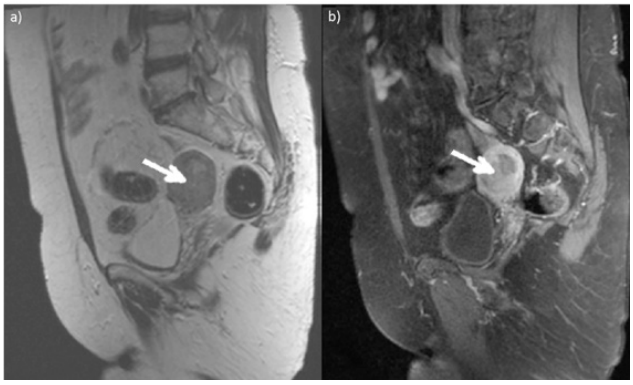

Figure 2. Pelvic MRI: a) T2W and b) T1W C+ images show endometrial carcinoma with infiltration of myometrium > 50% (arrows); complete loss of the junctional zone (stage Ib).

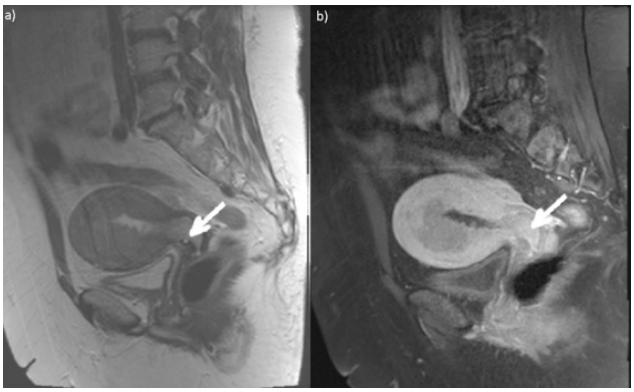

Figure 3. Pelvic MRI: a) T2W and b) T1W C+ images show a tumor protruding into the cervical canal with the affected epithelium of the cervical glands and intact stroma (arrows) (stage I).

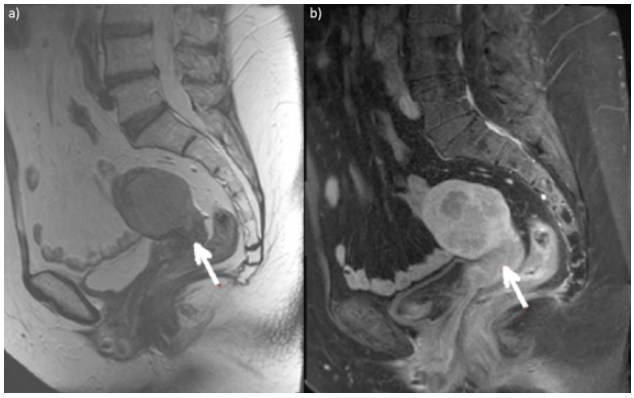

Figure 4. Pelvic MRI: a) T2W and b) T1W C+ images show cervical stromal invasion without a clear distinction between epithelium and stoma (arrows) (stage II).

lack of the interruption of the zone of subendometrial enhancement . Dynamic contrast-enhanced sequences are useful when the junctional zone cannot be seen well (often in postmenopausal patients). There is a clear distinction between the endometrium and myometrium on T2W sequences and contrast enhancement on dynamic T1W sequences [14,32,37].

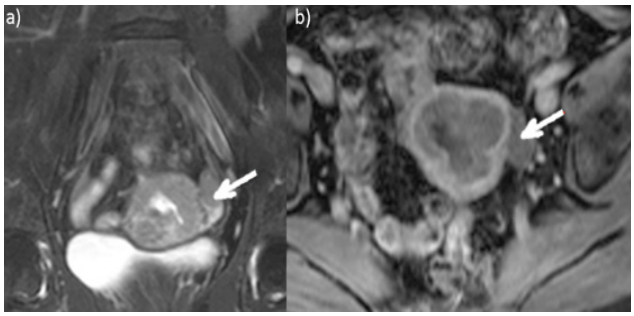

Figure 5. Pelvic MRI: a) T2W and b) T1W C+ images show adnexal metastasis (arrows) (stage IIIa).

In addition, stage Ia includes tumors affecting up to 50% of the myometrium. An obtained MRI image shows a complete disruption of the junctional zone of the subendometrial enhancement. The inner edge of myometrium is uneven.

Stage Ib: the tumor affects more than 50% of the uterine muscle (Figures 2a,b). MR image shows a complete loss of the junctional zone of the subendometrial enhancement. The tumor signal penetrates deep into the myometrium, whereas only the outer myometrium layer remains intact [28].

The inner axis of the cervix and endocervical canal are wavy and enhanced. The stroma of the cervix is of low density and appears intact (Figures 3a,b).

Stage II: The invasion of the cervix. Absence of cervical invasion can be determined by the visualization of the entire cervical canal and the presence of clear contour of the cervical epithelium on TW2 images or on postcontrast T1W images, when there is a clear post-contrast enhancement.

The presence of cervical stromal invasion is shown in Figures 4a,b. There is no clear distinction between epithelium and stoma. Post-contrast images do not show a clear distinction either. Therefore, the assessment of the invasion of the cervix by MRI is significantly less sensitive and reliable compared to the assessment of the myometrial invasion [28].

Stage III: The tumor penetrates the uterine serosa, affects the vagina or the lymph nodes.

IIIa: The tumor penetrates the uterine serosa. There is a complete interruption of the continuity of the outer layer of the uterus, loss of uterine configuration and a possible invasion of the ovaries and the fallopian tubes by the tumor (Figures 5a,b).

IIIb: the vagina is affected by the tumor. A segmental loss of hypointense structure of the

vaginal wall is seen on the images.

IIIc: affected lymph nodes. Images show enlarged lymph nodes. Nodes larger than 1 cm are considered pathological. The role of MRI in the detection of lymph nodes is debatable [33]. In a study Manfredi et al. [16] the sensitivity of MRI for the detection of lymph node metastasis was 50% and the specificity 90%. Sensitivity may be increased by the application of specific contrasts [28,39].

This stage is divided into 2 substages:

IIIC1: characterized by pelvic lymph node involvement, and *IIIC2*, characterized by paraaortic lymph node involvement which significantly influences survival, since the patients with paraaortic lymph nodes have worse outcomes.

Stage IV: the tumor has spread to the bladder epithelium, intestine or distant metastases have developed.

IVa: The tumor is affecting the bladder epithelium or intestine. The signal of the normal boundaries between the uterus and the bladder or the bladder and rectum is disrupted. In case of suspicion of disease spread to the bladder and rectum, rectoscopy and cystoscopy should be conducted to confirm the diagnosis.

IVb: Tumor metastases are registered in distant organs [28].

Conclusion

MRI is not officially included in the FIGO staging system. However, it is widely accepted as a suitable imaging technique for preoperative staging, treatment planning and monitoring of patients with endometrial cancer. This method provides high resolution images with good contrast without exposure to radiation.

Conflict of interests

The authors declare no confict of interests.

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