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Early-stage endometrial carcinoma; risk factors for recurrence

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ABSTRACT

Background: Endometrial carcinoma (EC) is the most common gynecological malignancy in developed countries. The overall prognosis is excellent, as most cases are diagnosed at an early stage with low-grade histology, but once the recurrence occurs, the median survival decreases severely. **Aims and Objectives:** The aim of this study was to identify the risk factors associated with recurrence in early-stage EC and explore their impact on overall survival (OS) after recurrence. **Materials and Methods:** Records from patients diagnosed with EC were retrospectively reviewed. 220 patients were identified as early-stage, low-risk EC who underwent primary surgical treatment between January 2010 and December 2022, and their baseline characteristics were analyzed. Cox regression analysis was used to identify various factors for tumor recurrence. Survival analysis was done using the Kaplan-Meier method. **Results:** In a cohort of 220 patients, we observed tumor recurrence in 44 (20%) patients and 34 (15.45%) deaths over a median follow-up of 72 months (range, 12–144 months). Multivariate analysis confirmed two risk factors: myometrial invasion (MMI) of any depth and lymphovascular invasion (LVI) as independent predictors of recurrence. The prognosis was worse for patients with recurrence than for those without. The OS for the recurrent group was 38.6%, compared to 96.0% in the non-recurrent group. In our study, the median time to recurrence was 19 months (confidence interval 18–30) months. **Conclusion:** The presence of MMI and LVI are important predictors for recurrence in early-stage low-risk EC.

Key words: Endometrial carcinoma; Early stage; Recurrence; Risk-factors

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INTRODUCTION

Uterine cancer is the second-most common gynecologic malignancy across the world, preceded by cervical cancer, which is the most common gynecology malignancy in the world. More than 90% of uterine cancers have an endometrial origin, and the remaining 10% are mesenchymal in origin; hence, endometrial carcinomas (ECs) are the most common subtype.[1] Usually, ECs are diagnosed at an early stage, with a 5-year overall survival (OS) of more than 90% for the International Federation of Gynecology and Obstetrics (FIGO) stage.[2,3] Various factors such as stage of disease, histological subtype type and grade, depth of myometrial invasion (MMI), and lymphovascular space invasion have prognostic significance for recurrence in EC.[4] Low-risk EC is defined as patients with disease confined to the uterus only, histologic grade 1 or 2, endometrioid histologic subtype, and less than half of MMI.[5-7] Such patients have a low risk of pelvic lymph node (LN) metastasis (<5%), vaginal recurrence (1–3%), and lung metastases (<1%).[7] Surgery is the mainstay of treatment for such patients, without the need for any further adjuvant therapy in the majority of them.[8] The prognosis for low-risk EC is excellent, and the recurrence rate is low; therefore, risk factors for recurrence in them have not been distinctly identified. The aim of our study was to find the risk factors for recurrence in patients with low-risk EC.

Aims and objectives

The aim of this study was to identify the risk factors associated with recurrence in early-stage EC and explore their impact on overall survival (OS) after recurrence.

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MATERIALS AND METHODS

Our study is retrospective in nature and is based on observations made in patients with a diagnosis of primary EC who were operated on in our institute between January 2010 and December 2022. After the ethical approval of the institute, we reviewed the hospital records and study notes entered in the patient files of 380 patients.

Inclusion criteria

(a) endometrioid histology; (b) histological grade 1 or 2; (c) No or < 50% MMI.

Exclusion criteria

(a) non-endometrioid histology; (b) histological grade 3; and (c) patients with FIGO stage IB–IV disease. Based on these criteria, out of 380 patients, only 220 were identified as having low-risk EC and were included in the study. At the time of registration at the institute, informed consent was obtained from all patients regarding the use of their medical information for research purposes without revealing patient identity.

Tumor staging and architectural grading were done using standard 2009 FIGO criteria. After surgical staging, the majority of the patients in our study (210 of the 220) were recommended for observation only, and adjuvant vault brachytherapy (VB) was given to 10 patients. Patients underwent routine surveillance in our out-patient department clinics, which included a physical examination and pelvic examination, which were done as per the National Comprehensive Cancer Network guideline criteria: every 3–6 months for the first 2–3 years, then 6 monthly till 5 years, and annually thereafter. Based on symptoms such as vaginal bleeding, abdominal pain, and lower back pain, imaging was advised. Tumor recurrence was confirmed by a clinical pelvic examination, and in cases of suspicious findings, it was further supplemented with imaging studies and tissue biopsies. We investigated the age at diagnosis, menopausal status, body mass index (BMI), histological grade, extent of surgery, extent of lymphnode dissection, tumor size, and involvement of the lower uterine segment as possible predictors for the occurrence of recurrence.

Statistical analyses

All statistical analyses were performed using SPSS software (version 24.0, IBM Chicago, USA). Recurrence-free interval (RFI) was defined as the time from primary surgery to detection of recurrence. Patients with no evidence of recurrence were censored by the last date of follow-up. OS was defined as the time interval from primary surgery to death or the last follow-up. The survival analysis was done by the Kaplan-Meier method, and the results were compared using the log-rank test. We used the Cox proportional hazards model for both univariate and multivariate analysis to identify independent predictors for recurrence. A multivariate analysis of all factors found significant on univariate analysis was performed. A $P<0.05$ was considered significant.

RESULTS

220 patients were identified as low-risk based on criteria already mentioned in the material and method sections. All these patients were discussed on the institutional multispecialty tumor board for further management after surgery, and 210 patients were advised observation, and adjuvant VB was given to the remaining 10 patients. During the follow-up period, out of a cohort of 220 patients, 44 recurred. Table 1 shows a comparison of the demographic and clinicopathological characteristics of recurrent and non-recurrent cases. The pattern of the recurrences detected is shown in Table 2. We observed isolated vaginal recurrences in 16 (36.36%) patients, isolated pelvic recurrences in 12 (27.27.6%) patients, and 7 (16%) patients had simultaneous involvement of both vagina and pelvis. 9 (20.4%) patients had distant failure: 4 had isolated lung metastases, 3 had isolated liver metastases, and 2 had paraaortic relapse with liver metastases. None of the recurrences were seen in patients who had received adjuvant VB. All 16 patients with vaginal recurrences as the only site of first failure were treated with a combination of pelvic external beam radiation therapy (EBRT) and vaginal brachytherapy (VBT); 12 (27.3%) patients with isolated pelvic recurrences were treated with pelvic EBRT concurrent with weekly cisplatin. 7 (16%) patients with vaginal and pelvic co-failures were treated with pelvic concurrent chemoradiotherapy (CCRT) and VBT. Patients with systemic failures were treated with palliative chemotherapy. 10 out of 16 patients with isolated vaginal failure had no evidence of disease following treatment of recurrent disease; remaining 6 patients had residual disease after RT and were then treated with palliative chemotherapy. 8 out of 12 patients with isolated pelvic recurrence achieved a complete response to CCRT, but 4 had progressive disease involving distant sites also and died of disease. The median duration from surgery to occurrence of recurrence in our study was 19 months (confidence interval [CI] 18–30) months. The median follow-up for the entire cohort of 220 patients was 72 months (range, 12–144 months). The median follow-up for the recurrent cohort was 36 months (range, 12–84 months). The OS for the recurrent group was 38.6%, compared to 96.0% in the non-recurrent group. Kaplan–Meier survival curves for both recurrent and non-recurrent cases are shown in Figure 1. Table 3 shows the results of a univariate Cox regression analysis of clinical and pathological risk factors associated with recurrence. It was revealed that age ≥60 years, surgery type: hysterectomy only,

Table 1: Clinicopathologic characteristics of 220 patients

Baseline characteristics	Total number of patients (220)	Recurrence (44)	Nonrecurrence (176)	P
Age (years)				
≥60	130 (59.1)	39 (88.6)	91 (51.7)	0.000
<60	90 (40.9)	5 (11.4)	85 (43.3)	
Menopausal status				
Postmenopausal	186 (84.5)	38 (86.4)	148 (84.1)	0.819
Premenopausal	34 (15.5)	6 (13.6)	28 (15.9)	
BMI ≥30 kg/m^2				
Yes	141 (64.1)	31 (70.5)	110 (62.5)	0.000
No	79 (35.9)	13 (29.5)	66 (37.5)	
Grade				
2	81 (36.8)	11 (25)	70 (39.8)	0.081
1	139 (63.2)	33 (75)	106 (60.2)	
Lymphnode dissection				
Nil	28 (12.7)	12 (27.3)	16 (9.1)	0.002
PLND	151 (68.6)	28 (63.6)	123 (69.9)	
PPLND	41 (18.6)	4 (9.1)	37 (21)	
Type of surgery				
Hysterectomy	27 (12.3)	11 (25)	16 (9.1)	0.008
TAH BSO	193 (87.7)	33 (75)	160 (90.9)	
MMI				
Yes	37 (16.8)	37 (84.1)	0	0.000
No	183 (82.2)	7 (15.9)	176 (100)	
LVI				
Present	49 (22.3)	32 (72.7)	17 (9.7)	0.000
Absent	171 (77.7)	12 (27.3)	159 (90.3)	
Lower uterine segment involvement				
Present	27 (12.3)	27 (61.4)	0	0.000
Absent	193 (87.7)	17 (38.6)	176 (100)	
Tumor size >2 cm				
Yes	36 (16.4)	25 (56.8)	11 (6.2)	0.000
No	184 (83.6)	19 (43.2)	165 (93.8)	
Adjuvant Brachytherapy				
Yes	10 (4.54)	0	10 (5.68)	0.000
No	210 (95.45)	44 (100)	166 (94.31)	

BMI: Body mass index, PLND: Pelvic lymph node dissection, PPLND: Pelvic and para-aortic lymph node dissection, TAH BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy, MMI: Myometrial invasion, LVI: Lymphovascular invasion

Table 2: Pattern of recurrences in 44 patients

Site	n (%)
Vaginal	16 (36.36)
Pelvic	12 (27.27)
Vaginal+Pelvic	7 (15.90)
Lung	4 (9.09)
Liver	3 (6.81)
Para-aortic+Lung	2 (4.54)

presence of MMI, lymphovascular invasion (LVI) positivity, tumor size ≥2cm, and involvement of the lower uterine segment were factors predictive of recurrence. Table 4 shows the results of multivariate analysis and confirms two risk factors: MMI of any depth and LVI as an independent predictor of recurrence.

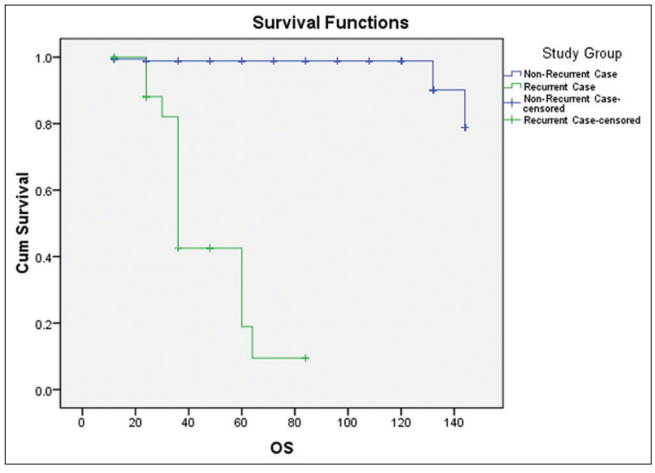

Figure 1: Overall survival of early-stage endometrial cancer patients based on recurrence status

DISCUSSION

The prognosis in cases of early-stage EC is generally good. We observed a recurrence rate of 20%. In other studies, a recurrence rate of 10–15% was observed, which is lower than our observation.[8] A possible explanation for the slightly high recurrence rate in our patients could be

Table 3: Univariate analysis

Predictive risk factor	Recurrence		
	HR	95% CI	P
Age ≥60 years	6.072	2.392–15.411	0.000
Postmenopausal status	1.169	0.494–2.765	0.723
BMI ≥30 kg/m^2	1.429	0.748–2.732	0.280
Grade 2	0.543	0.274–1.075	0.080
Lymph node dissection pelvic only	2.106	0.694–6.391	0.189
Surgery hysterectomy only	2.557	1.292–2.557	0.007
MMI	60.463	25.563–143.012	0.000
LVI	12.960	6.638–25.305	0.000
Tumor size ≥2 cm	9.835	5.343–18.103	0.000
Lower uterine segment involvement	28.608	14.041–58.289	0.000

MMI: Myometrial invasion, LVI: Lympho-vascular invasion, BMI: Body mass index, CI: Confidence interval

Table 4: Multivariate analysis

Predictive risk factor	Recurrence		
	HR	95% CI	P
Age ≥60 years	0.290	0.068–1.239	0.095
Postmenopausal	2.260	0.467–10.930	0.311
BMI ≥30 kg/m^2	0.907	0.439–1.877	0.793
Grade 2	1.192	0.498–2.853	0.693
Lymph-node dissection Pelvic only	0.862	0.286–2.598	0.792
Surgery hysterectomy only	6.308	0.557–71.496	0.137
MMI	0.045	0.015–0.148	0.000
LVI	2.149	0.084–0.902	0.033
Tumor size ≥2 cm	1.901	0.304–11.878	0.492
Lower uterine segment involvement	0.318	0.061–1.666	0.175

MMI: Myometrial invasion, LVI: Lymphovascular invasion, BMI: Body mass index, CI: Confidence interval

because of the absence of centralized pathological review of slides in some of our cases; there may be a subgroup of patients with unknown negative prognostic factors leading them to recur; and last but not least, another reason may be that we have also included grade 2 histologies, which have been excluded by most. Our data showed that the vaginal cuff was the most common site for recurrence, followed by the pelvis, which is consistent with the results of Huijgens, Mertens, and Iavazzo et al., discussing the recurrence in patients with all stages of endometrioid EC and early-stage EC in particular respectively.[9,10] Half of our patients experienced recurrence within 24 months, and a median RFI of 19 months (CI 18–30) months was observed, which is close to the observation of published literature. In the study of Huijgens and Mertens, a significant number of patients with EC experienced recurrences during the first 2 years (37.5% of patients experienced recurrence in the 1st year, 54.2% in the 2nd year), and 8.3% in the 3rd year reported a median RFI of 17 months.[9]

Patients with early-stage EC are more likely to experience recurrences if they have histological variables like deep MMI, LVI positivity, high histologic grade, and lower uterine segment involvement.[11,12] Some studies have suggested the importance of molecular factors such as TP53 or beta-catenin mutations to affect recurrence in early-stage EC.[13]

In clinical practice, all these factors are mainly taken into consideration when deciding about adjuvant treatment after primary surgery. However, in patients with early-stage low risk (Stage IA, Grades 1 and 2), most of these factors are absent, and hence most of the patients are either put on observation only and a few are supplemented with adjuvant VB. Our study identified MMI and LVI are independent prognostic factors for the occurrence of recurrence which is in accordance with the literature. The study done by Han et al., suggested that the presence of MMI is a negative prognostic factor for recurrence in early-stage EC.[14] Various other authors confirmed the presence of LVI in early-stage EC as a predictive factor for recurrence.[10,15,16] In addition to these risk factors, recent research has mainly focused on various molecular markers as predictive factors for recurrence. The prognostic significance of the four molecular subgroups was originally proposed by The Cancer Genome Atlas (TCGA) and later confirmed by a study done by Stelloo et al.[17,18] They concluded that L1CAM and p53 were independently associated with a worse outcome, whereas POLE mutations, microsatellite stability, and CTNNB1 wild-type had a more favorable outcome.[17] A secondary analysis of the PORTEC-3 study has shown that molecular classification of EC has a strong prognostic value in patients with high-risk features compared to clinic-pathological factors, and this may help to identify those who will benefit from adjuvant treatment.[19] In our institute, we lack the facility and infrastructure to investigate these molecular markers, especially for retrospective patient populations. Though the prognostic role of theses molecular markers is now well established in early-stage patients, the importance of clinicopathological factors cannot be underestimated. Therefore, integrated knowledge of both clinicopathological factors and molecular markers is needed to identify the subgroup of patients who may benefit from adjuvant treatment. According to reports, patients who receive adjuvant radiotherapy are less likely to experience a recurrence.[20] In our study, we did not observe any recurrence in patients who had received adjuvant radiation, but we had only 10 patients in our study who received adjuvant VB, making it difficult to draw a conclusion from the small subgroup. However, larger randomized case-control trials with adequate numbers of patients in both the observation group and adjuvant VB group would be required to prove this.

Limitations of the study

There are several limitations to our study: firstly, the retrospective nature of the study; secondly, the absence of a centralized pathological review of slides; and thirdly, the lack of lab facilities for doing molecular prognostic factors. Nonetheless, we identified certain factors that predict a significantly higher risk of recurrence, suggesting that some subpopulations of the IA G1 and G 2 may benefit from closer attention in follow-up.

CONCLUSION

In conclusion, people with stage IA low-grade EC have a low probability of developing recurrence as they do not meet the usual criteria for adjuvant treatment. In our study, the recurrence rate was 20%, and the survival rate for patients who recurred was much lower than for those who did not. Despite the fact that these patients are deemed low-risk, finding additional risk factors for recurrence may help to identify the patients who would benefit from more frequent surveillance or adjuvant treatment rather than salvage therapy.

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Authors Contribution:
AA- Definition of intellectual content, Literature survey, Prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **KF-** Concept, data collection, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **SN-** Design of study, statistical Analysis and manuscript revision; **MAS-** Review Manuscript; **MTR-** Review Manuscript; **AMN-** Literature survey and preparation of Figures; **SQW-** Coordination and Manuscript revision.

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