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Review Article

Role of MRI (Magnetic Resonance Imaging) in Preoperative Staging of Endometrial Cancer: A Review

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Abstract

Endometrial cancer is the most common malignancy of female genitourinary tract. It is primarily the cancer of post-menopausal women that occurs mostly in women during the 6th and 7th decades of age. Preoperative examination may include clinical assessment, pap smear test, Trans-Vaginal Ultrasound (TVU), abdomino-pelvic CT scan and pelvic MRI. MRI can be used as the sole imaging method before surgery in patients with endometrial cancer to evaluate myometrial invasion appropriately.

The staging accuracy by means of MRI in patients with endometrial cancer has been reported between 83 to 92%. According to MRI assessment, endometrial cancer can be staged by evaluating myometrial invasion, cervical, vaginal and nodal involvement. This paper comprehensively reviews the role of pre-operative MRI in endometrial cancer.

Keywords: Endometr; Cancer; MRI

Epidemiology

Endometrial cancer is the most common malignancy of female genitourinary tract which accounts for the fourth prevalent cancer among women (following breast, lung and colon cancers) [1,2]. It has been reported that endometrial cancer is the seventh most common cancer all over the world which is more common in developed countries than developing countries [3]. The incidence of this malignancy is ten times higher in North America and European countries than developing countries [3,4]. It is primarily the cancer of post-menopausal women that occurs mostly in women during the 6th and 7th decades of age. The incidence of this cancer in women younger than 40 years reports between 2-5% and near 25% of affected patients are premenopausal women [5,6].

The prognosis of this cancer depends on different factors such as: depth of myometrial invasion, histologic grade, disease stage and lymphatic stage. Survival of affected patients range from 20-91% with higher survival for white women than black ones (77% vs 60%) [7,8].

Risk Factors

Obesity, diabetes mellitus, nulliparity, estrogen therapy, tamoxifen regimen, BMI≥ 25, physical inactivity and blood pressure above 140/90 mm Hg are among considerable endometrial cancer risk factors. Women with Stein-Leventhal syndrome, granulose/theca cell tumors of the ovary are at risk for endometrial cancer development [9-12]. Long lasting estrogen exposure will lead to endometrial hyperplasia which is a leading cause of atypical hyperplasia and endometrial cancer development [3]. Women who are receiving tamoxifen regime treatment can develop endometrial cancer. Tamoxifen which has anti-estrogen effects stimulates endometrium like exogenous estrogen. In premenopausal women, being overweight is associated with insulin resistance, increased ovarian androgen, an ovulation and chronic progesterone deficiency.

On the other hand, in post menopausal women, obesity can lead to endometrial proliferation stimulation, angiogenesis and decreased apoptosis [3]. According to progesterone production by placenta, pregnancy is a preventive factor for endometrial cancer such as intra-uterine devices which produce levonorgestrel [3,13].

Endometrial cancer can be a part of Hereditary Non-Polyposis Colon Cancer (HNPCC) which is a mendelian dominant syndrome of right sided colon, endometrium and other organ cancers. Between 40% and 60% of women with HNPCC have risk factor of endometrial cancer development [14,15].

Pathologies

Between 80-90% of all endometrial cancers are endometroid type-cancers that refer to endometrial type glands [16]. These types of endometrial cancers could range from well differentiated carcinoma (grade1) to anaplastic carcinoma (grade3) [17,18].

According to International Federation of Gynecology and Obstetrics (FIGO) staging system, endometrial cancer grade 1 consists of well formed glands with less than 6% solid non-squamous areas [19]. Grade 2 consists of 6-50% solid non- squamous areas while carcinomas with histological findings compatible with grade3 include more than 50% non- squamous areas [20].

Near 10% of endometrial carcinomas are type 2 which are poor prognosis and at high risk for recurrence as well as metastasis [21,22]. Mucinous carcinoma, Serous carcinoma, Clear-cell carcinoma, Mixed carcinoma, Squamous-cell carcinoma, Transitional-cell carcinoma, Small-cell carcinoma, Undifferentiated carcinoma are classified as type 2 endometrial carcinomas.

FIGO Staging

According to FIGO staging system, myometrial and uterine

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FIGO Staging: Staging Classification (FIGO) for Endometrial Cancer Based on Surgical Findings and Histology.

Stage I	Tumour confined to the corpus uteri
Stage IA	myometrial invasion less than 50%
Stage IB	Invasion equal to or more than half of the myometrium
Stage II	Tumour invades cervical stroma, but does not extend beyond the uterus
Stage III	Local or regional spread of the tumour
Stage IIIA	Tumour invades the serosa of the corpus uteri and/or adnexaeb
Stage IIIB	Vaginal and/or parametrial involvement
Stage IIIC Stage IIIC1 Stage IIIC2	Metastases to pelvic and/or para-aortic lymph nodes Positive pelvic nodes Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	Tumour invades bladder and/or bowel mucosa, and/or distant metastases
Stage IVA	Tumour invasion of bladder and/or bowel mucosa
Stage IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes.

serosa invasion, adnexal involvement, peritoneal cytology, intra abdominal and lymph nodes involvement should be considered in accurate cancer staging (Table 1).

Preoperative Examination

Although preoperative examination is not as accurate as surgical staging, it helps clinicians to tailor treatment.

Preoperative examination may include clinical assessment, pap smear test, Trans-Vaginal Ultrasound (TVU), abdomino-pelvic CT scan and pelvic MRI.

Although higher sensitivity has been reported for CT scan than MRI for detection of retroperitoneal lymph nodes involvement, previous meta analysis showed that diagnostic performance of dynamic contrast-enhanced MRI for myometrial invasion detection is higher than CT or TVU [23].

Magnetic Resonance Imaging (MRI)

MRI can be used as the sole imaging method before surgery in patients with endometrial cancer to evaluate myometrial invasion appropriately.

The staging accuracy by means of MRI in patients with endometrial cancer has been reported between 83 to 92% [24,25]. According to MRI assessment, endometrial cancer can be staged by evaluating myometrial invasion, cervical, vaginal and nodal involvement.

Techniques

Patient preparation

To obtain good diagnosis, it is better to prepare patients before MRI. Supine position is the standard examination position. Patients should void before MR examination [26,27].

One of the major concerns is motion artifacts especially over the focus areas of endometrium and cervix. To reduce this problem it is better for patients to fast 3-6 hours before examination along with Intra-muscular administration of anti-peristaltic agents such as Hyoscine butyl bromie or glucagon [28,29].

If available, a multi channel pelvic phased array coil (using 4 coil configuration), which offers higher signal to noise ration, lower scan time and parallel imaging, is recommended.

Sequences

Although T-1 weighted images provide good information in cases with recent bleeding, they cannot provide good intrinsic uterine tissue contrast. But they are helpful in evaluating uterine borders and surrounding fat and lymph nodes [29].

T-2 weighted images can provide appropriate evaluation of uterine body, cervix, vagina and description of the tumor. Axial oblique, coronal and sagittal planes are mostly obtained to assess the tumor.

The axial oblique images are obtained in plane vertical to uterine corpus.

Pre MRI contrast administration of 0.1 mg/kg gadolinium agent is needed. Contrast administration helps differentiation of tumor from debris and outlines the tumor in patients with indistinct junctional zone. (In patients with GFR<30cc/min contrast administration is not recommended).

Axial oblique images acquire 4 minutes after contrast injection while sagittal images acquire 25 seconds, 1 &2 minutes after contrast injection. These sequences improve sensitivity and negative predictive value of MR evaluation for endometrial cancer assessment [30,31].

The maximum tumor enhancement occurs 60-90 minutes after contrast injection.

It takes between 60 to 90 seconds after contrast injection to differentiate myometrium from tumor correctly (28).

Normal anatomy of uterus

Uterus is a pear-shaped structure which could be evaluated on T-2 weighted images.

Differentiation between enometrium and myometrium on T-1 images is not possible due to similar relaxation times [29].

On T-2 weighted images, three distinct zones of uterus can be identified.

The high signal inner layer is endometrium. The middle layer, myometrium, is low signal in the deep part (junctional zone) and intermediate signal intensity at outer layer.

The difference between inner and outer layer signal intensities is due to lower water content of the inner layer in comparison with outer layer.

The junctional zone, the most inner layer of myometrium, plays an important role in evaluating myometrial infiltration by endometrial carcinoma if its integrity is intact, myometrial infiltration could be excluded.

On T1- Weighted non contrast images, the zonal anatomy of uterus is not seen, because junctional zone and myometrium have similar intermediate signal intensity. After intravenous contrast injection, differentiation between endometrium and myometrium according to asynchronous contrast enhancement will be possible.

Yamashita et al described different uterine enhancement pattern

Table 1: Showes sensitivity, specificity and accuracy of preoperative MRI in evaluating endometrial cancer in different studies.

First author	No of patients	Myometrial invasion sensitivity, specificity and accuracy	Cervical invasion sensitivity, specificity and accuracy	Metastatic lymph nodes sensitivity, specificity and accuracy
Akaeda [40]	21	100% 100% 100%	100%, 89%, 91%	-
Cabrita [34]	162	83% 72% 77%	42% 92% 81%	17% 99% 89%
Manfredi[29]	37	87 91 89	80 96 92	50 95 90
Hori [33]	30	60, 85 , 77	43, 91 , 80	50 88 83
Sala [41]	50	97, 100, 98	88, 100, 98	80, 100

in different phases and age groups [30].

In post menopausal women and during proliferative phase, thin sub endometrial enhancement followed by entire myometrial enhancement can be observed. In secretory phase, early enhancement of junctional zone can be detected. While entric endometrial enhancement is observed during menstruation.

Stage I

In stage I, The tumor is limited to uterine body. Based on the degree of myometrial invasion, stage I could be divided into 2 subgroups.

Irregular endometrium – myometrium interface or disruption of junctional zone should be considered as sign of myometrial invasion.

The junctional zone is hypo intense on T2 – weighted images and shows early enhancement after contrast injection [32]. T1 – weighted images showing enhancement during equilibrium phase and a hypovascular lesion within the enhancing myometrium could be observed. If the myometrial invasion is less than 50%, the tumor stage is IA and if the invasion is equal or more than 50% the tumor stage is IB. Previous studies showed that MRI accuracy for detecting depth of myometrium invasion by endometrial carcinoma could vary from 68% to 80% by means of T2- weighted images while dynamic images during injection could improve accuracy of assessment to 83% - 91% [28-30] according to improved contrast to noise ratio between endometrial cancer and myometrium.

Stage II

The previous FIGO staging system, divided Stage II into two subgroups: IIA (endo-cervical glandular invasion) and IIB (cervical stromal invasion).

The new FIGO staging system, considers stage IIA as stage I and stage IIB as stage II.

Disruption of low signal intensity of cervical stroma by the higher signal intensity of endometrical carcinoma on T2 – weighted images is considered as cervical stromal invasion. Contrast enhanced images will help to differentiate tumor from debris [24,28].

The sensitivity, specificity and accuracy of MRI in evaluating cervical invasion has been reported as 67% - 100%, 92% - 100% and 92% [28,31].

Stage III

In stage III tumor spreads outside the uterus to serosa and/or adnexa, (IIIA) vagina and/or parametrium (IIIB) or to pelvic or para-aortic lymphnodes (IIIC) [32].

Transmyometrial extensions, interruption of the low signal intensity of the serosa / involvement of adenex or positive peritoneal cytology are characteristics of stage IIIA tumors.

In patients with stage IIIB, as upper vagina is involved, disruption of the low signal intensity of vaginal wall could be detected.

Metastases to pelvic and/or para-aortic lymph nodes are characteristic of IIIC tumors.

According to the good contrast – to – noise ratio of the lymph nodes (as they are low to moderate signal intense) and surrounding fat (high signal intense), lymph nodes could be visualized well on T1-Weighted images.

The sensitivity of MRI for detecting metastatic lymph nodes ranging from 17% to 80% (33-37) by considering cut off point 10mm.

When cut off point reduces to 8mm, sensitivity of metastatic lymph nodes increased while specificty decreased. (sensitvitiy increased from 44% to 66%) while specificity decreased from 98% to 73% [35].

Stage IV

If the tumor invades other organs such as bladder, rectum, bowel or distance metastasis such as lung, liver ... the stage will be IV.

In stage IVA bladder involvement will be present as focal or diffuse disruption of the low-signal intensity of posterior bladder wall, nodular or irregular bladder wall, protrusion of mass into bladder lumen and presence of bullous edema [36,37].

Segmental thickening and loss of the anterior wall of rectum are characteristics of rectum involvement.

Sensitivity and specificity of MRI in evaluating bladder or rectum involvement ranged from 71 – 100% and 88-91% [38,39].

Distant metastasis such as abdominal lymph node involvement (without pelvic lymph node involvement) and peritoneal involvement are characteristic of stage IVB.

A study lemducted by hardesty et al showed that preoperative MRI had or similar cast and accuracy to surgery in patients with endometrial cancer [42]. Therefore, preoperative MRI could help the physician to triage patients for appropriate and suitable management.

Dynamic Contrast-Enhanced MRI

By means of dynamic Contrast-enhanced MRI more accurate staging of endometrial cancer could be possible. Tumors can be distinguished from blood products and debris due to different enhancement [30,43]. After administration of contrast agent, tumors will enhance earlier than normal endometrium which are hypointense in comparison with intense endometrium and hyper

intense myometrium. Myometrial invasion could be assessed 50-120 seconds after agent application while maximum intensity difference occurs between myometrium and tumor happens.

Three or four minutes after contrast injection, delayed phase images will be obtained to evaluate stromal invasion.

Studies showed that combination of T2-weighted images and dynamic Contrast-enhanced MRI will improve accuracy of MR evaluation up to 98% [44-48].

Diffusion Weighted MRI

Water mobility, cellularity of the tissue and integrity of the cell membranes could be evaluated by means of Diffusion weighted MRI [49-51]. High signal intensity and restricted diffusion on diffusion weighted MRI are characteristics of endometrial tumors. Diagnostic accuracy of Diffusion weighted MRI for evaluating myometrial invasion ranged from 62% to 90% [52,53]. Its application in patients with endometrial cancer for further assessment is not well established and more researches are needed to demonstrate its usefulness.

Pitfalls of MRI in Evaluating Endometrial Cancer

It's should be considered that, as endometrial cancer mostly occurs in postmenopausal women and myometrium and endometrium become thinner in these cases, on T2 – weighted images, lower signal intersity of myometrial outlier will be observed. Therefore, the junctional zone could not be clear [29-31].

The other pitfall of MRI is over estimation of parametrial invasion in large tumors due to stromal edema. (In large tumors accuracy estimated as 70% while in small tumors accuracy reported as 96%).

Conclusion

Preoperative MRI could be valuable for staging endometrial cancer.

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