Diagnostic Accuracy of Pre-operative Magnetic Resonance Imaging in Assessing Prognostic Pathological Parameters in Endometrial Carcinoma

Tahira Yasmeen[1], Sadaf Nasir[2*] and Hanna Naqvi[3]

[1]*Department of Obstetrics and Gynaecology, Liaquat National Hospital and Medical College, Karachi, Pakistan*
[2]*Department of Radiology, Liaquat National Hospital and Medical College, Karachi, Pakistan*
[3]*Department of Histopathology, Liaquat National Hospital and Medical College, Karachi, Pakistan*

Abstract

Introduction: The 2nd most common gynecological malignancy and sixth among commonly diagnosed cancer is Endometrial carcinoma (EC). The risk and prognosis of the disease are assessed by appropriate staging according to the International Federation of Gynecology and Obstetrics (FIGO) classification. Size and grade of the tumor, depth of myometrial invasion, endocervical stromal invasion, and pelvic and paraaortic lymph node involvement play an important role in the prognosis of the disease. For preoperative staging of endometrial cancer, magnetic resonance imaging (MRI), transvaginal ultrasonography (TVUS), and computed tomography (CT) are widely used as diagnostic tools. Accurate pre-operative staging provides a better platform to decide the therapeutic plan and extent of surgery.

Objective: To determine the efficiency of magnetic resonance imaging in the preoperative determination of the prognostic parameters in endometrial carcinoma taking histopathology as the gold standard is the objective of the study.

Material and Methods: This is a retrospective study conducted at Liaquat National Hospital (LNH), Stadium Road Karachi, Pakistan. Four years record (2015-2018) was retrieved and fifty-one patients who had undergone preoperative MRI followed by surgery and biopsy-proven endometrial carcinoma were included in the study.

Results: A total of 51 records were reviewed. The mean age of the patient was 61.45 ± 7.83 years. The frequent histological type was endometroid (n=37, 72.55%). For deep myometrial invasion, MRI sensitivity, specificity, PPV, and NPV were 95.83%, 77.87%, 79.31%, 94.45% respectively. In assessing endocervical invasion, MRI sensitivity, specificity, PPV, and NPV were 83.33%, 80%, 35.71%, and 97.30% respectively. For lymph node invasion, these diagnostic accuracy parameters were 71.43%, 97.73%, 83.33%, 95.56% respectively. For tumor size, sensitivity, specificity, PPV, and NPV of MRI were 100%, 36.36%, 67%, 100% respectively.

Conclusion: MRI shows high precision in the pre-operative assessment of the prognostic parameters in endometrial carcinoma and hence helpful in planning the adequate extent of the surgery.

Keywords: *Specificity, endometrial carcinoma, negative predictive value (NPV), diagnostic accuracy, positive predictive value (PPV), sensitivity.*

INTRODUCTION

Endometrial carcinoma is among the top fifteen causes of cancer death in women worldwide and sixth among commonly diagnosed cancers. Declining rates of hysterectomy for benign causes are considered to be the cause of the rapidly increasing incidence of endometrial cancer in the United States [1]. In 2013, the estimated number of cases was 49,560 while 8190 deaths were reported due to uterine cancer [2]; however, by 2018, there was an upsurge of new cases to an estimated 63,230 and deaths to 11,350 [3], making endometrial carcinoma the fourth commonest cancer in women and the fifth commonest cause of cancer death in the United States [4]. Recently no improvement in five-year, age-adjusted survival for endometrial cancer was noted; which according to 2015 US Surveillance, Epidemiology, and End Results (SEER) database was 83.18% and 81.81% in 1985 [5]. Seventy-five percent of patients present with stage1diseasemainly during the 6th and 7th decades of life with abnormal vaginal bleeding being the most common presenting complaint [6]. For therapeutic planning of the patient risk stratification according to the prognostic parameters should be done preoperatively by the surgeon. Patient age, histological grade, myometrial invasion endocervical invasion, and the presence of lymph node metastases help in predicting the prognosis.

According to FIGO 1998 recommendation routine surgical staging laparotomy for endometrial carcinoma includes total abdominal hysterectomy and bilateral salpingo-oophorectomy with peritoneal washings with or without pelvic and para-aortic lymphadenopathy depending on preoperative risk stratification [6]. However, with the advancement in the field of radiology and the introduction of lesser invasive techniques for surgical therapy, preoperative imaging was found to help stage and plan the management of the patient. For preoperative risk stratification of endometrial cancer, multiple radiological imaging techniques can be used. These include transvaginal ultrasonography (TVUS),

**Corresponding Author: Sadaf Nasir, Department of Radiology, Liaquat National Hospital and Medical College, Karachi, Pakistan; Email: dr.sadaf@live.com*
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computed tomography (CT), and magnetic resonance imaging (MRI).

Many studies have been conducted which have shown the accuracy of MRI and its correlation with histopathological findings [6]. However, local data is limited. There are only a few tertiary care hospitals in our country equipped with specialized gynecological malignancies management, and we are among one of those centers. So the rationale of our study is to review our local data including preoperative imaging and postoperative histopathological findings. We chose four pathological parameters of endometrial carcinoma as these are good prognostic markers and also differentiates between surgically resectable versus irresectable disease.

METHODOLOGY

This is a retrospective study conducted at the Department of Obstetrics & Gynecology, Liaquat National Hospital (LNH), Karachi, Pakistan. Records were retrieved between a period of 2015 to 2018, and fifty-one patients who had biopsy-proven endometrial carcinoma and had undergone pre-operative MRI and surgery were included in the study. Patients with a history of some previous uterine malignancy/ recurrent disease, synchronous tumors (ovarian and endometrial), those who received neoadjuvant chemotherapy/radiotherapy and patients with incomplete medical records were excluded from the study. Data was collected by the principal investigator and kept confidential. Patients' age (in years), presenting symptoms, history of uterine surgery, MRI findings, and histopathology findings including tumor type (**Fig. 1**), tumor size (in cm), depth of myometrial invasion, endocervical stromal invasion and lymph nodal metastasis were recorded on predesigned proforma.

Descriptive statistics were computed to summarize data.

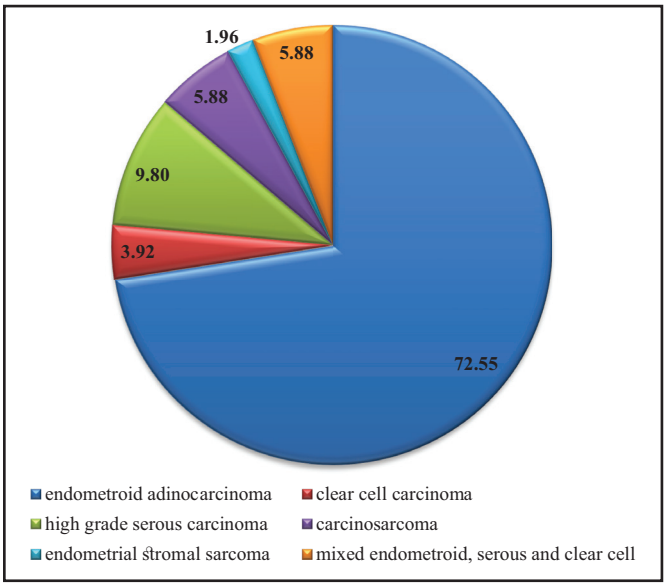


Fig. (1): Frequency of tumor type.

Frequency and percentages were computed to present categorical variables. Continuous variables were summarized as mean ± standard deviation. To measure diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) were computed. The agreement between histopathology and MRI findings was calculated using Kappa statistics. Two-tailed p-value <0.05 was considered as statistically significant. Statistical package SPSS version 20 was used for data analysis.

RESULTS

Total 51 records were analyzed and the average age of patients was 61.45 ± 7.83 years. Most of the patients presented with post-menopausal bleeding (n=31, 60.78%). Abnormal uterine bleeding (AUB) and the pain was present in 16 (31.4) and 8(15.69%) patients respectively. Only one patient (1.96%) had a history of ovarian cancer.

A total of 27 (52.94%) patients had more than half of myometrial invasion. Out of these 27, 21 (77.8%) were detected accurately by MRI, whereas 24 (47.05%) patients had less than half of myometrial invasion on biopsy, and 23 (95.85%) of them were correctly detected on imaging finding. Therefore, the overall concordance between MRI and histopathology for the depth of myometrial was observed on 44 (86.27%) cases with sensitivity and specificity of 95.83% and 77.87% respectively. PPV and NPV were 79.31% and 94.45% respectively. There was a significant moderate agreement between the two measures (k=0.728, p<0.001).

14 (27.45%) cases showed endocervical invasion and 37 (72.54%) had no endocervical invasion on final biopsy report. MRI correctly detected 5 (35.7%) patients with endocervical invasion while the correct detection rate for the absence of endocervical invasion was 97.3% (n=36) which indicates the overall concordance on 41 (80.39%) cases between MRI and histopathology with significant weak agreement (k=0.401, p=0.001). For endocervical invasion, MRI showed sensitivity of 83.33%, specificity of 80%, PPV of 35.71% and NPV of 97.30%.

According to histopathology findings, lymph node involvement was not observed in 44 (86.27%) patients. Out of these 44, 43 (97.7%) were also found not having lymph node involvement on imaging reports. Out of the 7 (13.73%) cases with lymph node involvement on biopsy, MRI correctly identified this in 5 (71.4%) cases. On comparing lymph node invasion between MRI and histopathology, a concordance on 48 (94.12%) cases was observed. The kappa statistics showed significant moderate agreement between two findings (k=0.74, p<0.001). MRI had sensitivity, specificity, PPV, and NPV of 71.43%, 97.73%, 83.33%, and 95.56% respectively in assessing lymph node invasion.

29 (56.86%) patients had tumor size ≤4 cm and MRI also determined tumor size of ≤4 cm for all these 29 (56.86%) patients. However, for the remaining 22 (43.13%) patients with tumor size >4cm, MRI correctly identified 8 (36.4%) patients. The overall concordance between MRI and histopathology finding was seen on 37 (72.55%) cases with sensitivity, specificity, PPV, and NPV of 100%, 36.36%, 67%, and 100% respectively. The agreement between MRI and histopathology for determining tumor size was significantly minimal (k=0.394, p<0.001).

DISCUSSION

Cancers of the female genital tract are one of the most common malignancies after breast, lung, and colorectal carcinomas [7]. In Asian people, endometrial carcinomas are the third commonest among gynecological cancer with an incidence of 4.3% for all ages and 1.9% mortality globally, 2012). Uterine cancer led to over 8,000 deaths annually in the United States, hence considered the second most lethal gynecological cancer [8]. In the present study mean age of patients was 61.45 ± 7.83 years which is somewhat closer with a study conducted by Malik TY in 2016 in Pakistan in which mean age at the time of presentation was 56.6 ± 10.51 years in Type I endometrial cancer. Whereas, the mean age of patients with type 2 endometrial cancer was 61.08±6.69 [9]. The frequent tumor in the present study was endometroid (n=33,80.39%) which is consistent with the Malik TY study in which Type I tumors accounted for 92% of cases while 8% were type II tumors [9]. Out of 41 patients, 31 (60.78%) patients presented with post-menopausal bleeding. The pain was present in 8 (15.69%) patients. Postmenopausal bleeding is the first commonest symptom of endometrial cancer. This was also stated by Sorosky JI and Khati NJ in their studies [10-12],

The best modality for assessing primary tumors greater than 10mm in size is MRI, as it can accurately determine the size of the tumor, the extent of myometrial invasion & nodal metastasis, with almost 95% accuracy for stage IB or higher [13-18]. Upfront, surgery is still the mainstay treatment in patients with endometrial carcinoma.

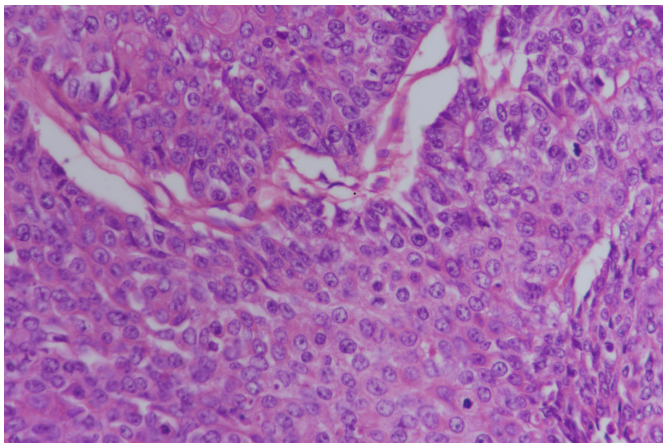


Fig. (2): Tumor cells showing predominantly solid configuration and nuclear atypia in a high grade endometrioid adenocarcinoma.

Table 1: Diagnostic accuracy of MRI for depth of myometrial, endocervical invasion and lymph node involvement.

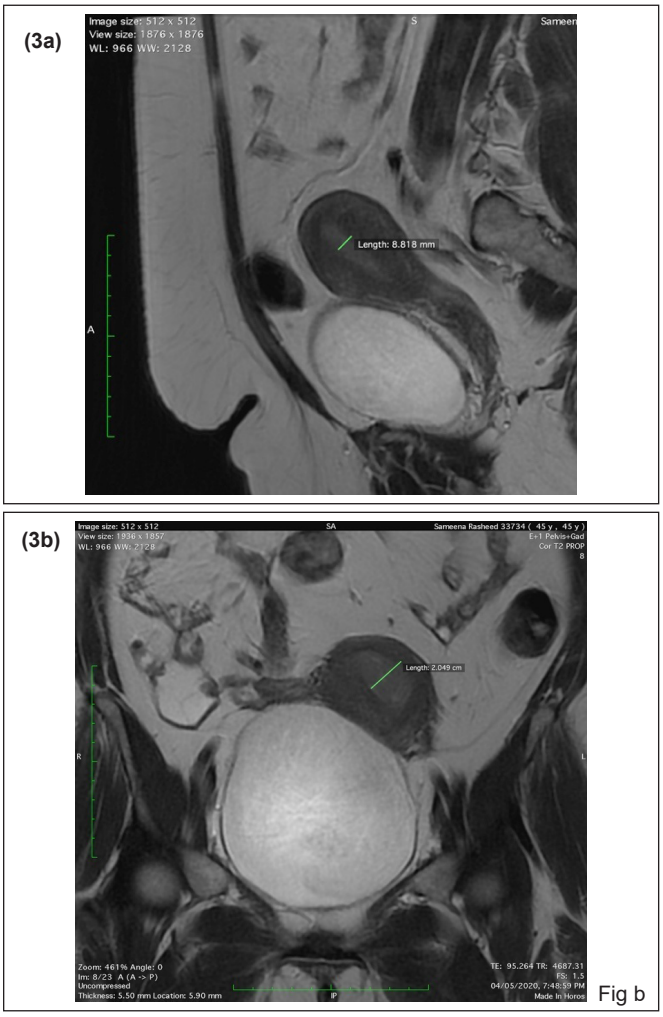
-	Depth of Myometrial	Endocervical Invasion	Lymph node Involvement	Tumor Size
Sensitivity (%)	95.83	83.3	71.43	100
Specificity (%)	77.78	80	97.73	36.36
PPV (%)	79.31	35.71	83.33	67
NPV (%)	95.45	97.30	95.56	100

Table 2: Agreement between histopathology and MRI findings.

	Histopathology Findings			Kappa Statistics	p-value
MRI findings	**Positive n (%)**	**Negative n (%)**	**Total n (%)**		
Depth of myometrial					
Positive (>50%)	21 (77.8)	1 (4.2)	22 (43.1)	0.728	**<0.001
Negative (<50%)	6 (22.2)	23 (95.8)	29 (56.9)		
Endocervicalinvasion					
yes	5 (35.7)	1 (2.7)	6 (11.8)	0.401	**0.001
no	9 (64.3)	36 (97.3)	45 (88.2)		
Lymph node involvement					
yes	5 (71.4)	1 (2.3)	6 (11.8)	0.736	**<0.001
no	2 (28.6)	43 (97.7)	45 (88.2)		
Tumor size					
≤4 cm	29 (100)	14 (63.6)	43 (84.3)	0.394	**<0.001
>4 cm	0 (0)	8 (36.4)	8 (15.7)		

However, preoperative risk stratification defines the extent of surgery depending on certain prognostic parameters. A preoperative assessment of these helps in the staging of the carcinoma as well as provides a platform for surgeons to strategically plan the treatment [19, 20]. Age of patient, histological grade, depth of myometrial invasion, invasion of cervical stroma, and lymph node involvement determine the prognosis of the disease (**Fig. 2**) [18-20]. Preoperative and Intraoperative analysis is useful in the assessment of depth of myometrial invasion but preoperative analysis has the advantage that staging of tumors about the cervical invasion and lymph node involvement can also be assessed. More so, Intraoperative gross analysis can sometimes be limited and the frozen section may add a burden of cost on the patient. Magnetic Resonance Imaging has shown an accuracy in assessing the prognostic parameters for endometrial carcinoma and can assist in prior surgical planning. In this study, we assessed the diagnostic accuracy of MRI (Table **1**) keeping histopathology as a gold standard and compared the results of four parameters (tumor size, depth of myometrial invasion, cervical invasion and pelvic lymph nodes metastasis) in cases of endometrial carcinoma, as these are the good prognostic markers for preoperative staging of the tumor and subsequently leading to good surgical planning.

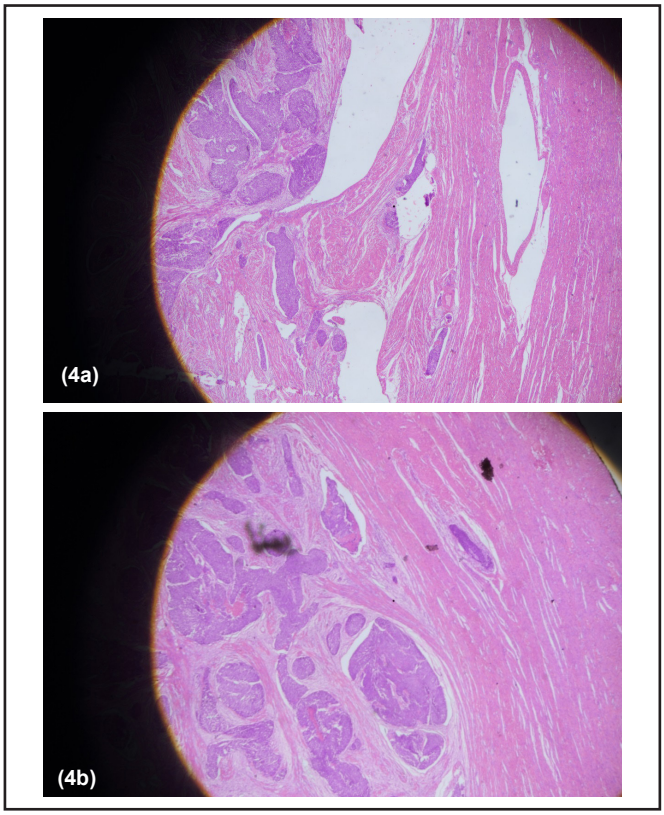
Local staging of endometrial carcinoma requires evaluation of the depth of tumor invasion into the myometrium. An intact low-SI junctional zone on T2WI, and a smooth band of early sub-endometrial



Figs. (3a & 3b): MRI Pelvis T 2 weighted sagittal (**Fig. 3a**) and coronal (**Fig. 3b**) Images showing thickened endometrium with intermediate signal intensity, suggestive of endometrial carcinoma. It is confined to endometrium without any evidence of surrounding myometrial invasion.

enhancement without any interruption on DCE images excludes the possibility of myometrial invasion [21, 22]. A disruption of this sub-endometrial band is highly suggestive of myometrial invasion. The tumor is staged as 1A if the depth of myometrial involvement is less than half of the total thickness of the myometrium, however, it is Stage 1B if the myometrial involvement is more than 50% of the total myometrial thickness [13, 21, 22]. The chances of pelvic and para-aortic lymph node metastases increase by six to seven-fold in patients with deep myometrial tumor invasion as compared to those having tumor limited to the endometrium (**Figs. 3a & 3b**) or showing only superficial myometrial invasion. Hence depth of myometrial invasion can aid in assessing the presence of nodal metastasis and is used as a predictor in most institutions. An interrupted hypo intense junctional zone, which appears hyper-intense on T2 weighted images in cases of endometrial adenocarcinoma is diagnostic of myometrial infiltration and helps assess the depth of tumor involvement [20]. In our study overall concordance between MRI and histopathology for the depth of myometrial invasion was observed on 44 (86.27%) cases with a significant moderate agreement between the two measures (k=0.73, p<0.001). Our results are comparable with the previous studies, 79% (Mubarak *et al.*) [6], 76% (Nougaret S *et al.*) [22], and 74% (Vargas HA). However, there is a significantly minimal agreement between MRI and histopathology for tumor size determination. The reason might be preoperative Diagnostic dilatation and curettage after MRI, which may reduce the size, concomitant other endometrial abnormalities like polyps, blood clots, *etc.*

It is difficult to assess on MRI if the tumor is invading the cervical canal or has infiltrated the cervical stroma. To stage cervical stromal invasion is a more important factor. On T2WI if there is a disruption of cervical stroma shown by interruption of the routine low SI of the cervical stroma by the intermediate SI of the tumor, this is suggestive of cervical stromal invasion. Direct stromal invasion with sparing of endocervical mucosa can be seen in cases of endometrial carcinoma due to tumor invasion through the adjacent myometrium. In DWI, an elevated SI on high b values and diminished SI on ADC maps causing the breakup of the cervical storm is indicative of cervical stromal invasion. On DCE imaging, loss of routine intensification of the cervical stroma is diagnostic of cervical stromal invasion [22-24]. In our study, the agreement between MRI and histopathology for endocervical invasion is significantly weak with a sensitivity of 83.33%, specificity of 80%. Although the



Figs. (4a & 4b): Endometrioid adenocarcinoma with deep myometrial invasion.

agreement is weak the sensitivity and specificity in our study is quite better than the previous similar studies (Vagrus *et al.*) with sensitivity and specificity of 69% and 77% respectively.

The depth of myometrial invasion correlates directly with the risk of lymph node metastasis and hence provides useful information for surgeons to plan the extent of surgery. The prevalence of lymph node metastasis is 3% for cases with superficial myometrial invasion and 46% for cases with deep myometrial invasion (**Figs. 4a & 4b**) [25].

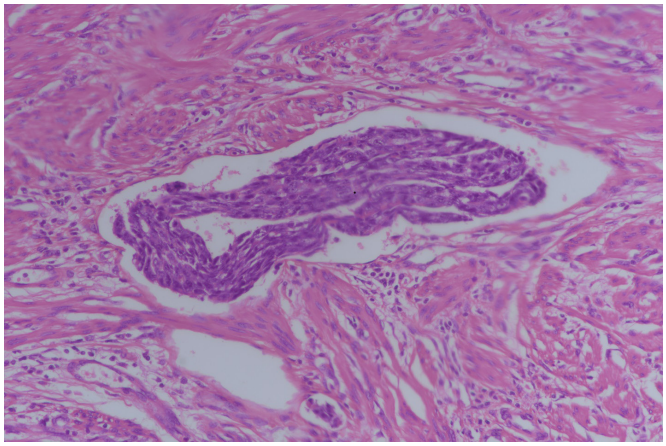


Fig. (5): Focus of lymphovascular invasion in deep myometrium.

The number of lymph nodes involved is important not only in staging but also in outlining the treatment plan of uterine cancer [15, 22-24, 26]. For example involvement of pelvic lymph nodes is staged as stage IIIC1 according to FIGO staging 2019 whereas parametric nodal involvement is staged as stage IIIC2. The factors associated with increased risk for nodal spread include type II tumors, poorly differentiated cancers, LVSI (**Fig. 5**), and more than 50% myometrial invasion [22, 23]. Nodal metastasis is also associated with the site of the tumor in the uterus. The parametrium, paracervical, and obturator lymph nodes drain the middle and lower parts of the uterus while the common iliac and paraaortic nodes are the regional nodes for uterine fundus. The involvement of inguinal nodes should be considered as metastatic disease. In cervical cancers, FIGO stage IIIC is also subdivided into IIIC1 (pelvic nodes) and IIIC2 (paraaortic nodes) (Table **2**). The lymphatic spread of cervical cancers occurs along the obturator, external iliac, internal iliac, common iliac, and paraaortic nodes [26]. The most recognized principle is the nodal size (short axis > 1 cm) for discriminating between benign and malignant nodes [27, 28]. MRI has a sensitivity of (43%) and specificity of (73%) in the identification of metastatic lymph nodes as it cannot distinguish between inflammation and metastases and is inaccurate in the identification of micro metastases [28]. Some morphologic features in MRI are more suspicious for nodal metastases including rounded shape and erratic outline, altered SI on T2WI, central necrotic areas, and nodal group formation. Central node necrosis has a PPV of 100% for the diagnosis of nodal metastases [13, 29]. In our study on comparing lymph node invasion between MRI and histopathology, a concordance on 48 (94.12%) cases were observed. The kappa statistics showed significant moderate agreement between two factors ($k=0.74$, $p<0.001$). MRI had sensitivity, specificity, PPV, and NPV of 71.43%, 97.73%, 83.33%, and 95.56% respectively in assessing lymph node invasion. Our sensitivity and specificity are slightly higher than the previous study similar study Manfredi et al. with a sensitivity of 50% and specificity of 95% [29]. Our data also corroborates with the findings in other studies, Hwang et al. (2009) reported sensitivity of 92.5%, specificity of 74. 5%, PPV 71.42% and NPV 93.54% for the detection of myometrial invasion [30]. Santhanum et al. (2017) reported accuracy of tumor size 72%, myometrial invasion 76%, endocervical, and nodal involvement 96% [31].

CONCLUSION

MRI shows high accuracy in providing pre-surgical staging of endometrial carcinoma and is found to be accurate in the planning extent of surgery.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

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