Original Article

A Study of Clinico-Pathological Characteristics of Endometrial Carcinoma with Respect to Grading

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Abstract

Background: Endometrial cancer is an emerging health concern in India, largely affecting postmenopausal women due to lifestyle changes and demographic factors. This study aims to analyze the clinicopathological characteristics of EC in Indian patients to improve diagnosis, prevention, and treatment.

Materials and Methods: This retrospective study included 50 patients who underwent radical hysterectomy for EC at a tertiary care center over six years. Data was collected on demographic and tumor characteristics and clinical outcomes, including age, parity, menopausal status, tumor type, FIGO grade, stage, size, myometrial invasion, lymphovascular invasion, and lymph node metastasis. Statistical analysis determined the significance of these factors in prognosis and survival.

Results: The mean age at diagnosis was 62 years, with 86% of patients being postmenopausal. The most common type was endometrioid carcinoma (82%). Significant prognostic factors included tumor size, myometrial invasion, lymphovascular invasion, lymph node status, and FIGO staging. High-grade tumors exhibited a higher incidence of lymphovascular invasion (80% vs. 42.5%, p-value = 0.033) and poorer survival outcomes (50% vs. 81.3% alive, p = 0.049). FIGO staging, lymph node metastasis, and lymphovascular invasion were statistically significantly correlated with mortality.

Conclusion: EC primarily affects postmenopausal women, with endometrioid carcinoma being the most common type. Prognostic factors such as tumor size, myometrial invasion, lymphovascular invasion, and lymph node status influence treatment decisions and patient outcomes. High-grade tumors are associated with more aggressive disease and worse survival rates, highlighting the importance of thorough nodal evaluation and tailored treatment approaches. This study enhances the understanding of EC, aiding in the development of improved diagnostic and management strategies.

Keywords:

Endometrial Carcinoma, Radical Hysterectomy, Tumor Grading, FIGO Staging

Introduction

Endometrial cancer (EC), although historically associated with developed countries, is increasingly recognized as a significant health concern in India. According to the GLOBOCAN 2022 report, there are an estimated 420,368 new cases of endometrial carcinoma globally. In India, there were 17,420 new cases, with an age-standardized incidence rate (ASR) of 2.5 per 100,000

women. Endometrial cancer resulted in approximately 6,845 deaths in India, with an ASR of 0.96 per 100,000 women [1].

The prevalence and incidence of endometrial cancer in India are influenced by various factors, including demographic, lifestyle, and healthcare access disparities. Recent changes in lifestyle patterns, such as delayed childbearing, decreased parity, obesity, urbanization, and the adoption of Westernized diets that are high in fat and low in fiber, have led to an increased incidence in India [2]. EC mostly occurs in post-menopausal women at a mean age of 60 years, most commonly presenting with abnormal or post-menopausal uterine bleeding. The study of endometrial cancer encompasses a multidisciplinary approach, integrating clinical, pathological, and epidemiological insights to understand its etiology, progression, and optimal management strategies.

Pathological prognostic factors, such as tumor type, histological grade, extent of myometrial invasion, peritoneal cytology, lymph node metastasis, and staging, are pivotal in deciding the treatment strategies and predicting outcomes [3]. The most common histological type of endometrial cancer is endometrioid carcinoma, which is estrogen-dependent and grouped as type I, having a better prognosis. Other histologic types include serous papillary carcinoma and mixed carcinoma (including clear cell carcinoma), which are estrogen-independent and grouped as type II, having a poor prognosis [4].

Radical hysterectomy remains the mainstay treatment. Regional nodal dissection is performed in patients with advanced endometrial carcinoma. Further treatment modalities, such as radiation therapy and/or chemotherapy, are based on FIGO stage and pTNM staging.

India ranks fifth globally in terms of endometrial cancer incidence [1]. Despite this, there is limited data on the exact prevalence rates across different regions in India. This study was carried out to understand the unique epidemiological and clinicopathological characteristics of endometrial cancer for better understanding, early diagnosis, prevention, and treatment. The analysis in this study was done to find the relationship between tumor grade and various clinicopathological characteristics, as well as their impact on survival outcomes, employing statistical methods to determine the significance of these associations.

Materials and Methods

This retrospective study examined all patients who underwent hysterectomy for endometrial carcinoma between January 2018 and August 2023. Exclusion criteria consisted of cases of endometrial carcinoma where hysterectomy was performed outside GCSMCH&RC, as well as hysterectomy specimens lacking histopathological evidence of malignancy. This study was approved by the institutional ethics committee [GCSMC/EC/Research project/APPROVE/2023/577] and was carried out in accordance with ethical principles.

Data were gathered from the patients' medical records, which included age at diagnosis, parity, menopausal status, tumor type, grade and stage, tumor size, myometrial invasion, lymphovascular invasion, and lymph node metastasis. The analysis of the data was presented in frequencies and percentages. The results were presented in tables, bar charts, and figures. The Chi-square test was used to analyze the data, calculate the p-value, and determine statistical significance.

Treatment: Patients with low-risk factors, such as Stage IA endometrioid carcinoma with low-grade tumors and negative or focal lymphovascular invasion, were recommended to forego adjuvant therapy. Those categorized as intermediate risk, including Stage IA endometrioid with high-grade tumors and negative or focal lymphovascular invasion, Stage IB endometrioid with low-grade tumors and negative or focal lymphovascular invasion, and Stage IA non-endometrioid without myometrial invasion, were advised to undergo vault brachytherapy. High intermediate-risk patients, such as those with Stage IA endometrioid carcinoma with substantial lymphovascular invasion, Stage IB endometrioid carcinoma with high-grade tumors, and Stage II carcinoma, were

recommended external beam radiotherapy. Patients deemed high-risk, including Stage III-IVA with no residual disease and Stage I-IVA non-endometrioid with myometrial invasion and no residual disease, were advised a combination of radiotherapy and chemotherapy. For patients with advanced metastatic disease, including Stage III-IVA with residual disease and Stage IVB, palliative therapy was recommended.

Follow-Up: Low-risk patients were followed up every six months for two years, followed by yearly follow-up. High-risk patients were followed up every three months for two years, then every six months for five years, followed by an annual follow-up. Vault smear, USG whole abdomen, and, when required, CECT whole abdomen were the investigation modalities used during follow-up.

Results

In this retrospective study, 50 cases of carcinoma of the endometrium were included; all patients underwent Radical Hysterectomy from January 2018 to August 2023. The demographic and clinical characteristics of the patients are mentioned in [Table 1]. The study predominantly included individuals aged 55 to 70 years. The mean age at diagnosis was 62 years, with 62% presenting with postmenopausal bleeding.

Pathologic Characteristics: [Table 1] shows the various histopathologic characteristics of endometrial carcinoma. The size of the tumor at presentation ranged from 1.0 cm to 9.0 cm, with 4.8 cm (largest diameter) being the average size. The most common histology of carcinoma was Endometrioid carcinoma in 82% of cases. Other histologies included Serous Carcinoma (6%), Carcinosarcoma (6%), Mucinous Carcinoma (2%), Clear Cell Carcinoma (2%), and Adenosquamous Carcinoma (2%) [Fig. 1]. In Endometrioid carcinoma, FIGO Grade 2 (38%) was the most common. The stage distribution of patients in our study was as follows: 26% of patients were in stage IA, 32% in stage IB, 8% in stage IIA, 2% in stage IIB, 6% in stage IIIA, 16% in stage IIIB, and 10% in stage IIIC [Fig. 2].

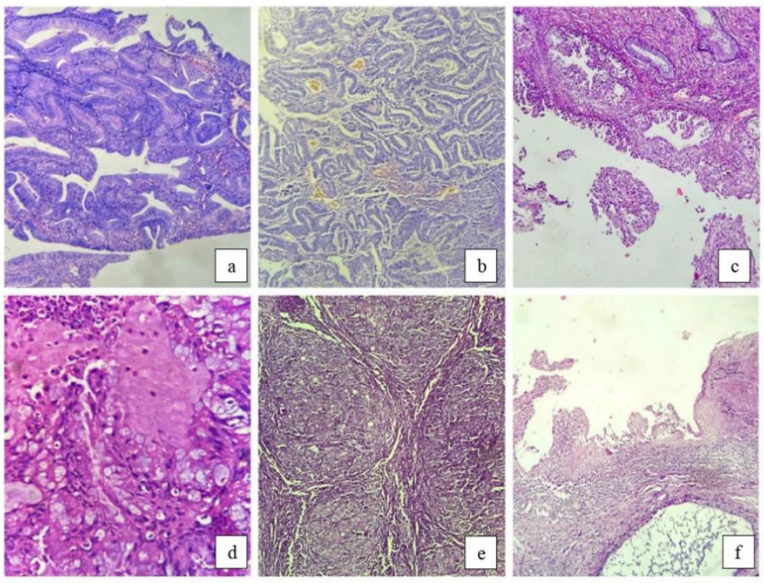

Figure 1: 1a. Endometrioid carcinoma Grade 1 (H&E x100), 1b. Endometrioid carcinoma Grade 2 (H&E x100), 1c. Serous Carcinoma (H&E x100), 1d. Mucinous Carcinoma (H&E x400), 1e. Lymph node Metastasis (H&E x100), 1f. Cervical involvement by Serous carcinoma

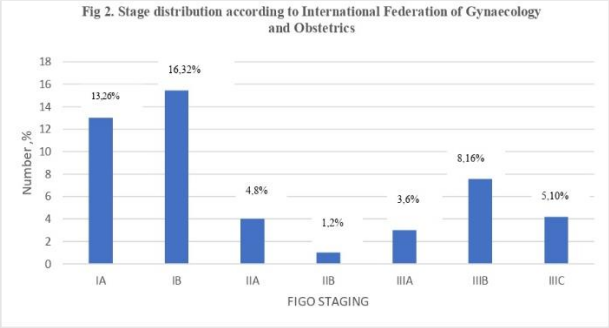

Figure 2: Stage distribution according to International Federation of Gynecology and Obstetrics

Among the 50 patients, 29 (58%) had myometrial invasion exceeding 50%, while 21 (42%) had invasion below 50%. Cervical involvement was noted in 5 cases (10%), parametrium in 6 cases (12%), and uterine serosa involvement in 1 case (2%). Margins were free of the tumor in all patients. The total number of nodes examined varied from 5 to 56, differing for each patient. Out of the total, 45 patients (90%) were diagnosed with node-negative status, while 5 patients (10%) were diagnosed with node-positive status [Table 1].

The clinico-pathological characteristics of low-grade and high-grade EC are outlined in [Table 2]. Lymphovascular invasion is associated with tumor aggressiveness, with a significantly higher occurrence in high-grade cases compared to low-grade cases (80% vs. 42.5%, p-value = 0.033). High-grade tumors are associated with significantly poorer patient survival compared to low-grade tumors, with a higher proportion of deaths observed (81.3% vs. 50%, p-value = 0.049).

Among the 42 patients, 13 required no adjuvant therapy, while 29 did. Of these, 10 patients (20%) were advised to undergo radiotherapy, and 19 patients (38%) received chemotherapy along with radiotherapy. Notably, 23 out of the 29 patients needing adjuvant therapy followed their prescribed treatment, indicating high compliance.

[Table 3] presents a comparative analysis of prognostic factors and treatment outcomes in 42 patients with endometrial carcinoma. The factors examined include myometrial invasion, lymph node status, lymphovascular invasion, FIGO staging, and treatment received. The table displays the distribution of patients based on each factor and their corresponding survival status (alive or dead), calculated using chi-square analysis. The p-values are provided to indicate the statistical significance of the associations observed. The p-value for lymph node metastasis, lymphovascular invasion, and FIGO staging was found to be statistically significant (i.e., <0.05).

Discussion

Endometrial carcinoma is a leading malignancy among females, generally seen in postmenopausal women, with only 25% of cases occurring in the premenopausal/perimenopausal period [4]. Pre-operative imaging and biopsy are necessary to identify the disease. Clinicopathological analysis determines the extent of the disease. Sampling of the endometrium through endometrial biopsy and curettage is the most used test when endometrial carcinoma is suspected. The risk of progression to end-stage disease increases in under-diagnosed patients. Hence, the present study was undertaken to understand the clinicopathological correlation in patients suffering from endometrial carcinoma.

Table 1: Demographic, clinical and histopathological characteristics

Characteristics	Number	Frequency (%)
Age		
<50 years	8	16
51-69 years	31	62
>70 years	11	22
Parity		
Nulliparous	3	6
Multiparous	47	94
Menopausal Status		
Premenopausal	7	14
Post-menopausal	43	86
Symptoms		
Asymptomatic	6	12
Menorrhagia	5	10
Abdominal Pain	8	16
Post-menopausal bleeding	31	62
Histopathological Characteristics		
Tumour Size		
<3cm	12	24%
3-6 cm	30	60%
>6 cm	8	16%
Type of Carcinoma		
Endometroid Carcinoma	41	82
Serous Carcinoma	3	6
Carcinosarcoma	3	6
Mucinous Carcinoma	1	2
Clear Cell Carcinoma	1	2
Adenosquamous Carcinoma	1	2
Myometrial Invasion		
Less than ½	21	42
More than or equal 1/2	29	48
Lymph node status		
Positive	5	10
Negative	45	90
Lymphovascular Invasion		
Positive	8	16
Negative	42	84
Parametrium Involvement		
Present	6	12
Absent	44	88
Cervical Involvement		
Present	5	10
Absent	45	90
Patient status (42 patients)		
Alive	31	73.8
Dead	11	26.2
Disease free interval (42 patients)		
>2 years	15	35.7
<2 years	27	64.3

Table 2: Comparison of clinico-pathological characteristics of low-grade and high-grade endometrial carcinoma

Characteristics	Low-grade (40)	High- grade (10)	P-value
Menopausal status			0.541
Premenopausal (below 50)	5 (12.5%)	2 (20%)	
Postmenopausal (above 50)	35(87.5%)	8 (80%)	
Tumour Size			0.770
<3cm	9 (22.5%)	3(30%)	
3-6 cm	25(62.5%)	5(50%)	
>6 cm	6(15%)	2(20%)	
Myometrial Invasion			0.566
Less than ½	16 (40%)	3 (30%)	
More than or equal 1/2	24 (60%)	7 (70%)	
Cervical Involvement			0.238
Present	3 (7.5%)	2 (20%)	
Absent	37 (92.5%)	8 (80%)	
Lymph node status			0.239
Positive	3 (7.5%)	2 (20%)	
Negative	37 (92.5%)	8 (80%)	
Lymphovascular Invasion			**0.033**
Positive	17 (42.5%)	8 (80%)	
Negative	23 (57.5%)	2 (20%)	
Patient status and disease-free interval in low-grade and high-grade groups			
	Low-grade (40)	**High-grade (10)**	**P-value**
Patient status (42 patients)	32	10	**0.049**
Alive	26 (81.3%)	5 (50%)	
Dead	6 (18.7%)	5 (50%)	
Disease free interval (42 patients)			0.887
>2 years	12 (37.5%)	4 (40%)	
<2 years	20 (62.5%)	6 (60%)	
***No follow up for 8 patients**			

Table 3: Impact of Clinical Parameters on Survival Outcomes in Endometrial Cancer Patients: An Analytical Overview

Prognostic Factors	Alive	Dead	P-value
Myometrial invasion (for 42 patients)			0.066
<1/2	17	2	
>1/2	15	8	
Lymph Nodes status (42 patients)			**0.001**
Positive	1	4	
Negative	31	6	
Lymphovascular invasion (42 patients)			**0.011**
Present	11	8	
Absent	21	2	
FIGO Stage (42 patients)			**0.003**
IA	10	1	
IB	11	1	
IIA	2	1	
IIB	1	0	
IIIA	1	2	
IIIB	5	2	
IIIC	0	5	
Treatment (42 patients)			0.122
Taken	17	6	
Not Taken	3	3	
No treatment advised	12	1	
***No follow up for 8 patients out of 50**			

A total of 50 patients were included in the study. The mean age of the patients was 62 years, which was slightly higher than in studies by Goutham S et al. [4], Veerendra Angadi et al. [5], and Jezan HS et al. [6] (56, 55, and 60 years, respectively). The majority of the patients were postmenopausal (86%), similar to other studies [4, 5, 6, 7, 8, 9, 10]. The most common EC was endometrioid carcinoma (82%), consistent with most other studies [4, 5, 7, 8, 9, 10].

The average tumor size measured 4.8 cm in the largest diameter in this study and 3.9 cm in Goutham S et al. [4]. The median size in our study was 4.5 cm, whereas in the study by Hou X et al. [7], it was 3.5 cm. The study conducted by Hou X et al. [7] showed an increased risk of mortality with increasing tumor size.

Myometrial invasion, lymphovascular invasion, and lymph node metastasis are significant risk factors associated with the development and progression of endometrial carcinoma.

Lymphovascular invasion (LVI) occurs when tumor cells infiltrate the walls of blood vessels or lymphatic channels. LVI is a strong predictor of lymph node positivity and ultimately affects overall survival [4]. In this study, 16% of cases exhibited LVI, while 84% did not. This differs from the findings of Angadi V et al. [5] (35.2%) and Goutham S et al. [4] (2.9%). Variation in LVI reported in various studies could be due to interobserver variation, as LVI is a subjective finding unless confirmed by IHC. Further analysis revealed that LVI was present in 42.5% of low-grade carcinoma cases and 80% of high-grade cases, with a statistically significant p-value of 0.033. Regarding survival outcomes, the analysis showed a statistically significant p-value of 0.011 concerning LVI, similar to Angadi V et al. [5] (p-value 0.001), indicating that the absence of LVI is associated with higher overall survival.

Lymph node (LN) status is a strong predictive factor of recurrence. Determining the nodal status of patients is mandatory to optimally tailor adjuvant therapies and reduce local and distant recurrences [6]. In this study, lymph node involvement was noted in 10% of cases. Similarly, Goutham S et al. [4] and Gorzelnik K et al. [13] found positive nodal status in 11% and 11.7%, respectively. In another comprehensive study by Ueno Y et al. [11], lymph node metastasis varied across clinical centers, with percentages of 17.1%, 10.9%, 18.4%, and 17.1% in Kanagawa Cancer Centre, municipal hospitals, National Cancer Centre Japan, and university hospitals, respectively. Notably, low-grade carcinoma exhibited lymph node involvement in 7.5% of cases, contrasting with 20% in high-grade carcinoma. The analysis of survival outcomes revealed a statistically significant p-value of 0.001 for lymph node involvement. Similarly, a study by Gorzelnik K et al. [13] also observed a statistically significant p-value of < 0.0001, indicating that patients with lymph node involvement had a poorer prognosis.

These findings highlight the potential impact of lymph node metastasis and lymphovascular invasion on patient outcomes and provide valuable insights for clinical management and prognostication in endometrial carcinoma.

Myometrial invasion is one of the key components of the staging system for endometrial cancer according to FIGO staging. Assessing the depth of myometrial invasion is essential for determining disease extent, guiding treatment decisions, and predicting patient outcomes. In this study, we observed that 42% of cases showed myometrial invasion $< 50\%$, while 48% exhibited invasion $\geq 50\%$. In other studies, Goutham S et al. [4], Iskandar et al. [8], and Dane C et al. [12] reported more cases with myometrial invasion less than 50% (77.1%, 55.2%, and 88%, respectively), with the remaining percentages exhibiting invasion $> 50\%$. Furthermore, when analyzed in low-grade carcinoma cases (40), 40% exhibited myometrial invasion $< 50\%$, while 60% showed invasion $\geq 50\%$. Conversely, in high-grade carcinoma cases (10), 30% displayed invasion $< 50\%$, with 70% showing invasion $\geq 50\%$. In the study by Dane C et al. [12], the overall survival rate was 96% for patients with myometrial invasion $< 50\%$ versus 66% for those with myometrial invasion $> 50\%$ (p-value < 0.0001). However, we did not find any statistical significance between

myometrial invasion and survival outcome (p-value 0.066). This may be attributed to a smaller number of high-grade cases and the fact that, even among patients with low-grade endometrial carcinoma, a majority (60% of 40 cases) exhibited more than 50% myometrial invasion.

The FIGO staging system is crucial for determining the prognosis and guiding the treatment of EC. Advanced staging and deeper invasion require additional radiotherapy and chemotherapy. In our study, most patients presented at an earlier stage, most commonly in FIGO Stage I (58%). This was similar to studies by Goutham S et al. [4], Angadi V et al. [5], and Jezan HS et al. [9], who also reported FIGO Stage I as the most common stage (62.9%, 44.68%, and 50.9%, respectively). We found a significant association of FIGO stage with survival (p-value 0.003), with stages I and II showing high survival rates compared to stage III, which was linked to increased mortality. This aligns with the study by Angadi V et al. [5] (p-value < 0.001), which also reported higher overall survival in patients with stage I disease compared to those with late-stage disease.

Limitation: The study conducted was a retrospective, single-center analysis, and hence, the data is not representative of the national epidemiology of EC. Our center usually caters to a low socioeconomic status, which may be one of the reasons for less awareness and late presentation of the patients. The limited number of cases included in the study could result in hospital bias. A larger number of cases need to be studied to find a better association between various morphological patterns.

Conclusion

This study highlights several significant observations. Endometrial carcinoma predominantly affects postmenopausal women, with a mean age of diagnosis around 62 years. The most common histological type observed was endometrioid carcinoma, consistent with global trends. Tumor size, myometrial invasion, lymphovascular invasion, lymph node status, and FIGO staging emerged as critical prognostic factors influencing treatment decisions and patient outcomes. Notably, high-grade endometrial carcinomas demonstrated more aggressive behavior, with a higher incidence of lymphovascular invasion and poorer survival outcomes compared to low-grade tumors. Lymph node metastasis significantly correlated with disease recurrence and mortality, emphasizing the importance of thorough nodal evaluation in treatment planning. In summary, this research enriches our understanding of endometrial carcinoma, paving the way for enhanced diagnostic strategies and tailored treatment modalities, ultimately improving patient survival and quality of life.

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