BOHR Journal of Obstetrics and Gynaecology
2023, Vol. 1, No. 1, pp. 29–34
DOI: 10.54646/bjog.2023.05
www.bohrpub.com

ORIGINAL RESEARCH

Diagnostic accuracy in the detection of depth of myometrial invasion with MRI in early-stage endometrial cancer

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Received: 20 October 2023; **Accepted:** 02 November 2023; **Published:** 15 November 2023

Objective: To study the diagnostic accuracy of pre-operative magnetic resonance imaging (MRI) in early-stage endometrial cancer with postoperative International Federation of Gynecology and Obstetrics (FIGO) staging after comprehensive staging surgery.
Methods: Retrospectively, the medical records of 78 patients with early-stage endometrial cancer were analyzed for the involvement of the myometrium with the tumor by diagnostic MRI and compared with histopathological reports after surgical staging.
Results: The median age of patients was 56 years (ranging from 32 to 73). The median body mass index (BMI) of these women was 29 (ranging from 20 to 40). On histopathology, 72 women (92.3%) had type I endometroid endometrial cancer and 6 (7.7%) had type II carcinoma; four had papillary serous carcinoma, one had clear cell carcinoma and one had undifferentiated carcinoma. However, 43 (55.1%) had a grade I tumor, 12 (15.1%) had a grade II tumor and 17 (21.6%) had a grade III tumor. Further, 35 (44.8%) were staged laparoscopically, and 43 (55.1%) underwent open staging laparotomies. Pre-operative MRI radiological staging was carried out on all patients before surgery. However, 52 (66.7%) had stage IA disease, which suggested less than half of myometrial infiltration by tumor. Further, 21 (26.9%) showed more than half myometrial infiltration stage IB. One (1.2%) patient had stage IIIC1 disease with pelvic nodes of 2.5 × 2 cm near the obturator fossa; one (1.2%) patient had retroperitoneal nodes and para-aortic nodes of the largest 2 × 2 cm; three patients (3.8%) showed involvement of the endocervix with the tumor. Patients were histopathologically staged postoperatively according to the FIGO classification following complete staging surgery. Further, 46 (59%) were stage IA, 26 (33.3%) were stage IB, 3 (3.8%) showed stage II and 3 (3.8%) had stage IIIC1. The sensitivity for MRI for stage IA was 95.65% with (85 to 99.4%) 95% CI. The specificity was 75%, with 56.6 to 88.55% of the 95% CI. The positive likelihood ratio was 3.83, with a 95% confidence interval of 2.09 to 6.99. The sensitivity of MRI for stage IB was 69.23%, ranging from 48.2 to 85.6% of the 95% CI. The specificity was 94.23%, with 84 to 98% of the 95% CI. The positive likelihood ratio was 12, with a 95% confidence interval of 3.8 to 37.
Conclusion: A pre-operative MRI contributes to the accurate staging of endometrial cancer to allow planning for the scale of the surgery. This is important for pre-operative counseling. The depth of myometrial infiltration aids in the planning of pelvic and para-aortic lymphadenectomy. Our study is comparable with the results of previous studies.

Keywords: endometrial cancer, depth of myometrial infiltration, MRI

Introduction

Endometrial cancer (EC) is the sixth most common cancer in the world, and it is the leading cause of death worldwide, with nearly 200,000 cases diagnosed each year (1).

The third most frequent genital cancer in women in India is EC.

The evaluation of EC is done by basic ultrasonography (USG) or transvaginal USG. Endometrial biopsy performed in the office using pipelle or dilatation and curettage is

used to confirm EC (2). Once the diagnosis is confirmed, further workup needs evaluation for the stage of the disease, which is done by magnetic resonance imaging (MRI) of the abdomen and pelvis.

In the assessment of EC, MRI is crucial. The best method for determining the extent of myometrial invasion and cervical involvement prior to surgery is MRI. The MRI gives a fair diagnosis of radiological staging, which includes the location of the tumor/lesion size, the depth of myometrial invasion, the presence of disease in the endocervix and extrauterine surfaces, as well as the involvement of nodes, the parametrium, the adnexa and other adjacent structures in locally advanced disease (3–5).

The stage, the extent of lymphatic and myometrial invasion, the histologic grade and the nodal status all affect the prognosis. The most significant morphologic prognostic factor, which correlates with tumor grade, the presence of lymph node metastases and overall patient survival, is the depth of myometrial invasion (6). With superficial myometrial invasion, the prevalence of lymph node metastases rises to 3%; however, with deep myometrial invasion, it rises to 46%.

Prior to surgery, it is crucial to know the extent of the myometrial invasion and the histologic grade in order to customize the surgical strategy for these patients (7, 8). While endometrial sampling can be used to determine the histologic grade, MRI can accurately measure the depth of myometrial invasion.

Pre-operative MRI is a vital step in the evaluation of ECs as it can accurately evaluate the depth of myometrial invasion, which is an important morphological prognostic factor. The standard imaging protocol should include T2-weighted images in at least two planes orthogonal to the uterine cavity. Diffusion-weighted images, pre-contrast fat suppressed T1 images and dynamic gadolinium-enhanced three-dimensional (3D) gradient recalled echo T1-weighted images. In addition to this, axial and coronal FIESTA sequences are performed for evaluation of the upper abdomen (9, 10).

On non-enhanced T1 images, ECs appear hypointense to normal endometrium and heterogeneous intermediate signal intensity to hyperintense endometrium. Endometrial tumors are relatively hyperintense compared to normal myometrium on T2-weighted images. The endometrial tumors show restricted diffusion on diffusion-weighted imaging and appear hyperintense on the same.

On post-contrast imaging, they appear hypointense due to the relative intense enhancement of the surrounding myometrium, thereby aiding an inaccurate assessment of the depth of myometrial invasion (11, 12). Furthermore, MRI can aid in staging by detecting parametrial invasion, infiltration of the cervix, vagina, adnexal structures and adjacent bowel and or bladder. It also aids in the diagnosis of pelvic and para-aortic lymphadenopathy (13).

TABLE 1 | 2009 FIGO staging system for endometrial cancer stage description.

IA	Tumor confined to uterus, < 50% myometrial invasion
IB	Tumor confined to uterus, > 50% myometrial invasion
II	Cervical stromal invasion
IIIA	Tumor invasion into serosa or adnexa
IIIB	Vaginal or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Para-aortic node involvement
IVA	Tumor invasion into bladder or bowel mucosa
IVB	Distant metastases (including abdominal metastases) or inguinal lymph node involvement
FIGO	

The gold standard of confirmation is final histopathology after comprehensive surgical staging. Based on the histopathological tumor type, grade, and depth of myometrial invasion, risk categories are created for EC patients. The International Federation of Gynecology and Obstetrics FIGO (14) system is used to surgically stage EC; pre-operative staging is crucial for determining the course of treatment.

MRI is frequently used to assess the depth of myometrial invasion in the early stages. Low-risk patients can be chosen for pelvic or para-aortic lymph node sampling with this information, avoiding radical surgery and lymphadenectomy (15–18).

FIGO's 2009 staging system (**Table 1**) correctly classifies myometrial invasion as IA or IB if it is less than or greater than 50%. However, determination of myometrial invasion may be challenging due to an irregular endo-myometrial junction, exophytic tumor growth, adenomyosis, extensive leiomyomas and different patterns of myometrial invasion; MRI helps in preoperative staging (19).

The type of surgery is determined by the tumor's pre-operative and intra-operative classification (13). This includes the tumor's grade, depth of myometrial invasion, tumor size, sentinel node, frozen section, and, depending on the findings, pelvic lymphadenectomy and para-aortic lymphadenectomy (20).

Methods

Retrospective study

The medical records of the patients with EC who were evaluated and treated from January 2014 to December 2015 were analyzed. The diagnosis of EC was confirmed by endometrial biopsy (either by pipille or dilatation and curettage). A pre-operative MRI was performed on all these patients prior to surgical staging.

TABLE 2 | The parameters, such as age, body mass index, parity and history of treatment for infertility were noted.

Characteristics	Median	
Age (yrs)	56	range (32–73)
BMI	29	range (20–40)
Menopausal status	Premenopausal	33
Comorbidities	Postmenopausal	45
Diagnostic confirmation on	Diabetes	26 (33.3%)
histopathology	Hypertension	18 (23.1%)
	Diabetes and	26 (33.3%)
	hypertension Other chronic illness	08 (10.3%)
	Endometrial biopsies (office procedure)	31(39.7%)
Type of endometrial	Dilatation and curettage	47 (60.3%)
cancer	Type I	72 (92.3%)
	Type II	06 (7.7%)
Grade of tumor	Grade I	43 (55.1%)
	Grade II	12 (15.1%)
	Grade III	17 (21.6%)
Type II endometrial	Uterine serous papillary	4
cancer	Clear cell cancer	1
	Undifferentiated adenocarcinoma	1
Surgery Laparoscopic	43	(55%)
staging Open staging	35	(44.8%)
Observation	32 (41%)	
Radiotherapy	43 (55.2%)	
Chemotherapy + RT	3 (3.8%)	

Clinical and pathological variables, grade, stage and histopathological type were noted and compared with radiological stage according to MRI. Patient with stage IA grade I endometroid carcinoma characteristics' variables.

The inclusion criterion was histologically confirmed EC, with an MRI done pre-operatively followed by surgery.

The exclusion criteria were the following:

1. Patients who were treated for another primary or who had synchronous primary.
2. A patient who had advanced disease with vaginal and parametrical involvement was treated with concurrent chemo and radiotherapy.
3. A patient with advanced disease.
4. A patient who did not have an MRI pre-operatively.

The demographics were followed up. Patients with stage I high risk, high intermediate risk or stage II high risk received adjuvant radiotherapy.

TABLE 3a | Pre-operative MRI (as per 2009 FIGO staging).

MRI Findings Stage 1A	52 (66.6%)
Stage 1B	21 (26.9%)
Stage 2	1 (1.2%)
Stage IIIC1	1 (1.2%)
Stage IIIC2	Nil

Results

A total of 183 patients were registered and indexed under carcinoma of the uterus for 2 years, from 2017 to 2019. Patients who received upfront radiotherapy and chemotherapy, as well as those treated with other primary with EC, were excluded. The study's inclusion criteria were met by 78 patients. The median age of the patients was 56 years (ranging from 32 to 73).

The median BMI of these women was 29 (ranging from 20 to 40). Diabetes was present in 26 (33.3%) of the patients, hypertension in 14 (17.9%), diabetes and hypertension in 3 (3.8%) of the patients and bronchial asthma in 1 patient. The diagnosis of EC was confirmed by office endometrial biopsy by Pipelle in 31 (39.7%) patients, dilatation and curettage D&C was performed on 47 (60.3%) patients.

On histopathology, 72 (92.3%) had type II endometroid EC, 6 (7.7%) had type II carcinoma, 4 had papillary serous carcinoma, 1 had clear cell carcinoma and 1 had undifferentiated carcinoma. Further, 43 (55.1%) had a grade I tumor, 12 (15.1%) had a grade II tumor and 17 (21.6%) had a grade III tumor. However, 35 (44.8%) patients were staged laparoscopically, and 43 (55.1%) patients underwent open staging laparotomies.

Prior to surgery, all patients underwent pre-operative MRI (**Table 3a**) radiological staging. However, 52 (66.7%) patients had stage IA disease, which suggested less than half of myometrial infiltration by tumor. Further, 21 (26.9%) patients showed more than half myometrial infiltration at stage IB. Moreover, 1 (1.2%) patient had stage IIIC1 disease with pelvic nodes of 2.5 × 2 cm near the obturator fossa, 1 (1.2%) patient had retroperitoneal nodes and para-aortic nodes of the largest 2 × 2 cm and 3 patients (3.8%) showed involvement of the endocervix with the tumor.

TABLE 3b | Post-Surgical histopathological stage (as per 2009 FIGO staging).

Post-operative FIGO Stages	Numbers	Per Cent
Stage IA	46	59.0
Stage IB	26	33.2
Stage II	1	1.3
Stage IIICi	2	2.6

TABLE 4 | Sensitivity and specificity for stage IA.

Statistics	Values	95% CI
Sensitivity	95.65%	85.16% to 99.47%
Specificity	75.00%	56.60% to 88.54%
Positive Likelihood Ratio	3.83	2.09 to 6.99
Negative Likelihood Ratio	0.06	0.01 to 0.23
Positive Predictive Value (*)	84.62%	75.05% to 90.95%
Negative Predictive Value (*)	92.31%	75.30% to 97.93%
Accuracy (*)	87.18%	77.68% to 93.68%

TABLE 5 | Sensitivity and specificity for stage IB.

Statistics	Values	95% CI
Sensitivity	69.23%	48.21% to 85.67%
Specificity	94.23%	84.05% to 98.79%
Positive Likelihood Ratio	12.00	3.88 to 37.07
Negative Likelihood Ratio	0.33	0.18 to 0.58
Positive Predictive Value (*)	85.71%	66.01% to 94.88%
Negative Predictive Value (*)	85.96%	77.41% to 91.63%
Accuracy (*)	85.90%	76.17% to 92.74%

Following complete staging surgery, patients were histopathologically staged according to the FIGO classification (**Table 3b**). Based on the same, 46 (59%) were in stage IA, 26 (33.3%) were in stage IB, 2 (2.6%) showed stage II and 1 (1.2%) hadstageIIIC1. Grade I tumors were found in 43 (55.1%), grade II in 12 (15.1%) and grade III in 17 (21%). Post-operatively, 43 (55.1%) patients received adjuvant radiotherapy, and 3 (3.8%) received adjuvant chemotherapy and radiotherapy.

The sensitivity for MRI for stage IA (**Table 4**) was 95.65% with an 85 to 99.4 % 95 % CI. The specificity was 75%, with 56.6 to 88.55% of the 95% CI. The positive likelihood ratio was 3.83, with a 95% confidence interval of 2.09 to 6.99.

The negative likelihood ratio was 0.006, with a 95% confidence interval of 0.001 to 0.23. The positive predictive value was 84.6%, with a 95% CI of 75 to 90.9. The negative predictive value was 92.3% with a 77.3 to 90.9% CI.

The accuracy was 87.18% with a 95% confidence interval of 77.6–93.6%.

The sensitivity of MRI for stage IB (**Table 5**) was 69.23% with 48.2 to 85.6% of the 95% CI. The specificity was 94.23%, with 84 to 98% of the 95% CI. The positive likelihood ratio was 12, with a 95% confidence interval of 3.8 to 37.

The negative likelihood ratio was 0.33 with 0.18 to 0.58 of 95% CI.

The positive predictive value was 85.71%, with a 95% CI of 66–94%. The negative predictive value was 85.90%, with a 95% CI of 77.4 to 91.6%. The accuracy was 85.90%, with a 95% CI of 76 to 92%.

Discussion

The accurate and precise pre-operative assessment of stages of EC is very essential to determining the type of surgical staging. The depth of myometrial involvement and grade of the tumor preoperatively help in deciding the inclusion of pelvic and para-aortic nodal dissection at the time of surgery. MRI imaging has a potential impact on the type of surgical staging.

In recent decades, MRI staging protocols have been evolved for the detection of myometrial invasion, observation of an intact junctional zone on T2W1 images, and the smooth, uninterrupted band of early sub-endometrial enhancement. On the other hand, disruption of the sub-endometrial band indicates myometrial invasion. An invasion of less than 50% of the thickness of the myometrium can be detected on MRI, which is helpful to decide on the surgical management and adjuvant treatment (20, 21).

The sensitivity for this study for myometrial invasion is 95%, which is comparable to studies conducted previously. Pre-operative MRI has been suggested as an alternative to surgical staging for assessing the severity of EC and identifying patients with high-risk factors like nodal involvement. As metastasis to the pelvic lymph node depends on tumor invasion of the myometrium, the decision to perform a pelvic lymphadenectomy may be influenced by the MRI results.

Approximately 72 (92.3%) of patients had endometrioid EC, and 6 (7.7%) patients had type II EC, which is as per the previous studies. In cases of type I EC, the European Society of Urogenital Radiology (ESUR) advises using MRI to identify patients with stage IA disease who would not benefit from lymphadenectomy.

In addition to helping patients of childbearing age with grade 1 endometrioid adenocarcinoma identify those with the endometrium-confined disease who could benefit from fertility-sparing treatment, MRI is useful in cases of type II carcinomas to detect extrauterine spread (22).

In our study, 43 (55.1%) of the patients had low-risk stage 1A EC.

In our study, 46 patients (59%) accurately staged IA with a sensitivity of 95%. Specificity is 75%, which is comparable with previous studies. Research by Geels et al. revealed that the study included 335 consecutive patients with endometrioid EC. The majority received a FIGO stage I diagnosis, as was to be expected. More than 50% of the myometrium had been invaded in 37.6% of the patients (23).

The depth of myometrial invasion can be assessed with a sensitivity of 69% and specificity of 94%, which is almost comparable with previous studies.

According to our findings, MRI can help distinguish between myometrial invasion and accurately measure its depth up to 75% of the time.

Sushant Das et al. in their research article, "Usefulness of DWI in preoperative assessment of deep myometrial invasion in patients with endometrial carcinoma: a systematic review and meta-analysis," compared the accuracy of MRI in the 7 evaluated studies, which involved 320 women diagnosed with EC. Of those diagnosed, 79 had deep myometrial invasion, while 241 had superficial or no invasion on histopathological examination.

The trials were published between 2000 and 2013. Further, 7 studies enrolling a total of 320 individuals met the study inclusion criteria. The summary area under the ROC curve was 0.91. There was no evidence of publication bias (P = 0.90, bias coefficient analysis). The sensitivity and specificity of DWI for detection of deep myometrial invasion across all studies were 0.90 and 0.89, respectively.

Positive and negative likelihood ratios with DWI were 8 and 0.11, respectively. The worst-case scenario (pre-test probability, 50%) and post-test probabilities were 89% and 10% for positive and negative DWI results, respectively (10, 24). The results are comparable with our study.

Since the retrospective nature, relatively small population (only patients who would undergo pre-operative MRI and surgical staging were included), and range of sequence parameters are limitations to our study, further prospective studies in larger populations to support our results are needed.

Conclusion

A pre-operative MRI is helpful to accurately stage EC and plan for the size of the surgery. This is crucial for pre-operative counseling. The depth of myometrial infiltration aids in the planning of pelvic and para-aortic lymphadenectomy. Our study is comparable with the results of previous studies.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *Cancer J Clinic.* (2019) 69:7–34.
2. Goksedef BPQ, Akbayir O, Qorbacoiglu A, Guraslan H, Sencan F, Erol O. Comparison of preoperative endometrial biopsy grade and final pathologic diagnosis in patients with endometrioid endometrial cancer. *J Turkish Ger Gynecol Assoc.* (2012) 13:106–10.
3. Zamani F, Goodarzi S, Hallaji F, Zamiri A, Deilami T, Malek M, et al. Diagnostic value of pelvic MRI for assessment of the depth of myometrial invasion and cervical involvement in endometrial cancer: Comparison of new versus old FIGO staging. *Iran J Radiol.* (2012) 9:202–8.
4. Zhang L, Liu A, Zhang T, Song Q, Wei Q, Wang H. Use of diffusion tensor imaging in assessing superficial myometrial invasion by endometrial carcinoma: A preliminary study. *Acta radiol.* (2015) 56:1273–80.
5. Gil RT, Cunha TM, Horta M, Alves I. The added value of diffusion-weighted imaging in the preoperative assessment of endometrial cancer. *Radiol Bras.* (2019) 52:229–36.
6. Park JY, Lee JJ, Choi HJ, Song IH, Sung CO, Kim HO, et al. The Value of Preoperative Positron Emission Tomography/Computed Tomography in Node-Negative Endometrial Cancer on Magnetic Resonance Imaging. *Ann Surg Oncol.* (2017) 24:2303–10.
7. Todo Y, Sakuragi N. Methodological considerations in the analysis of the therapeutic significance of lymphadenectomy in endometrial cancer. *Taiwan J Obstet Gynecol.* (2013) 52:8–13.
8. Helpman L, Kupets R, Covens A, Saad RS, Khalifa MA, Ismiil N, et al. *Assessment of endometrial sampling as a predictor of final surgical pathology in endometrial cancer*. Berlin: Nature Portfolio (2014).
9. Takeuchi M, Matsuzaki K, Harada M. Evaluating Myometrial Invasion in Endometrial Cancer: Comparison of Reduced Field-of-view Diffusion-weighted Imaging Dynamic Contrast-enhanced MR Imaging. *Magn Reson Med Sci.* (2018) 17:28–34.
10. Das SK, Niu XK, Wang JL, Zeng LC, Wang WX, Bhetuwal A, et al. Usefulness of DWI in preoperative assessment of deep myometrial invasion in patients with endometrial carcinoma: a systematic review and meta-analysis. *Cancer Imaging.* (2014) 14:32.
11. Sironi S, Taccagni G, Garancini P, Belloni C, DelMaschio A. Myometrial invasion by endometrial carcinoma: Assessment by MR imaging. *Am J Roentgenol.* (1992) 158:565–9.
12. Yin X-H, Jia H-Y, Shi M, Wu H, Li Y-M. Magnetic resonance imaging for detection of depth of myometrial invasion and cervical invasion in patients with endometrial carcinoma. *Int J Clin Exp Med.* (2015) 8:19501–5.
13. Tanaka T, Terai Y, Yamamoto K, Yamada T, Ohmichi M. The diagnostic accuracy of fluorodeoxyglucose-positron emission tomography/computed tomography and sentinel node biopsy in the prediction of pelvic lymph node metastasis in patients with endometrial cancer: A retrospective observational study. *Medicine.* (2018) 97:e12522.
14. FIGO. (2009)
15. Zhou Q, Singh R, Yunzhe L, Mo Z, Huang J. Preoperative Histopathological Grading and Clinical Staging versus Surgico-Pathological Grading and Surgical Staging in Endometrial Carcinoma Patients: A Single Centre Retrospective Study. *Glob J Med Res E Gynecol Obstet.* (2018) 18:1.
16. Pelikan HMP, Trum JW, Bakers FCH, Beets-Tan RGH, Smits LJM, Kruitwagen RFPM. Diagnostic accuracy of preoperative tests for lymph node status in endometrial cancer: A systematic review. *Cancer Imaging.* (2013) 13(3):314–22.
17. Kim TH, Kim HS, Kim TJ, Chang SJ, Kim DY, Ryu SY, et al. Survival impact based on the thoroughness of pelvic lymphadenectomy in intermediate or high-risk groups of endometrioid-type endometrial cancer: A multi-center retrospective cohort analysis. *Gynecol Oncol.* (2016) 141:440–6.
18. Wu WJ, Yu MS, Su HY, Lin KS, Lu KL, Hwang KS. The accuracy of magnetic resonance imaging for preoperative deep myometrium assessment in endometrial cancer. *Taiwan J Obstet Gynecol.* (2013) 52:210–4.
19. Otero-Garrfa MM, Mesa-Alvarez A, Nikolic O, Blanco-Lobato P, Basta-Nikolic M, de Llano-Ortega RM, et al. *Role of MRI in staging and follow-up of endometrial and cervical cancer: pitfalls and mimickers*. Berlin: Springer Verlag (2019).
20. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, et al. Current recommendations and recent progress in endometrial cancer. *CA Cancer J Clin.* (2019) 2019:258–79.
21. Tanaka T, Terai Y, Ono YJ, Fujiwara S, Tanaka Y, Sasaki H, et al. Preoperative MRI and intraoperative frozen section diagnosis of myometrial invasion in patients with endometrial cancer. *Int J Gynecol Cancer.* (2015) 25:879–83.

22. Pal N, Broaddus RR, Urbauer DL, Balakrishnan N, Milbourne A, Schmeler KM, et al. Treatment of low-risk endometrial cancer and complex atypical hyperplasia with the levonorgestrel-releasing intrauterine device. *Obstet Gynecol.* (2018) 131: 109–16.

23. Geels YP, Pijnenborg JMA, Van Den Berg-Van Erp SHM, Snijders MPML, Bulten J, Massuger LFAG. Absolute depth of myometrial invasion in endometrial cancer is superior to the currently used cut-off value of 50%. *Gynecol Oncol.* (2013) 129:285–91. doi: 10.1016/j.ygyno.2013.02.013

24. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: Explanation and elaboration. *BMJ Open.* (2016) 6: 1–17.