Original Article

Prognostic characteristics and recurrence patterns of grade 1 endometrial carcinoma: a large retrospective analysis of a tertiary center

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Background: Endometrial cancer (EC) is the most common tumour of the female reproductive system, and low-grade EC is the histological type with the best prognosis for its less aggressiveness. Abnormal uterine bleeding is one of the first symptoms that appears and that allows an early diagnosis, while the disease is still confined into the uterus. The objective of this study was to identify risk factors associated with recurrence in low-grade EC across International Federation of Gynaecology and Obstetrics (FIGO) 2009 stages I to IV.

Methods: This is a retrospective study that collected patients surgically treated at the Thames Valley Cancer Centre from March 2010 to January 2020 for low-grade EC. All cases were debated at the multidisciplinary team discussion, both prior to and following surgery, to decide the surgical approach and the need for adjuvant treatments. Clinical, surgical and histopathological data were gathered from electronic patient record and used for the statistical analysis.

Results: A total of 238 patients were included. Overall survival (OS), disease-free survival (DFS), and cancer-specific survival (CSS) were favourable, with follow-up nearing 10 years. However, 14 patients (5.88%) experienced recurrence, 11 of whom (78.5%) were initially diagnosed at stage I. The median time from surgery to relapse was 30 months. The vaginal vault was the most common site of recurrence (42%), followed by pelvic lymph nodes and distant metastases. Only myometrial invasion (P=0.049) and serosal involvement (P=0.01) were statistically significant predictors of recurrence in both univariate and multivariate analyses.

Conclusions: This study confirms that deep myometrial invasion and serosal involvement are significant predictors of recurrence and poor outcomes in grade 1 EC. Other factors, such as lymphovascular space

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invasion and lymph node positivity, were not confirmed as significant. Before recommending adjuvant treatment for low-grade EC patients exhibiting these risk factors, further prospective trials are necessary.

Keywords: Endometrial cancer (EC); endometrioid endometrial cancer (EEC); low-grade endometrial cancer (low-grade EC); grade 1; recurrence

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Introduction

Endometrial cancer is (EC) the most common malignancy of the female reproductive tract in developed countries, with grade 1 endometrioid endometrial cancer (EEC) representing a significant proportion of these cases (1,2). Grade 1 (G1) EC is defined by a solid non-glandular tumour growth of up to 5% (3); grade 2 ranges from 6% to 50%, and grade 3 exceeds 50%. G1 tumours typically exhibit slow growth and are often confined to the uterus. While grade 1 carcinomas are exclusively of the endometrioid subtype, endometrioid histology can also be classified as grade 2 (G2) or grade 3 (G3).

All other histological subtypes of EC are classified as grade 3, indicating a high-grade tumour (4). Recurrence rates for grade 1 EC are generally low, particularly in early-stage disease. However, several clinicopathological factors—such as depth of myometrial invasion, lymphovascular space invasion (LVSI), adnexal or serosal involvement, and tumour grading—have been identified as potential risk factors for recurrence (5,6). Additionally, factors such as lymph node status (7-9), the surgical approach (10), and the use of adjuvant therapy (11) may influence the risk of recurrence, although their roles in low-grade EC remain less well defined. Beyond the aforementioned factors, Nwachukwu *et al.* (5) also identified tumour size (≥2 cm), type of surgery, any degree of myometrial invasion, and a time interval of ≥6 months between biopsy and surgery as predictors of recurrence in stage IA G1 EC. In contrast, other studies do not support these findings (6,12). For instance, Han *et al.* (6) found that only myometrial invasion and tumour grade were associated with increased recurrence risk in International Federation of Gynaecology and Obstetrics (FIGO) 2009 stage IA and IB EC, respectively. When considering low-risk EC, LVSI and primary tumour diameter (PTD) ≥2 cm have been associated with a higher recurrence risk.

This study differs from the aforementioned research by including G1 EC cases from FIGO 2009 stages I to IV. Our aim is to investigate the clinicopathological and treatment-related factors associated with recurrence, in order to better define high-risk subgroups within this population. By improving our understanding of these associations, we hope to identify patients who may benefit from more intensive follow-up or treatment, while sparing low-risk individuals from unnecessary interventions. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-1635/rc).

Highlight box

Key findings

- Low-grade endometrial cancer (EC) typically presents at an early stage. However, myometrial invasion, serosal involvement, and advanced International Federation of Gynecology and Obstetrics (FIGO) stages significantly impact prognosis and recurrence rates.

What is known and what is new?

- Myometrial invasion, serosal involvement, and lymphovascular space invasion (LVSI) are established risk factors for recurrence and poorer prognosis in EC.
- Importantly, even low-grade EC may recur or have an unfavorable prognosis, particularly when associated with deep myometrial infiltration, serosal involvement, or diagnosis at an advanced stage.

What is the implication, and what should change now?

- While molecular classification is emerging as a promising tool, it is still in development. Therefore, histopathological features should continue to guide prognosis and treatment decisions, including in cases of low-grade EC.

Methods

Out of all patients with EC who were treated across the Thames Valley Cancer Alliance Network (five recruiting sites: John Radcliffe Oxford University Hospitals NHS Foundation Trust, Churchill Hospital Oxford University Hospitals NHS Foundation Trust, Nuffield Orthopedic

Centre Oxford University Hospitals NHS Foundation Trust, Buckinghamshire Healthcare NHS Trust and Royal Berkshire NHS Foundation Trust) between March 2010 and January 2020, those with confirmed grade 1 EC were included in our study. This study is part of a larger research involving histological types of gynaecological uterine cancer (13-16). Patients with concomitant second primary cancer and patients that did not have primary surgical treatment were excluded from our cohort; similarly, we excluded patients with inadequate data on our records. Data extraction was performed retrospectively from electronic patients' record. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was registered as a service evaluation protocol at the Oxford University Hospitals Trust requirements (registration number 5832). The design, analysis, interpretation of data, drafting and revisions conform to the Committee on Publication Ethics guidelines and the Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement validated by the Enhancing the Quality and Transparency of Health Research Network (17-19). Informed consent was obtained from all individual participants to allow data collection and all information gathered from this research was anonymized to protect the privacy of every participant.

Patients' medical history were recorded. The Age-Adjusted Charlson Comorbidity Score (AACCS) was used to assess comorbidities, and patients were divided in three groups: 0–1, 2–3 and >3 (20). Histopathological report were all checked, and features obtained, such as FIGO Stage (3), depth of myometrial invasion, cervical stromal involvement, serosal involvement, adnexal, parametrial, LVSI and pelvic lymph node involvement and the presence of distant metastases. All tumours were classified according to the European Society of Gynaecological Oncology (ESGO)—European Society for Radiotherapy and Oncology (ESTRO)—European Society of Pathology (ESP) risk stratification model (21). Treatment details regarding interval from diagnosis to surgery, mode of surgery (laparotomy or laparoscopy), operating service (general gynaecology or gynaecology oncology), pelvic lymphadenectomy and administration of adjuvant treatment where offered were recorded. All cases, before and after the surgery, were discussed among specialist in a multidisciplinary team (MDT) discussion to assess both the primary and the adjuvant treatment.

Follow-up was clinic-based under Gynaecological Oncologists and/or Clinical Oncologists in 3 months' intervals for the first year, 4 months' intervals for the second, biannually for the third and annually thereafter for 2 more years.

Continuous variables were compared using samples *t*-test, while categorical variables with Person Chi-squared. Kaplan-Meier were used to calculate the survival rates of our population, and the comparisons were made using log-rank tests. Variables potentially related to an increased risk of recurrence or mortality were assessed with univariate and multivariate Cox proportional hazard analysis.

Statistical analysis

All statistical analyses were performed using IBM©SPSS Statistics 22.0. Statistical significance was considered for $P<0.05$.

Results

General population

Out of 847 EC cases treated within the Thames Valley Cancer Alliance Network, 283 cases of grade 1 EC were identified. Six cases with synchronous ovarian cancer, one with synchronous gastric cancer, and 38 with missing data were excluded, leaving 238 patients for final analysis, representing 28% of the total cohort. The median age was 64 years (range, 27–88 years), and the median body mass index (BMI) was 32 kg/m^2 (range, 21–50 kg/m^2).

Presenting symptoms included post-menopausal bleeding in 84.8% (n=202/238), incidental finding of thickened endometrium in 8.4% (n=20/238), and other nonspecific symptoms in 6.7% (n=16/238). All patients underwent ultrasound assessment of endometrial thickness. Preoperative histology from hysteroscopic or pipelle biopsies reported endometrial hyperplasia in 27.7% (n=66/238), confirmed G1 EC in 58.8% (n=140/238), with the remaining cases showing higher-grade components prompting further imaging, primarily computed tomography and magnetic resonance imaging.

Laparoscopic hysterectomy with bilateral salpingo-oophorectomy was performed in 96.2% (n=229/238) of cases; 2.9% (n=7) of these were converted to laparotomy. Pelvic lymph node dissection was performed in only 6.7% (n=16/238), with no positive nodes detected.

A summary of the variables analysed in the study is provided in *Table 1*. Chi-squared and Fisher tests identified the following factors as significantly associated with recurrence: AACCS >3 (P=0.003), surgical approach (P=0.03), FIGO stage (P=0.02), myometrial invasion >50% (P=0.004), uterine serosal invasion (P=0.004), and

Table 1 Clinicopathological characteristics of G1 EC

Variable	Total, N (%)	Recurrence		Cancer-specific mortality	
		N	P value	N	P value
AACCS			0.003*		0.006*
0–1	1 (0.4)	1		1	
2–3	75 (31.5)	2		0	
>3	162 (68.1)	11		1	
Surgical approach			0.03*		>0.99
Laparoscopy	229 (96.2)	12		2	
Laparotomy	9 (3.8)	2		0	
FIGO stage			0.02*		0.09
Early (I, II)	227 (95.4)	11		1	
Advanced (III, IV)	11 (4.6)	3		1	
Depth of myometrial invasion			0.004*		0.36
<50%	191 (80.3)	7		1	
≥50%	47 (19.7)	7		1	
Cervical stroma involvement			0.22		>0.99
No	234 (98.3)	13		2	
Yes	4 (1.7)	1		0	
Serosal involvement			0.004*		0.03*
No	235 (98.7)	12		1	
Yes	3 (1.3)	2		1	
Parametrial involvement			0.80		>0.99
No	237 (99.6)	14		2	
Yes	1 (0.4)	0		0	
Pelvic lymph node involvement			0.80		>0.99
No	237 (99.6)	14		2	
Yes	1 (0.4)	0		0	
LVSI			0.16		>0.99
No	191 (80.3)	10		2	
Yes	47 (19.7)	4		0	
ESGO-ESTRO-ESP risk stratification			0.01*		0.02*
Low	163 (68.5)	6		1	
Intermediate	20 (8.4)	2		0	
High-int	44 (18.5)	3		0	
High	11 (4.6)	3		1	

*, statistically significant variable. AACCS, Age-Adjusted Charlson Comorbidity Score; EC, endometrial cancer; ESGO, European Society of Gynaecological Oncology; ESP, European Society of Pathology; ESTRO, European Society for Radiotherapy and Oncology; FIGO, International Federation of Gynaecology and Obstetrics; High-int, high-intermediate; LVSI, lymphovascular space invasion.

Table 2 Univariate analysis for the risk of recurrence

Variable	Recurrence	
	HR (95% CI)	P value
Serosal involvement	15.68 (3.47–70.89)	0.003*
No		
Yes		
Surgical approach	4.91 (1.1–22)	0.04*
Laparoscopy		
Laparotomy		
Parametrial involvement	0.049 (0.024–1.123)	0.86
No		
Yes		
Distant metastasis	38.71 (4.66–354.52)	0.007*
No		
Yes		
Stage category	5.87 (1.64–21.07)	0.006*
Early (I, II)		
Advanced (III, IV)		
Depth of myometrial invasion	5.95 (2.06–17.17)	0.005*
<50%		
≥50%		
Cervical stroma involvement	5.06 (0.66–38.75)	0.12
No		
Yes		
LVSI	2.41 (0.81–7.19)	0.12
No		
Yes		

*, statistically significant variable. CI, confidence interval; HR, hazard ratio; LVSI, lymphovascular space invasion.

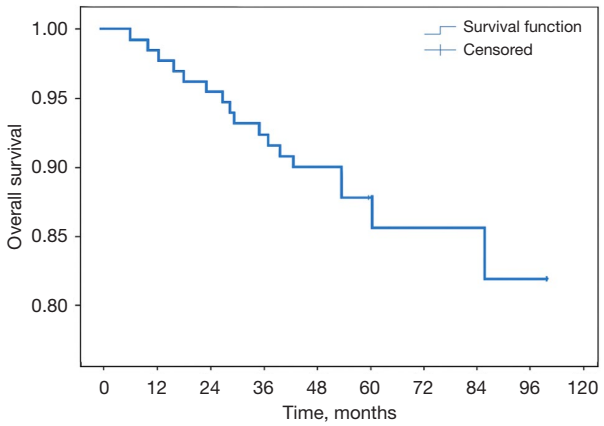

Figure 1 The 5-year overall survival.

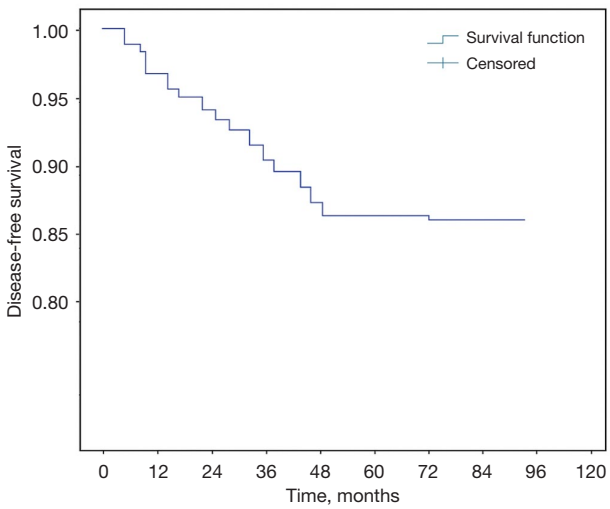

Figure 2 The 5-year disease-free survival.

ESGO-ESTRO-ESP risk stratification (P=0.01). However, not all these factors remained significant in disease-free survival (DFS) analysis (*Table 2*). AACCS (P=0.006), serosal involvement (P=0.03), and ESGO-ESTRO-ESP risk stratification (P=0.02) were also associated with increased risk of cancer-specific death.

Follow-up data demonstrated favourable outcomes, with a 5-year overall survival (OS) rate of 95.2% and mean OS of 104.44 months [95% confidence interval (CI): 101.61–107.27; *Figure 1*], as well as for the 5-year DFS frequence that was 93.2%, while the average DFS was of 104.43 months (95% CI: 101.60–107.27; *Figure 2*). With regards to the 5-year cancer-specific survival (CSS), results were extremely positive, though, with a rate of 98.5%, and a mean CSS of 109.2 months (95% CI: 108.1–110.30; *Figure 3*).

Recurrence group

The recurrence rate was 5.88% (n=14/238). Median age in this group was 65 years (range, 34–83 years), with a median BMI of 32.5 kg/m^2 (range, 20–44 kg/m^2). Stage I disease accounted for 78.5% of recurrences (11/14 cases). AACCS ≥3 was present in 78.5% (11/14) of patients. Post-

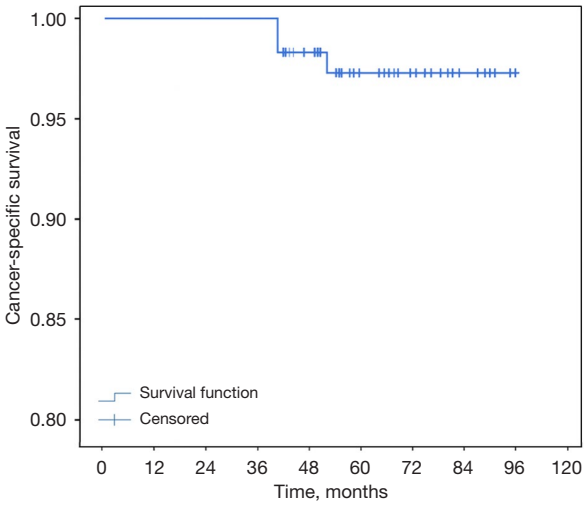

Figure 3 The 5-year cancer-specific survival.

menopausal bleeding was the most common symptom, reported in 71.4% (10/14). None had known BRCA mutations, Lynch syndrome, Cowden syndrome, or breast cancer history. One patient (7.1%) presented with irregular vaginal bleeding following prior hormone therapy for G1 EC outside the UK. Two patients (14.2%) had prior abdominal surgeries.

All patients had Eastern Cooperative Oncology Group (ECOG) performance status 0–1, except one with status 2. Preoperative histology confirmed G1 EC in 57% (8/14), with one showing mucinous differentiation. All cases were discussed at gynaecologic oncology MDT, recommending total hysterectomy and bilateral salpingo-oophorectomy. One patient underwent systematic lymph node dissection due to suspected higher stage; histology was negative.

Postoperative pathology showed mean tumor length of 27.2 mm; 50% (7/14) had deep myometrial invasion (≥50%). One patient had cervical stromal involvement; no adnexal involvement was observed. Tumor extension beyond the serosa was seen in 14% (2/14), with a mean tumor-free distance to serosa of 3.35 mm in others. Parametrial involvement was absent. LVSI was positive in 28% (4/14).

Five patients received adjuvant therapy: one with deep myometrial invasion, serosal involvement, and LVSI received pelvic radiotherapy plus carboplatin and paclitaxel chemotherapy; one with deep myometrial invasion and LVSI received vaginal brachytherapy; one with deep myometrial invasion, cervical involvement, and LVSI received carboplatin chemotherapy; one with myometrial invasion and serosal involvement declined offered vaginal brachytherapy; one was medically unfit for further treatment.

Median time from surgery to relapse was 30 months (range, 3–60 months). Six (42%) recurrences occurred within 2 years, and 50% (7/14) within 3 years. The most common recurrence site was the vaginal vault (42%, 6/14). Eight recurrences (57%) were asymptomatic and detected during follow-up. Other recurrence sites included lung, left common iliac node, precaval lymph node, distal ureter, and rectum. Symptomatic patients reported pain, gastrointestinal symptoms, vaginal bleeding, or general decline. Biopsies confirmed recurrence as G1 EC in most, with two cases upgraded to G2. Treatment included surgery, chemotherapy, radiotherapy, or palliative care following MDT discussion.

Average OS in the recurrence group was 69 months (range, 29–120 months), and cancer-specific death rate was 0.84% (2/238). Both deaths were due to disease progression and comorbidities.

Stastistical analysis

Univariate analysis identified several factors significantly reducing DFS: advanced cancer stage [hazard ratio (HR) =5.87, P=0.006], deep myometrial invasion (HR =5.95, P=0.005), serosal involvement (HR =15.68, P=0.003), distant metastasis (HR =38.71, P=0.007), and surgical approach. Laparotomy was associated with a higher recurrence risk compared to laparoscopy (HR =4.91, P=0.04), suggesting open surgery may carry greater risk. Factors such as BMI, menopausal status, cervical and adnexal involvement, and LVSI showed no significant impact on recurrence.

In multivariate analysis, only myometrial invasion and serosal involvement confirmed their statistical significance in terms of recurrence (P=0.049 and 0.02, respectively). The Cox model indicates that patients with >50% myometrial invasion have a 4.5-fold increased risk of recurrence, while those with serosal involvement have a 9.4-fold increased risk (*Table 3*). Although surgical approach was significant in univariate analysis, it lost significance in multivariate logistic regression (P=0.11), suggesting its effect on recurrence risk may be confounded by other factors.

Discussion

Low-grade endometrioid EC is the most common histological subtype of uterine cancer and is generally

Table 3 Multivariate analysis for DFS

Variable	P value	Hazard ratio
Surgical approach (open *vs.* LPS)	0.12	6.100
Lymph node dissection	0.73	1.455
Myometrial invasion ≥50%	0.049*	4.563
Cervix involvement	0.98	0.001
Adnexal involvement	0.95	0.000
Serosal involvement	0.02*	9.497
Parametrial involvement	0.99	0.024
Pelvic lymph node invasion	0.98	0.000
Lymphovascular invasion	0.60	1.368

*, statistically significant variable. DFS, disease-free survival; LPS, laparoscopic surgery.

Table 4 Comparison of OS, DFS and CSS among G1, G2 and G3 EEC

Grade	5-year		
	OS (%)	DFS (%)	CSS (%)
G1	95.2	93.2	98.5
G2	88.0	91.6	93.3
G3	77.8	83.8	83.6

CSS, cancer-specific survival; DFS, disease-free survival; EEC, endometrioid endometrial cancer; OS, overall survival.

associated with a favourable prognosis (22).

Nowadays, research is primary focused on molecular classification, which represents a major breakthrough and turning point in the management of EC. The PORTEC-3 trial clearly demonstrated prognostic value of molecular subgroups in predicting response to chemotherapy and pelvic external beam radiotherapy (23). Moreover, molecular classification is increasingly recognized as a helpful device for refining recurrence risk assessment and guiding adjuvant treatment strategies (24).

We decided to concentrate our analysis on clinicopathological features as potential predictors of recurrence. Our study confirms this finding, showing excellent outcomes in terms of OS, DFS, and CSS. All three outcomes had a mean duration of nearly 10 years, consistent with results reported in previous studies (25,26). However, despite these positive outcomes, some cases of G1 EC present at an advanced stage, which may negatively impact survival.

In our univariate analysis, the surgical approach appeared to influence the risk of recurrence. Nevertheless, this result should be interpreted with caution. First, open surgery is typically chosen for more advanced stages, consequently this group carries a higher intrinsic risk of adverse events, as advanced stage disease emerges to be an unfavourable prognostic factor. Second, statistical significance was not reached in the multivariate analysis, underlining the non-causality. Therefore, we do not intend to discourage the use of open surgery when necessary to achieve optimal cytoreduction. Additionally, disease stage was statistically significant in the univariate analysis. Another variable significant in univariate but not in multivariate analysis were AACCS. This suggests that the effect may be largely attributable to the burden of comorbidities and competing events rather than tumor-related mechanism.

Our findings support existing literature identifying myometrial and serosal invasion as risk factors for recurrence (5,6). On the other hand, we did not confirm LVSI as a significant factor for relapse (P=0.12). One possible explanation for this discrepancy lies in differences in patient selection: our study included G1 EC across all FIGO stages, not just stages IA and IB. Nevertheless, our findings contrast with those of another study (27), which found a strong association between LVSI and recurrence risk (odds ratio 5.8; P=0.001). However, their analysis focused exclusively on low-risk EC—defined as disease confined to the uterus, grade 1 or 2, endometrioid subtype, and <50% myometrial invasion. The inclusion of grade 2 (G2) EC may partially explain the divergent results, as Zouridis *et al.* (15) recently demonstrated that G2 EC has distinct prognostic features. Furthermore, pelvic lymph node involvement was not associated with an increased risk of recurrence in either the univariate or multivariate analysis. This finding is consistent with other studies (8) and highlights key differences between low-grade and high-grade EC (28). *Table 4* illustrates the comparison of OS, DFS and CSS among G1, G2 and G3 EC, based on our previous results.

Unexpectedly, distant metastases were significant only in the univariate analysis, not in the multivariate model. This may be due to the limited number of recurrence events: out of 238 patients included in the study, only 14 experienced a relapse. While this limits the statistical power of the analysis, it also reflects the excellent OS and DFS in patients with G1 EC.

In our cohort, pelvic lymph node dissection was performed in only 16 out of 238 patients, while sentinel lymph node mapping was not carried out in any case. All

treatment strategies were debated in the MDT discussion, and lymph node dissection was reserved for patients with high-risk features, such as suspicious nodal involvement, deep myometrial invasion, cervical stroma invasion or parametrial infiltration, and adnexa spread. The role of pelvic lymphadenectomy and sentinel lymph node assessment has long been debated, both prior to (29) and following (30) the publication of The Genome Cancer Atlas results, which introduced molecular classification as a new standard for risk stratification on molecular classification.

The retrospective design and the rarity of events represent important limitations of this study. Nonetheless, the low incidence of death and recurrence is an expected finding when investigating a tumour type generally considered low risk, such as G1 EC. Furthermore, data collection concluded before the incorporation of molecular classification into international guidelines, preventing us from including this crucial parameter in our analysis. Despite these weaknesses, we believe that our findings may provide a valuable contribution, serving as a complementary tool to molecular stratification and ultimately supporting a more refined and individualized risk assessment for patients with G1 EC.

Conclusions

In conclusion, low-grade EEC is associated with excellent survival outcomes, as demonstrated by our OS, DFS, and CSS data. Our study confirms that deep myometrial invasion, serosal involvement, and advanced stage are significant predictors of recurrence and poorer outcomes, even in grade 1 disease. This research contributes to the ongoing debate on lymph node mapping in low-grade EC, as only a small proportion of our cohort underwent pelvic lymph node assessment, yet survival outcomes remained excellent. These findings may support the consideration of adjuvant therapy in selected cases of stage I low-grade EC. However, prospective studies with larger patient populations are needed before drawing definitive conclusions. In the meantime, patients with these high-risk pathological features may benefit from closer clinical follow-up.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-1635/rc

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