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Original Research Article

A clinical comparative study of preoperative clinical staging and surgical and histopathological staging in endometrial carcinoma

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ABSTRACT

Background: Endometrial cancer is the fourth most common carcinoma in women across the globe. Treatment and prognosis are influenced by surgical international federation of gynecology and obstetrics staging system with evaluation of the depth of myometrium invasion, cervical extension and the presence of lymph node and distant metastasis. This study aims to compare the MRI findings in preoperative staging of endometrial carcinoma with intra-operative findings and revised international federation of gynecology and obstetrics staging based on postoperative histopathology.
Methods: The study was prospectively carried out in department of obstetrics and gynecology of a Cama Hospital, Mumbai for a total period of 1.5 years; 30 patients diagnosed with endometrial carcinoma were selected.
Results: The patients were predominantly multiparous with most common presenting complaint as postmenopausal bleeding. The clinical- radiological staging was concordant with histopathological staging in 60% (18/30) cases. Upstaging was seen in 10% (3/30 cases), while 30% (9/30) showed down staging in the final histopathology. While comparing the surgical intra-operative staging, it was seen to corroborate with the final histopathology in 63.33% (19/30) cases.
Conclusions: The pre-operative radiological assessment especially MRI with high accuracy in determining myometrial invasion is an inseparable tool. The surgeon would have to rely on intra-operative assessment for further plan of action and effectively dealing with carcinoma.

Keywords: Clinical staging, Surgical staging, Histopathological staging, Endometrial carcinoma

INTRODUCTION

Endometrial cancer is the fourth most common carcinoma in women across the globe after breast, lung and colorectal cancer. However, it is the third most common malignancy in Indian women. Endometrial cancer tops the list among tumors of the female genital tract in developed countries.[1,2] Treatment and prognosis is influenced by surgical international federation of gynecology and obstetrics (FIGO) staging system with evaluation of the depth of myometrium invasion, cervical extension and the presence of lymph node and distant metastasis. Tumor grade and histological subtype are crucial in guiding the extent of surgery, adjuvant therapy and prognosis.[3,4] From its inception in 1958 endometrial carcinoma had been clinically staged as per the international federation of gynecology and obstetrics (FIGO).[5,6] However, inaccuracies in clinical staging and results of gynecologic oncology group (GOG) 33 contributed to alteration in surgical staging in 1988.[7] The surgical staging has been recently revised in 2009. Comprehensive surgical staging allows precise diagnosis of the disease and its extent, identification of high-risk patients for recurrence, tailoring of patients for adjuvant therapy translating to reduced relapses and prognostic determination.[5] However, the anatomical extent of lymphadenectomy and number of

lymph nodes removed for establishing prognostic and therapeutic benefit is controversial.[8-11] Although clinical evaluation with diagnostic imaging has not yet been proved to be accurate enough in the evaluation of tumor extent to replace surgical staging, it may enable optimization of the surgical procedure and a tailored therapeutic strategy. Pre-operative clinical and radiological staging holds significant importance.[12-14] First, it is valuable for patients who are not candidates for a hysterectomy due to morbid obesity or cardiopulmonary dysfunction that render them unfit for surgical procedure. Then, adjuvant therapy has to be prescribed based solely on clinical staging and potential risks.[15] Second, the clinical staging is suitable for young women desiring complete preservation of fertility wherein endometrial lesions are excised and hormone therapy is initiated.[16,17] Third, patients with clinical stage II disease who cannot undergo a radical hysterectomy due to associated co-morbidities may have to be treated by neo-adjuvant radiotherapy followed by simple hysterectomy.[18-20] This study aims to compare the MRI findings in preoperative staging of endometrial carcinoma with intra-operative findings and revised international federation of gynecology and obstetrics staging based on postoperative histopathology.

METHODS

Study design, location, duration and population

The study was prospectively carried out in department of obstetrics and gynecology of a tertiary care hospital for a total period of 1.5 years (18 months) from January 2019-June 2020 at tertiary care centre (department of obstetrics and gynecology of a tertiary care hospital). The study population consisted of patients with diagnosis of endometrial carcinoma who gave informed consent and underwent surgery.

Procedure

Total 30 patients were included in the study. All patients were confirmed with dilatation and curettage and then taken for study after informed consent. The electronic medical records of these patients, clinic-pathological data, demographic details, preoperative clinical staging based on radiological findings, tumor grade and histology pre-operatively, surgical staging, final histopathological diagnosis with grade and staging were studied. Preoperative investigations were: complete blood count, fasting blood sugar, liver function tests, blood urea, creatinine, electrolytes, thyroid function tests, tumor markers and chest X- ray. All the patients underwent a sonographic examination at first, followed by dilation and curettage and lastly either abdominopelvic CT scan or MR imaging. The surgical approach for hysterectomy was laparotomy. Upon entering the abdomen 100 ml of sterile saline were poured in the pelvis and the peritoneal washings had been collected. Then, followed a thorough intra-abdominal and pelvic exploration where suspicious areas were biopsied or excised. Subsequently, total extra-fascial hysterectomy and bilateral salpingo-oophrectomy was done. The uterus was then opened vertically along the anterior wall from the fundus to cervix using a surgical blade. On intraoperative gross examination main parameter of interest was myometrial invasion which was classified as confined to endometrium, invaded to inner half of myometrium and outer half of myometrium. In addition, cancer invasion into cervix which is defined as presence of endometrial cancer below the level of internal os, was examined for defining the surgical stage. The decision on whether or not to perform pelvic and para-aortic lymphadenectomy was made by surgeon based on preoperative and intraoperative findings. The specimen was sent for final histopathological examination.

RESULTS

This study enrolled 30 females diagnosed with endometrial carcinoma. The patients were predominantly multiparous (73.3%, 22/30) followed by 3/30 patients of para 2 (10%). One patient of para 1 (3.33%) and 4/30 nulliparous patients (13.33%).

Table 1: Distribution of age in study patients.

Age distribution (years)	Histopathological proven cases	N
<50	8	26.7
>50	22	73.3

Table 2: MRI findings in study patients.

MRI findings	N	%
Tumor size (cm)		
<2	8	26.66
2-4	18	60
>4	6	20
Myometrial invasion		
<50%	16	56.66
>50%	11	36.66
Cervical stroma involved	No	No
Serosa/adnexal invasion	3	10
Vagina/parametrium invasion	No	No
Lymph node invasion		
Pelvic lymph node	5	16.66
Para-aortic lymph node	2	6.66

The most common presenting complaint among the patients was postmenopausal bleeding (19/30, 63.33%), irregular bleeding (9/30, 30%) and pelvic pain (2/30, 6.67%). On clinical examination, 83.33% patients had uterine size 6-8 weeks while 10% had uterine size 8-12 weeks and 6.67% patients had large uterus of more than 12 weeks on gynecological examination. Otherwise, patients did not have any specific findings. No patient had any palpable abdominal mass. Parametrium and adnexa were found free. On ultrasonography, all 30 patients had endometrial thickness >4 mm.

Table 3: Comparison of pre-operative and post operative histopathology.

Pre-operative histopathology, (N=30)		Post-operative histopathology, (N=30)	
Diagnosis	**Frequency (%)**	**Diagnosis**	**Frequency (%)**
Atypical endometrial hyperplasia	1	**Atypical endometrial hyperplasia**	Nil
Endometroid	26 (86.67)	**Endometroid**	25 (83.33)
Grade 1	21 (70)	**Grade 1**	21 (70)
Grade 2	4 (13.33)	**Grade 2**	4 (3.3)
Grade 3	1 (3.33)	**Grade 3**	Nil
Mixed	1 (3.33)	**Mixed**	1 (3.33)
Serous	2 (6.67)	**Serous**	3 (10)
-		**Undifferentiated**	1 (3.33)

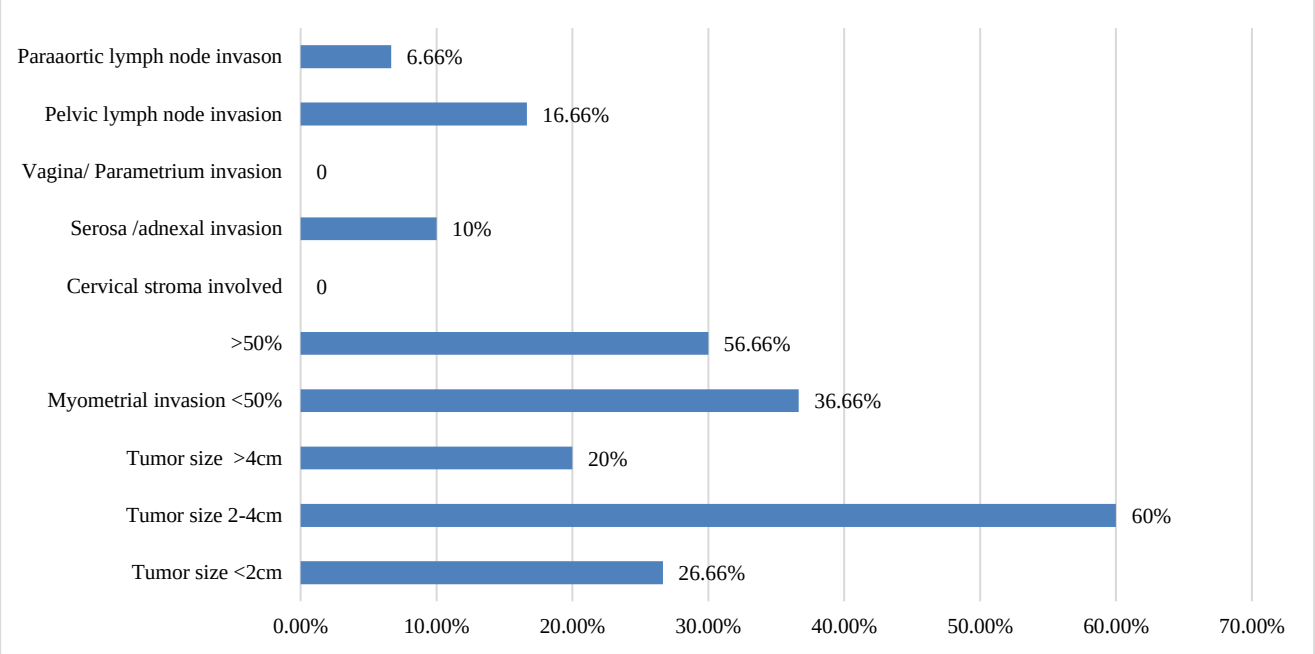

Figure 1: Distribution based on findings.

Table 4: Comparison of clinical-radiological staging with final histopathological staging.

Clinical stage		Histopathologic staging	
Stage Ia	11	Stage Ia	9
		Stage IIIa	1
		Stage IIIb	1
Stage Ib	9	Stage Ib	8
		Stage Ia	1
Stage IIIa	3	Stage II	2
		Stage IIIc2	1
Stage IIIc1	5	Stage Ia	1
		Stage Ib	1
		Stage IIIa	2
		Stage IIIc1	1
Stage IIIc2	2	Stage IIIa	1
		Stage IIIc1	1

The most common ultrasound finding was heterogenous mass seen in 14/30 (46.66%) patients and 6/30 (20%) presented with heterogenous endometrial thickening, 6/30 (20%) had intrauterine fluid collection. No patient underwent color Doppler to depict myometrial invasion.

Table 5: Comparison of intra-operative gross evaluation staging with final histopathological staging.

Intraoperative gross evaluation- staging		Histopathologic staging	
Stage Ia	6	Stage Ia	5
Stage Ib	14	Stage Ia	5
		Stage Ib	8
		Stage IIIa	2
Stage II	2	Stage II	2
Stage IIIa	3	Stage Ib	1
		Stage IIIa	2
Stage IIIc1	5	Stage Ia	1
		Stage IIIb	1
		Stage IIIc1	2
		Stage IIIc2	1

The clinical staging was concordant with histopthological staging in 60% (18/30) cases. Upstaging was seen in 10%

(3/30 cases), while 30% (9/30) showed down staging in the final histopathology. The discordance could have been due to low sample size, errors in pre-operative assessment, limitations of radiological imaging and the time elapsed between pre-operative assessment and the surgery. While comparing the surgical inta-operative staging, it was seen to corroborate with the final histopathology in 63.33% (19/30) cases. Upstaging was seen in 10% (3/30) cases, while 26.67% (8/30) showed down staging in the final histopathology. This entails that intra-operative assessment should be considered as the final surgical plan to avoid under-treatment for patient. There was no mortality in this study.

DISCUSSION

Endometrial carcinoma is usually diagnosed in its early stages as most females are prompt in reporting post-menopausal vaginal bleeding to their physicians. The likelihood of endometrial cancer being responsible depends on the woman's age; the probability is 9 percent for women in their 50s,16 percent for those in their 60s, 28 percent for those in their 70s, and 60 percent for those in their 80s.[21] Dalal et al in their study found that the age of presentation for endometrial carcinoma were in the ranges of 35 to 80 years with a mean age of 59.53 years.[22] Elwood et al observed that the age-adjusted incidence rate was 18.1/100,000woman-years with predominance of incidence in ages of 55-59 years with a gradual decline thereafter.[(23)] In our study also, the mean age of presentation was 57 years similar to the above studies. In a study done by Zandrino et al, 26 patients (87%) were postmenopausal with chief presenting symptoms being abnormal bleeding in majority followed by mucinous vaginal discharge and inter-menstural dysfunctional bleeding.[12] In this study, the most common presenting complaints among the patients were PMB (19/30, 63.33%), IB (9/30, 30.0%) and lower abdominal pain (2/30, 6.67%) which was similar to other studies.[8] Wu et al reported that that there was a significant inverse association between parity and risk of endometrial cancer (relative risk (RR) for parous versus nulliparous: 0.69, 95% confidence interval (CI) 0.65-0.74; I2=76.9%).[24] Elwood et al in their study also noticed the trend of reduced risk of endometrial cancer with increased parity with the relative incidence (RI) for multiparous women being 0.3 compared to nulliparous women. Early menarche (RI=1.6) and late menopause (RI=1.7) were also associated with increased risk of disease.[23] Endometrial cancer risk was also found to be directly linked with socioeconomic status, relative weight, diabetes, hypertension, and arthritis.[25] Their study findings supported the idea that hormone activity during and perhaps after reproductive life plays a pivotal role in pathophysiology. In this study, however, the patients were multiparous in 73.3% cases. In the study by Zhou et al also, 81.5 % patients were multiparous. Therefore, the role of other factors cannot be excluded.[26] In a meta-analysis by Raglan et al it was observed that there was an increased risk of endometrial cancer incidence and mortality in presence of risk factors such as increased BMI, high hip and waist circumference, increased Waist to hip ratio, diabetes mellitus and metabolic syndrome.[27] We observed the incidence of diabetes and obesity in our study as 20% and 33.33% respectively corroborating their association. Hypertension was seen in 40% cases. Most patients with endometrial cancer present with abnormal uterine bleeding or postmenopausal bleeding leading to subsequent evaluation.[8] We also observed that most common complaint among the patients was PMB (63.33%) while others were IB (30.0%) and lower abdominal pain (6.67%). Radiological investigations are summarized in Table (USG and MRI). MRI has been adopted as an accurate imaging tool in the pre-operative assessment of endometrial carcinoma.[28] The soft tissues are delineated better than other imaging modalities. The visualization of endometrial carcinoma is a hypo to iso-intense mass on T1 image with an intermediate intensity on T2 image which is less than surrounding non-pathological endometrium. The contrast acquirement is more in normal tissues and hence, neoplastic areas are less enhanced. The overall staging accuracy of MR imaging is reported to be 83-92%.[13]

Myometrium invasion

Rechichi et al evaluated the efficacy of MRI in assessment of myometrial invasion. It was found that among 47 patients, superficial invasion was seen in 72% and deep in 28%. The accuracy of MRI along with the sensitivity and specificity in assessment of myometrial invasion was found to be 92.3%, 76.5% and 60.0% respectively. In our study, we found that concordance was 72.73% in less than 50% invasion, however, it was 81.25 % in more than 50% invasion group. The overall sensitivity of MRI in detection of myometrial invasion was 96.3 % and specificity was 80 %.[29] Ali et al in their study found that myometrial invasion is crucial for prognosticating endometrial carcinoma and guiding further therapeutic management. Intra-operative assessment is prone for erroneous estimation of depth of invasion. In their study of 100 patients with diagnosis of endometrial carcinoma, they found that discordance was present in approximately 30% cases. They also encountered additional challenges in those cases with increased amount of smooth muscle metaplastic changes, highlighting the drawbacks of visual assessment of involved myometrial depth. In our study also, we found that depth of myometrial invasion as assessed by IGE, was accurate in 57.14% in less than 50% invasion and 68.19% in more than 50% invasion with an average discordance seen in 37.34% cases similar to above mentioned study.[30]

Cervix and LN invasion

Tamai K et al evaluated the success of MRI in evaluating cervical stromal involvement and stated that contrast enhanced MRI provides "one stop" tool for assessment of cervical invasion in Endometrial carcinoma and lymph node metastasis which in turn optimizes the surgical strategy.[31] It was also stated in their study that MRI assessment of myometrial and cervical invasion may be

used as an alternative to intra-operative gross evaluation. In essence, surgical visualization may not suffice and other pre-operative radiological tools as MRI and intra-operative frozen section should be used to substantiate. In this study, we witnessed MRI could identify correctly cervical invasion in 4 of 6 (66.67%) patients, however, intra-operative evaluation was concordant in 2 of 6 (33.33%) patients considerably lower than MRI findings, therefore, establishing the fact found in the aforementioned study. The accuracy was lower but comparable with the studies done by Hori et al and Rockall et al.[32] LN invasion was present in 3/30 (10%) patients as detected on HPR, however, MRI identified 2/3 (66.67%) of them. It is prudent to point here that MRI detected LN invasionin 7 patients, however, it was truly present in 2/7 patients (28.57%) as detected by final HPR, therefore, the concordance was lower. This illustrates that MRI overestimates the detection of LN invasion with high incidence of false positives. The success and concordance of assessing LN metastasis with MRI is much lower than reported in studies by Hori et al and Rockall et al however, in this study only 3 patients had lymph node invasion in final histopathology, hence, the findings could not represent a general scenario. The MRI diagnosis of lymph node involved with neoplasm is based on size criteria of 1cm or more in short axis. The reported sensitivity of MRI for detection of metastatic lymph nodes in endometrial carcinoma is has varied from 17-80% in literature.[13] Lymphadenectomy plays an important role in the complete staging of Endometrial carcinoma, guides the neoplastic extension which further advocates the adjuvant therapy delineating the final prognosis. However, the addition of lymphadenectomy adds in the procedural duration, may amount to elevated surgical bleeding, adjacent structure neurovascular injuries, urinary tract injury, prolonged ileus post-surgery, increased chances of thromboembolic phenomena, lymphocyst and lymphedema.[9,11,18] The accuracy of staging as assessed by clinical radiological versus histopathological and intra-operative surgical with final histopathology has been compared in current study.

The tumor stage has been considered as the chief prognostic factor for depicting the outcome of endometrial carcinoma.[8] The accuracy in pre-operative staging, therefore, forms the crux in final sequelae. In the present study, a discordance of 40 % was found which is comparable to the study by Zhou et al where a discordance of 35.8% was found and the other studies in literature which quote between 26.9% to 51% discordance.[26,33] The discordance in our study could have resulted because of the low sample size, errors in pre-operative assessment, limitations of radiological imaging and the time elapsed between the pre-operative assessment and the surgery. Upstaging was seen in 10% (3/30) cases, while 30% (9/30) showed down staging in the final histopathology. The study by Zhou et al reported upstaging in 21.4% cases.[26] This has been reported in varied amounts in literature ranging from 19.5% to 51%.[4,11] Solely, relying on the pre-operative assessment of stages could have resulted in under-treatment with no addition of lymphadenectomy. The surgical staging was corroborative with the final histopathological staging in 63.33% cases; however, the less sample size could have resulted to the differences in concordances of surgical versus pre-operative staging. Regardless, this strengthens the fact that intra-operative assessment should entail the final surgical plan to avoid under-treatment for the patient. The study by Lewis et al in 1970 studying 129 patients reported the frequency with pelvic and para-aortic lymph node metastasis correlating with the grade and myometrial invasion depth.[34] This may indirectly point to addition of lymphadenectomy and keeping a low threshold in such patients even if pre-operative staging points otherwise. Although, lymphadenectomy comes with its own set of complications especially the ones faced intra-operatively, the long term complications have been reported less frequently risk of 1.3% for lymphocyst and 0.7% for lymphedema formation.[9,11,18] The study by Orr et al also stated that the benefits greatly outweigh the risks.[18]

Preoperative D&C or biopsy tumor grade is not sufficient to determine which patients should be surgically staged. Daniel et al reported 15% to 20% of cases had their tumor grade upgraded in final pathology with 57% to 68% correlation of tumor grade between D&C and final pathology.[14] In the study by Zhou et al a concordance rate of 75.3% was observed between pre and post hysterectomy samples.[26] Similarly, Cowles et al reported this value to be 73.6%.[33] Suwannee Buranawattana-choke et al observed 74.5% concordance. There was higher concordance in the study by Kisielewski et al where a concordance rate of 83.75% was derived.[34,35] In our study, the pre and post histopathological concordance was seen in 26/30 patients (86.67%). The change in grade of neoplasm from pre-operative histopathology report can be explained by; Amount of tissue is more in surgical specimen. In the study by Su et al, it was highlighted that curettage is a blind procedure and usually extracts less than half of the endometrium in 60 % cases.[36] Neoplasm is seen in entirety with all its borders in the surgical specimen. There is usually time elapsed before the final surgery is undertaken in low socio-economic countries. In the hysterectomy specimen, a lot of heterogeneity is usually observed owing to varied histology, pleomorphic nuclei and cells and increased mitotic activity with lack of differentiation. Therefore, the curettage specimen may just represent a portion of the heterogeneous specimen. The females in post-menopausal age groups undergo endometrial atrophy due to which procurement of sufficient tissue for histopathology often becomes a hurdle.[37] The lack of technical expertise whilst curetting may also cause discordance.[37] The proportion of females above 50 years were found to be 73.33%. The discordance from the pre-operative histopathology could have resulted from inadequate tissue specimen due to endometrial atrophy. Elwood et al found that even if curettage reveals atypical hyperplasia, in 40 % of the patients, the final histopathology may contain adenocarcinoma.[23] In our study, also in one patient (3.33%), this was the case. The

alterations and discordances in pre-operative staging and grading advocate the detailed knowledge and need for thorough assessment in the operating room with reliance on frozen section wherever deemed necessary is of utmost importance in managing this carcinoma which would effectively translate in prognostic improvement. MRI assessment for depth of myometrial invasion significantly guides the staging and formal surgical plan especially in the early stages of the disease, hence, should be advocated as a routine diagnostic tool.

CONCLUSION

In conclusion, pre-operative radiological assessment especially MRI with high accuracy in determining myometrial invasion is an inseparable tool. MRI lacks in lymph node assessment in having low specificity, but its high accuracy in determining the early stages when used in addition with clinic-pathological staging may avoid the lymph node harvesting. The accuracy in assessing early stages would entail the MRI being used a guide for planning minimally invasive surgical approach leading to enhanced patient outcome. The pre-operative neoplastic grading was concordant in 86.67% females with pre-operative under reporting in 10% and over-reporting in 3.33%. While comparing, the clinic-pathological with final histopathological staging, similarity was observed in 60% cases, while intra-operative staging showed 63.33% similarity. The pre-operative staging was under-staged in 10% cases and over-staged in 30% cases. This illustrates the diligence by which the surgeon would have to rely on intra-operative assessment for further plan of action, should have the mental flexibility of deterring from a pre-determined course like from a planned fertility sparing, minimally invasive surgery to an extensive surgery with exhaustive lymphadenectomy and also the familiarity with a bare minimum surgical expertise for the lymphatic dissection should be obtained for effectively dealing with this carcinoma.

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