Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2026.23934

Turk J Obstet Gynecol

Prognostic determinants of survival in early-stage endometrial cancer: A retrospective analysis

Erken evre endometriyal kanserde sağkalımın prognostik faktörleri: Retrospektif analiz

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Abstract

Objective: The aim of this study was to investigate prognostic determinants of survival in early-stage endometrial cancer (EC), focusing on clinicopathological parameters including histologic grade, tumor stage, myometrial invasion, lymphovascular space invasion (LVSI), and preoperative CA-125, as well as the role of adjuvant therapies in disease-free survival (DFS) and overall survival (OS).

Materials and Methods: We retrospectively analyzed women treated surgically for International Federation of Gynecology and Obstetrics 2009 stage I-II EC at a tertiary center between January 2011 and January 2023. Demographic and pathological data were collected, including age, body mass index, reproductive history, menopausal status, comorbidities, tumor size, histologic subtype and grade, depth of myometrial invasion, LVSI, serum CA-125 levels, and surgical procedures. Adjuvant therapies—external beam radiotherapy, vaginal brachytherapy, and chemotherapy—were also documented. Associations between these variables and survival outcomes were assessed using Kaplan-Meier and Cox regression analyses.

Results: A total of 241 women with early-stage EC were included. Median age was 57 years (range: 34-86 years). Of these, 181 (75.1%) were stage IA, 47 (19.5%) were stage IB, and 13 (5.4%) were stage II. Histologic grades were grade 1 in 44.8%, grade 2 in 39.0%, and grade 3 in 16.2%. During a median follow-up of 75 months, recurrence occurred in 4.6% of patients and mortality in 7.9% of patients. Univariate analysis showed that elevated CA-125, higher stage, and higher grade were associated with worse OS. Multivariate analysis identified histologic grade as an independent predictor of both OS and DFS. Neither adjuvant radiotherapy nor chemotherapy improved survival outcomes.

Conclusion: Histologic grade was the strongest independent prognostic factor for OS and DFS in early-stage EC, surpassing tumor stage, myometrial invasion, and LVSI. These findings highlight the importance of comprehensive surgical staging, especially when high-grade tumors are detected intraoperatively, to ensure accurate risk stratification and appropriate use of adjuvant therapies.

Keywords: Adjuvant therapy, disease-free survival, endometrial cancer, histological grade, overall survival, prognostic factors

Öz

Amaç: Bu çalışmanın amacı, erken evre endometriyal kanserde (EK) sağkalımın prognostik belirleyicilerini araştırmak olup, histolojik grade, tümör evresi, myometriyal invazyon, lenfovasküler alan invazyonu (LVSI) ve preoperatif CA-125 düzeyine ek olarak adjuvan tedavilerin hastalıksız sağkalım (DFS) ve genel sağkalım (OS) üzerindeki rolünü incelemektir.

Gereç ve Yöntemler: Ocak 2011-Ocak 2023 tarihleri arasında üçüncü basamak bir merkezde Uluslararası Jinekoloji ve Obstetrik Federasyonu 2009 evre I-II EK nedeniyle cerrahi tedavi uygulanan kadınlar retrospektif olarak analiz edildi. Yaş, vücut kitle indeksi, üreme öyküsü, menopoz durumu, ek hastalıklar, tümör boyutu, histolojik alt tip ve grade, miyometriyal invazyon derinliği, LVSI varlığı, serum CA-125 düzeyi ve uygulanan cerrahi

PRECIS: Histological tumor grade is the strongest independent prognostic factor for overall and disease-free survival in early-stage endometrial cancer, while adjuvant therapies confer no significant survival benefit.

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Received/Geliş Tarihi: 14.09.2025 **Accepted/Kabul Tarihi:** 19.01.2026 **Epub:** 29.01.2026

Cite this article as: Melekoğlu R, Zeyveli Çelik N, Yılmaz E, Yaşar Ş. Prognostic determinants of survival in early-stage endometrial cancer: a retrospective analysis. Turk J Obstet Gynecol. [Epub Ahead of Print]

prosedür gibi demografik ve patolojik veriler kaydedildi. Ayrıca eksternal radyoterapi, vajinal brakiterapi ve kemoterapi gibi adjuvan tedaviler de dokümante edildi. Sağkalım sonuçları ile değişkenler arasındaki ilişkiler Kaplan-Meier ve Cox regresyon analizleri ile değerlendirildi.

Bulgular: Analize toplam 241 erken evre EK'li kadın dahil edildi. Medyan yaş 57 idi (34-86). Olguların 181'i (%75,1) evre IA, 47'si (%19,5) evre IB, 13'ü (%5,4) evre II idi. Histolojik grade dağılımı %44,8 grade 1, %39,0 grade 2 ve %16,2 grade 3 olarak bulundu. Medyan 75 aylık takip süresinde nüks %4,6, mortalite %7,9 oranında gerçekleşti. Univariate analizde yüksek CA-125, ileri evre ve yüksek grade'in OS üzerine olumsuz etkisi saptandı. Multivariate analizde histolojik grade hem OS hem de DFS için bağımsız prediktör olarak belirlendi. Adjuvan radyoterapi veya kemoterapinin sağkalım üzerine anlamlı katkısı gösterilmedi.

Sonuç: Erken evre EK'de histolojik grade, OS ve DFS için en güçlü bağımsız prognostik faktör olarak ortaya çıkmıştır. Bu bulgu, özellikle yüksek grade tümörlerin intraoperatif saptandığı olgularda doğru risk sınıflaması ve adjuvan tedavilerin dikkatli uygulanabilmesi için kapsamlı cerrahi evrelemenin önemini vurgulamaktadır.

Anahtar Kelimeler: Adjuvan tedavi, hastalıksız sağkalım, endometriyal kanser, histolojik grade, genel sağkalım, prognostik faktörler

Introduction

Endometrial cancer (EC) represents a growing global health burden and has become the most frequently diagnosed gynecologic malignancy in developed nations. According to GLOBOCAN 2020 data, EC accounts for more than 417,000 new cases annually and is the sixth most common cancer in women[1]. In the United States, approximately 66,200 new cases and 13,030 deaths were estimated for 2023, with mortality rates rising substantially with age and reaching 54.9 per 100,000 among women aged 70 years or older[2]. Although EC generally has a more favourable prognosis than other gynecological cancers such as ovarian or cervical carcinoma, it remains a significant cause of morbidity and mortality, especially in patients harboring high-risk pathological features.

The majority of EC cases are detected at an early stage because abnormal uterine bleeding commonly occurs early and prompts timely clinical evaluation. Early diagnosis contributes substantially to the relatively high survival rates reported for early-stage disease[3]. Nevertheless, not all early-stage patients have uniformly favourable outcomes. Subgroups of women experience disease recurrence or succumb prematurely, reflecting biological heterogeneity and the influence of multiple prognostic variables[4]. This clinical reality highlights the need to refine prognostic assessment and individualize treatment strategies beyond conventional staging.

Several clinicopathological factors have been established as important prognostic indicators in patients with EC. Among these factors, age at diagnosis, tumor histologic subtype, histologic grade, depth of myometrial invasion, lymphovascular space invasion (LVSI), and lymph node metastases are consistently reported to influence survival outcomes[5,6]. While low-grade endometrioid adenocarcinoma limited to the endometrium or inner myometrium is associated with an excellent long-term prognosis, patients with high-grade tumors or evidence of LVSI are at a considerably increased risk of recurrence and cancer-related death[7]. The presence of extrauterine spread, even if microscopic, further portends poor outcomes[8]. Accordingly, international guidelines recommend risk stratification to guide adjuvant therapy decisions, typically by incorporating these pathological features into treatment algorithms[9-11].

Surgical staging remains the cornerstone of EC management[12]. The standard approach involves total hysterectomy with bilateral salpingo-oophorectomy, with or without pelvic and para-aortic lymphadenectomy and, in selected cases, omentectomy. Intraoperative frozen-section evaluation of tumor grade and depth of myometrial invasion is commonly employed to determine whether more extensive staging procedures are necessary[13]. However, the reproducibility of frozen-section diagnosis varies significantly, and inter-institutional discrepancies in surgical practice persist. Consequently, optimal intraoperative risk stratification continues to be debated.

Adjuvant therapy in early-stage EC is highly individualized. Radiotherapy, administered either as external-beam radiotherapy (EBRT) or as vaginal brachytherapy, effectively reduces local and regional recurrence rates but has not consistently improved overall survival (OS) [14]. Chemotherapy is typically reserved for patients with advanced disease or those with multiple high-risk factors; however, its role in early-stage disease remains controversial, with inconsistent evidence regarding a survival benefit[15]. These considerations emphasize the urgent need for reliable prognosticators to identify which patients genuinely benefit from adjuvant modalities, thereby avoiding overtreatment in low-risk individuals and ensuring adequate therapy for those at high-risk.

Therefore, the present study aimed to analyze a large cohort of early-stage EC patients treated at a tertiary referral center over a 12-year period. By comprehensively evaluating clinicopathological and treatment-related parameters, we sought to identify independent prognostic determinants of OS and disease-free survival (DFS) and to assess the real-world impact of adjuvant therapies. The results of this study are expected to contribute to the refinement of prognostic assessment and therapeutic decision-making in early-stage EC, with the ultimate goal of improving patient outcomes and aligning clinical practice with evidence-based precision oncology.

Materials and Methods

This study was designed as a retrospective cohort analysis and conducted at the Department of Obstetrics and Gynecology, İnönü University Faculty of Medicine, a tertiary academic referral hospital serving a large regional population. The study period spanned twelve years (January 2011-January 2023), allowing inclusion of a substantial number of patients with early-stage EC managed according to contemporary surgical and adjuvant treatment standards. Institutional approval for the study protocol was obtained from the İnönü University Scientific Research and Publication Ethics Committee (decision number: 2022/3087, date: 26.04.2022). All procedures were performed in compliance with the ethical principles outlined in the Declaration of Helsinki. Because of the retrospective design, the requirement for individual informed consent was waived.

Patient eligibility was carefully defined to ensure the homogeneity of the study cohort. Only women with histopathologically confirmed endometrial adenocarcinoma diagnosed at International Federation of Gynecology and Obstetrics (FIGO) 2009 stage I or II were included. These patients had undergone primary surgical staging at our institution and had complete clinical, pathological, and follow-up records available. Patients with advanced disease (stage III–IV), non-endometrioid histologies such as serous carcinoma, clear cell carcinoma, or carcinosarcoma, as well as those with a history of previous or synchronous malignancies were excluded to eliminate confounding survival influences. After applying these criteria, 241 patients were deemed eligible for inclusion from an initial pool of 385 women diagnosed with EC during the study period.

Data extraction was performed through a systematic review of hospital medical records, operative notes, and pathology reports. A comprehensive dataset was assembled, covering demographic characteristics [including age at diagnosis, body mass index (BMI), reproductive history, and menopausal status], personal and family medical history (with particular attention to systemic comorbidities such as hypertension, diabetes, and cardiovascular disease), and lifestyle factors such as smoking. Tumor-related characteristics were meticulously recorded, including histological subtype, histological grade, tumor size, depth of myometrial invasion, LVSI, and preoperative serum CA-125 levels. Detailed surgical data were documented for each patient, including whether the surgical procedure was limited to total abdominal hysterectomy with bilateral salpingo-oophorectomy total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH+BSO) or whether it was extended to include systematic pelvic and para-aortic lymphadenectomy and infracolic omentectomy. Postoperative treatment records were also reviewed to determine the use of adjuvant therapies, including external-beam radiotherapy, high-dose-rate vaginal brachytherapy, and systemic chemotherapy.

Surgical procedures were performed by a dedicated gynecologic oncology team. The extent of surgery was tailored according to intraoperative frozen-section assessment, which provided immediate evaluation of the histological grade and depth of myometrial invasion. Patients with superficial myometrial invasion (<50%) and low-grade tumors (grade 1-2) were considered low-risk and typically underwent TAH+BSO alone. In contrast, patients with deep myometrial invasion (≥50%) or high-grade tumors (grade 3) were classified as high-risk and underwent comprehensive surgical staging, including pelvic and para-aortic lymphadenectomy, and infracolic omentectomy. Lymph node dissections were systematically performed, with the pelvic dissection encompassing common, external, and internal iliac, obturator, sacral, and parametrial nodal groups, while para-aortic dissection extended cranially from the aortic bifurcation to the level of the renal veins.

Pathological assessment was performed by specialized gynecologic pathologists. The maximum tumor dimension was measured macroscopically, while the percentage of myometrial invasion was calculated as the depth of tumor infiltration divided by the total myometrial thickness. LVSI was defined as the presence of unequivocal tumor emboli within endothelial-lined lymphatic or vascular spaces. Histological classification was carried out according to the World Health Organization criteria, and staging was confirmed using the FIGO 2009 classification system[16]. Final reporting was based on permanent sections, although intraoperative frozen-section data were also recorded to compare operative decision-making with definitive pathological findings.

Adjuvant treatment decisions were made within a multidisciplinary tumor board composed of a gynecologic oncology team, radiation oncologists, medical oncologists, and pathologists. EBRT was delivered with either a linear accelerator or cobalt-60 equipment. The standard treatment fields extended from the L5-S1 interspace superiorly to the obturator foramen inferiorly, including the whole pelvis and bilateral regional lymphatic drainage. The typical total EBRT doses ranged from 45 to 50 Gy and were delivered in fractions over five weeks. Vaginal brachytherapy was administered via a high-dose-rate Nucletron system with a vaginal cylinder applicator, with the prescribed dose delivered at a depth of 5 mm from the cylinder surface. The proximal half of the vagina was routinely treated to prevent local relapse, with a cumulative dose of approximately 18-24 Gy delivered in multiple fractions. Chemotherapy was not routinely offered to all patients with early-stage disease but was reserved for those deemed high-risk by the tumor board. The most commonly used regimen consisted of paclitaxel (175 mg/m²) and carboplatin (area under the curve 5-6), which was administered every three weeks for three to six cycles. In selected cases, cisplatin- and doxorubicin-based regimens were employed.

Follow-up data were meticulously collected from outpatient clinic records and hospital databases. The primary outcomes of interest were OS and DFS. OS was defined as the time interval between the date of pathological diagnosis and the date of death from any cause or the date of last follow-up. DFS was defined as the time interval between the date of surgery and the first documentation of local, regional, or distant recurrence, or death, whichever occurred first. Recurrence was confirmed either histologically or radiologically and classified as vaginal, pelvic, abdominal, lymphatic, or distant. Patients were followed at three-month intervals for the first two years after treatment, at six-month intervals for the next three years, and annually thereafter.

Statistical Analysis

Data were summarized as mean ± standard deviation, median (minimum-maximum), and frequency (percentage). The Kolmogorov-Smirnov test was used to assess normality. Depending on the distribution and data structure, independent-samples t-test, Pearson's chi-square test, and Fisher's exact test were applied. DFS was defined as the absence of metastasis or death from any cause. DFS and OS were estimated from the date of surgery. Factors including CA125 level, myometrial invasion, stage, LVSI, pathological grade, chemotherapy, external radiotherapy, and brachytherapy were evaluated for their effects on DFS, OS, and recurrence. The impact of each factor on DFS, OS, and recurrence was assessed by univariate analysis. A p-value <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 25.0 and the R programming language with appropriate packages.

Results

During the twelve-year study period, a total of 385 women were diagnosed with endometrial cancer at our institution. After applying the predefined eligibility criteria, 241 patients with FIGO 2009 stage I-II disease and complete clinicopathological data were included in the final analysis. The median follow-up duration was 75 months (range: 2-141 months), allowing robust assessment of both short- and long-term outcomes. At the time of data censoring, 222 patients (92.12%) were alive, 19 (7.88%) had died, and 11 (4.56%) had developed disease recurrence.

The median age of the study population was 57 years (range: 34-86 years), with the majority of patients postmenopausal at the time of diagnosis (70.95%). Comorbid conditions were common; 22.8% of patients had hypertension, 29.5% had diabetes mellitus, and smaller proportions had thyroid disease, cardiovascular disorders, asthma, or hepatic disease. The median BMI was 31.8 kg/m², which is consistent with the high prevalence of obesity reported in this patient population. Pathological evaluation revealed that 181 women (75.10%) had stage IA disease, 47 (19.50%) had stage IB disease, and 13 (5.40%) had stage II disease. With respect to tumor grade, 108 patients (44.82%) had grade 1 tumors, 94 patients (39.00%) had grade 2 tumors, and 39 patients (16.18%) had grade 3 tumors. Myometrial invasion greater than 50% was identified in 60 women (24.90%), whereas LVSI was detected in 41 women (17.01%). The median tumor diameter was 3 cm (range: 0.1-10 cm). Preoperative CA-125 levels were available for all patients, with a median of 12.8 U/mL (range: 2.7-273 U/mL). Peritoneal cytology was obtained in 154 patients and was positive in only two cases (0.83%). Because of the very low number of positive samples, it was not included in survival analyses.

Regarding primary surgical management, all patients underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy. Of 114 women (47.3%), surgery was limited to hysterectomy and oophorectomy; whereas 74 women (30.7%) also underwent pelvic and para-aortic lymphadenectomy, and 53 women (22.0%) underwent omentectomy in addition to hysterectomy and lymphadenectomy. Intraoperative frozen-section analysis plays a key role in guiding the extent of staging, with patients classified as high-risk (deep myometrial invasion or high-grade histology) more frequently undergoing extended procedures.

Adjuvant therapies were administered according to postoperative risk stratification and multidisciplinary tumor board recommendations. Eighty women (33.2%) received adjuvant radiotherapy; of these, 40 underwent external-beam pelvic radiotherapy (mean dose, 4,860 cGy) and 40 received vaginal brachytherapy (mean dose, 1,800 cGy). Chemotherapy was given to 19 patients (7.88%), with 17 treated with a paclitaxel-carboplatin regimen and 2 treated with cisplatin-doxorubicin. The median number of chemotherapy cycles was 4 (range: 2-6). Importantly, receipt of adjuvant therapy did not significantly correlate with survival outcomes in univariate and multivariate analyses. The baseline demographic and clinical characteristics of the cohort are summarized in Table 1.

When patients were stratified according to survival status, several significant differences emerged between patients who died and those who survived. Women who died had significantly higher gravidity and parity, higher preoperative CA-125 levels, and higher histological grade. Specifically, patients who died had a mean CA-125 level of 47.03 U/mL, whereas survivors had a mean level of 21.95 U/mL (p<0.001). In addition, 26.3% of the deceased patients had grade 3 tumors, compared with 15.3% of survivors (p=0.029). Body weight was also significantly higher in patients who died (92.4 kg vs. 84.3 kg; p=0.007). No significant associations were observed between survival and menopausal status, family history of cancer, smoking status, comorbid conditions, tumor size, or extent of surgery. Recurrence occurred in 11 of 241 patients (4.6%). Compared with non-recurrent cases, those with recurrence more often had grade II-III histology (grade II:

Table 1. Demographic and clinical data of the study cohort

Variable		Early stage endometrial cancer (n=241)
Age (year)*		57 (34-86)
Gravidity**		4.12±2.76
Parity*		3 (0-12)
History of dilatation curettage*		0 (0-3)
Abortion*		0 (0-8)
Weight (kg)**		84.9±13.58
Height (cm)**		163.8±6.99
BMI (kg/m^2)**		31.85±6.07
Menopause status***	Premenopause	70 (29.05)
	Postmenopause	171 (70.95)
Family history of cancer***	Absent	166 (68.87)
	Present	75 (31.13)
Smoking***	Non-smoker	227 (94.21)
	Smoker	10 (4.14)
	Quit smoking	4 (1.65)
Medical disease***	No	90 (37.34)
	Hypertension	55 (22.82)
	Diabetes mellitus	71 (29.46)
	Thyroid disease	9 (3.73)
	Cardiac disease	5 (2.07)
	Asthma	8 (3.32)
	Hepatic disease	3 (1.24)
CA-125 (U/mL)*		12.8 (2.7-273)
Tumor diameter (cm)*		3 (0.1-10)
Stage***	1a	181 (75.10)
	1b	47 (19.50)
	2	13 (5.40)
Grade***	I	108 (44.82)
	II	94 (39.00)
	III	39 (16.18)
Myometrial invasion***	<1/2	181 (75.1)
	>1/2	60 (24.9)
LVSI***	Absent	200 (82.99)
	Present	41 (17.01)
Peritoneal cytology***		
	Negative	152 (63.07)
	Positive	2 (0.83)
	Not available	87 (36.10)

Table 1. Continued

Variable		Early stage endometrial cancer (n=241)
Surgical procedure***	TAH+BSO	114 (47.30)
	TAH+BSO+PPLND	74 (30.71)
	TAH+BSO+PPLND+ omentectomy	53 (21.99)
Adjuvant chemotherapy***		19 (7.88)
Adjuvant chemotherapy regimen***		
	Paclitaxel+carboplatin	17 (7.05)
	Cisplatin+doxorubicin	2 (0.83)
Number of chemotherapy courses**		4.55±1.96
Adjuvant radiotherapy*		80 (33.20)
Adjuvant radiotherapy type***	External radiotherapy	40 (16.60)
	Brachytherapy	40 (16.60)
Total external pelvic radiotherapy dose (cGy)*		4860 (3430-14020)
Total brachytherapy dose (cGy)*		1800 (1200-3600)
External pelvic radiotherapy duration (days)*		25 (19-77)
Brachytherapy duration (day)*		3 (2-6)
Overall survival (months)**		139.609±2.464
Disease-free survival (months)**		144.093±2.025
Follow-up period (month)*		75 (2-141)
Recurrence***	No recurrence	230 (95.44)
	Recurrence is present	11 (4.56)
Location of recurrence***	Absent	230 (95.44)
	Abdomen	4 (1.66)
	Pelvic	6 (2.07)
	Lymph node	1 (0.41)
Mortality***	Absent	222 (92.12)
	Present	19 (7.88)

BMI: Body mass index, LVSI: Lymphovascular space invasion, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingoopherectomy, PPLND: Pelvic paraaortic lymph node dissection, *: Median (minimum-maximum), **: Mean ± standard deviation, ***: n (%)

54.5% vs. 38.3%; grade III: 27.3% vs. 15.7%) and deeper myometrial invasion (≥50%: 54.5% vs. 23.5%; p=0.062). The median tumor diameter was larger in the recurrence group [4.2 cm (1-7.5) vs. 3.0 cm (0.1-10); p=0.06], while the preoperative CA-125 levels were similar (median 10.7 U/mL vs. 12.9 U/mL; p=1.00). Adjuvant therapy was more frequent among recurrent cases: chemotherapy (27.3% vs. 7.0%; p=0.046), particularly paclitaxel–carboplatin (27.3% vs.

Table 2. Comparison of demographic and clinical data according to survival in patients with early stage endometrial cancer

		Mortality				p-value
	Survivor		Non-survivor			
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)		
Age (year)		57.2±10.09	57 (34-86)	61.42±12.03	62 (39-82)	0.092
Gravidity		3.97±2.66	4 (0-14)	5.79±3.39	6 (0-12)	**0.011**
Parity		3.08±2.08	3 (0-11)	4.53±3.22	4 (0-12)	**0.047**
Dilation curettage		0.36±0.75	0 (0-3)	0.53±0.7	0 (0-2)	0.109
Abortion		0.48±1.05	0 (0-8)	0.74±1.05	0 (0-4)	0.062
Weight (kg)		84.26±13.56	83 (54-150)	92.37±11.84	88 (73-113)	**0.007**
Height (cm)		163.58±6.98	164.5 (145-179)	166.37±6.78	167 (149-174)	0.076
BMI (kg/m^2)		31.69±6.05	31.21 (19.36-57.16)	33.67±6.16	31.05 (26.06-46.84)	0.156
CA-125 (U/mL)		21.95±29.79	12.45 (2.7-230)	47.03±59.01	30.7 (7.94-273)	**<0.001**
Tumor diameter (cm)		3.36±1.92	3 (0.1-10)	4.24±2.23	4.2 (0.7-9.5)	0.064
		Count	**Percent**	**Count**	**Percent**	
Menopause status	Premenopause	67	95.7%	3	4.3%	0.288
	Postmenopause	155	90.6%	16	9.4%	
Family history of cancer	Absent	152	91.6%	14	8.4%	0.853
	Present	69	92.0%	6	8.0%	
Medical disease	No	84	93.3%	6	6.7%	0.669
	Hypertension	51	92.7%	4	7.3%	
	Diabetes mellitus	63	88.7%	8	11.3%	
	Thyroid disease	9	100.0%	0	0.0%	
	Cardiac disease	4	80.0%	1	20.0%	
	Asthma	8	100.0%	0	0.0%	
	Hepatic disease	3	100.0%	0	0.0%	
Smoking	Non-smoker	210	92.51%	17	7.49%	0.583
	Smoker	10	100.0%	0	0.0%	
	Quit smoking	4	100.0%	0	0.0%	
Surgical procedure	TAH+BSO	109	95.6%	5	4.4%	0.076
	TAH+BSO+PPLND	64	86.5%	10	13.5%	
	TAH+BSO+PPLND+ omentectomy	49	92.5%	4	7.5%	
Grade	I	105	47.30%	3	15.8%	**0.029**
	II	83	37.40%	11	57.90%	
	III	34	15.30%	5	26.3%	
Myometrial invasion	<1/2	170	93.92%	11	6.08%	0.172
	>1/2	52	86.67%	8	13.39%	
LVI	Absent	184	92.0%	16	8.0%	1.000
	Present	38	92.7%	3	7.3%	

Table 2. Continued

		Mortality				p-value
	Survivor		Non-survivor			
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)		
Stage	1a	170	93.9%	11	6.1%	0.136
	1b	40	85.1%	7	14.9%	
	2	12	92.3%	1	7.7%	
Chemotherapy	None	205	92.3%	17	7.7%	0.651
	Received	17	89.5%	2	10.5%	
Adjuvant chemotherapy regimen	None	205	92.3%	17	7.7%	0.764
	Paclitaxel+carboplatin	15	88.2%	2	11.8%	
	Cisplatin+doxorubicin	2	100.0%	0	0.0%	
Number of chemotherapy courses		4.47±1.37	4 (2-6)	5±4.58	6 (0-9)	0.543
External radiotherapy	None	188	93.5%	13	6.5%	0.100
	Received	34	85.0%	6	15.0%	
Brachytherapy	None	186	92.5%	15	7.5%	0.531
	Received	36	90.0%	4	10.0%	
Total external pelvic radiotherapy dose (cGy)		4853.87±930.6	4600 (3430-9500)	7136.67±3962.31	4950 (4500-14020)	0.226
External pelvic radiotherapy duration (days)		26.61±4.77	25 (19-50)	38.67±21.08	27.5 (25-77)	0.140
Brachytherapy duration (day)		4.03±1.32	3 (2-6)	2.75±0.5	3 (2-3)	0.055
Total brachytherapy dose (cGy)		2416.67±791.92	1800 (1200-3600)	1650±300	1800 (1200-1800)	0.055

BMI: Body mass index, LVI: Lymphovascular invasion, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingoopherectomy, PPLND: Pelvic paraaortic lymph node dissection, SD: Standard deviation, min: Minimum, max: Maximum, statistically significant p values are indicated in bold

6.1%; p=0.027), and there was a trend toward higher use of EBRT (36.4% vs. 15.7%; p=0.090). Group-wise comparisons by OS status are shown in Table 2, and recurrence-related comparisons are summarized in Table 3.

Univariate Cox regression analyses identified elevated serum CA-125 [hazard ratio (HR): 1.009; 95% confidence interval (CI): 1.003-1.016; p=0.004], higher disease stage (HR: 2.69; 95% CI: 1.009-6.722; p=0.048), and higher histological grade (HR: 4.85; 95% CI: 1.35-17.40; p=0.015) as predictors of poorer OS. Kaplan-Meier survival curves illustrated that patients with grade 3 tumors experienced significantly worse survival compared with those harboring grade 1 or 2 tumors. Multivariate Cox regression analysis confirmed histological grade as the only independent predictor of OS (HR: 5.942, 95% CI: 1.593-22.158; p=0.008). Neither adjuvant chemotherapy nor EBRT nor vaginal brachytherapy demonstrated significant associations with OS after adjustment. The Cox proportional-hazards estimates for OS are reported in Table 4; the corresponding Kaplan-Meier curve is depicted in Figure 1, and Kaplan-Meier curves stratified by stage are shown in Figure 2.

DFS outcomes followed a similar pattern. The overall DFS was excellent, with a mean of 144 months. Eleven women experienced disease recurrence during follow-up, most commonly in the pelvic region (54.5%), followed by the abdominal cavity (36.4%), and in the lymph nodes (9.1%). Comparison of recurrent and non-recurrent cases revealed that a history of prior dilatation and curettage procedures, as well as receipt of adjuvant chemotherapy, was more common among recurrent cases. However, according to the univariate regression analysis, only adjuvant chemotherapy was a significant predictor of shorter DFS (HR: 4.830; 95% CI: 1.487-15.687; p=0.009). In multivariate analysis, histological grade was again retained as an independent prognostic factor for DFS (HR: 0.456; 95% CI: 0.060-3.438; p=0.046), underscoring its consistent impact across survival endpoints. The multivariable results for DFS are presented in Table 5; the Kaplan–Meier curve for disease-free survival is shown

Table 3. Comparison of demographic and clinical data according to recurrence in patients with early stage endometrial cancer

		Recurrence				p-value
	Non-recurrent		Recurrent			
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)		
Age (year)		57.4±10.4	57 (34-86)	60.36±7.62	61 (47-72)	0.31
Gravidity		4.04±2.74	4 (0-14)	5.73±2.72	6 (2-12)	0.05
Parity		3.13±2.17	3 (0-11)	4.55±2.81	4 (2-12)	0.08
Dilation curettage		0.35±0.72	0 (0-3)	1±1	1 (0-3)	**<0.001**
Abortion		0.51±1.06	0 (0-8)	0.18±0.4	0 (0-1)	0.40
Weight (kg)		84.7±13.63	84.5 (54-150)	89.09±12.35	89 (68-113)	0.21
Height (cm)		163.76±6.91	165 (146-179)	164.55±8.99	167(145-174)	0.53
BMI (kg/m^2)		31.79±6.09	31.21 (19.36-57.16)	33.13±5.62	31.05 (26.06-43.76)	0.38
CA-125 (U/mL)		23.9±33.89	12.9 (2.7-273)	24.43±26.13	10.7 (2.9-85)	1.00
Tumor diameter (cm)		3.38±1.96	3 (0.1-10)	4.38±1.8	4.2 (1-7.5)	0.06
Menopause status	Premenopause	70	30.4%	0	0.0%	0.067
	Postmenopause	160	69.6%	11	100.0%	
Family history of cancer	Absent	160	69.9%	6	50.0%	
	Present	69	30.1%	6	50.0%	
Medical disease	No	85	37.0%	5	45.5%	0.958
	Hypertension	52	22.6%	3	27.3%	
	Diabetes mellitus	68	29.6%	3	27.3%	
	Thyroid disease	9	3.9%	0	0.0%	
	Cardiac disease	5	2.2%	0	0.0%	
	Asthma	8	3.5%	0	0.0%	
	Hepatic disease	3	1.3%	0	0.0%	
Smoking	Non-smoker	218	96.03%	9	3.97%	0.739
	Smoker	10	100%	0	0.0%	
	Quit smoking	4	100%	0	0.0%	
Surgical procedure	TAH+BSO	109	95.61%	5	4.39%	0.905
	TAH+BSO+PPLND	71	95.95%	3	4.05%	
	TAH+BSO+PPLND+ Omentectomy	50	94.34%	3	5.66%	
Grade	I	106	46.1%	2	18.2%	0.181
	II	88	38.3%	6	54.5%	
	III	36	15.7%	3	27.3%	
Myometrial invasion	<1/2	176	67.0%	5	36.4%	0.062
	>1/2	54	23.5%	6	54.5%	
LVI	Absent	192	83.5%	8	72.7%	0.405
	Present	38	16.5%	3	27.3%	

Table 3. Continued

		Recurrence				p-value
	Non-recurrent		Recurrent			
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)		
Stage	1a	175	76.1%	6	54.5%	0.270
	1b	43	18.7%	4	36.4%	
	2	12	5.2%	1	9.1%	
Chemotherapy	None	214	93.0%	8	72.7%	**0.046**
	Received	16	7.0%	3	27.3%	
Adjuvant chemotherapy regimen	None	214	93.0%	8	72.7%	0.027
	Paclitaxel+carboplatin	14	6.1%	3	27.3%	
	Cisplatin+doxorubicin	2	0.9%	0	0.0%	
Number of chemotherapy courses			4 (0-6)	6.33±2.52	6 (4-9)	0.170
External radiotherapy	None	194	84.3%	7	63.6%	0.090
	Received	36	15.7%	4	36.4%	
Brachytherapy	None	193	83.9%	8	72.7%	0.398
	Received	37	16.1%	3	27.3%	
Total external pelvic radiotherapy dose (cGy)		5148.18±1829.02	4860 (3430-14020)	5850±2700	4500 (4500-9900)	0.610
External pelvic radiotherapy duration (days)		28.24±9.90	25 (19-77)	31.25±12.50	25 (25-50)	0.810
Brachytherapy duration (day)		3.97±1.30	3 (2-6)	3.0±0.0	3 (3-3)	0.250
Total brachytherapy dose (cGy)		2383.78±806.06	1800 (1200-3600)	1800±0	1800 (1800-1800)	0.250

BMI: Body mass index, LVI: Lymphovascular invasion, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingoopherectomy, PPLND: Pelvic paraaortic lymph node dissection, SD: Standard deviation, min: Minimum, max: Maximum, statistically significant p values are indicated in bold

in Figure 3 and the stage-stratified analysis is presented in Figure 4.

Discussion

The present retrospective cohort study evaluated the prognostic determinants of survival in 241 women with early-stage EC managed at a tertiary referral center over a twelve-year period. With a median follow-up of more than six years, our data confirm the overall favourable prognosis of patients with FIGO stage I-II disease and highlighted the persistent prognostic importance of tumour grade as the most consistent independent predictor of both OS and DFS. While factors such as elevated serum CA-125 levels, increased body weight, and higher stage were associated with poorer outcomes in univariate analyses, only histological grade remained independently significant in multivariate models. These findings reinforce the notion that histological aggressiveness is the principal determinant of clinical behavior in early-stage EC, and they align with the body of international evidence underscoring grade as a key prognostic marker.

Our results are concordant with those of large multicenter studies and population-based registries. Analyses by the Gynecologic Oncology Group (GOG) and the SEER database have consistently reported five-year survival rates of 85-90% or higher for stage I disease and have demonstrated that grade 3 histology carries a substantially higher risk of recurrence and mortality than grades 1 and 2[17]. Similarly, the PORTEC-1 and PORTEC-2 trials established that high-grade tumors, even when confined to the uterus, are associated with an increased risk of locoregional relapse, thereby justifying the use of adjuvant radiotherapy in selected high-risk patients[18,19]. Our findings support these observations, with grade 3 histology conferring nearly a sixfold higher hazard of death compared with low- or intermediate-grade disease. Importantly, this effect persisted after adjusting for other recognized prognostic variables, underscoring the dominant influence of tumor grade on outcomes.

Beyond histological grade, several additional pathological

Table 4. Cox regression analysis of factors associated with overall survival

	Univariate analysis				Multivariate analysis			
	HR	95% CI		p-value	HR	95% CI		p-value
		Lower limit	Upper limit			Lower limit	Upper limit	
CA-125	1.009	1.003	1.016	**0.004**	1.008	0.999	1.017	0.070
Myometrial invasion	0.827	0.178	3.83	0.808	0.538	0.110	2.629	0.444
Stage	2.69	1.009	6.722	**0.048**	0.759	0.118	4.887	0.772
LVI	1.35	0.39	4.65	0.636	0.595	0.134	2.635	0.494
Grade	4.85	1.35	17.4	**0.015**	5.942	1.593	22.158	**0.008**
Chemotherapy	2.1	0.498	9.46	0.302	1.912	0.305	11.967	0.489
External radiotherapy	2.68	1.02	7.07	0.046	3.543	0.871	14.411	0.077
Brachytherapy	1.28	0.42	3.85	0.663	0.637	0.171	2.373	0.501

CI: Confidence interval, HR: Hazard ratio, LVI: Lymphovascular invasion, statistically significant p values are indicated in bold

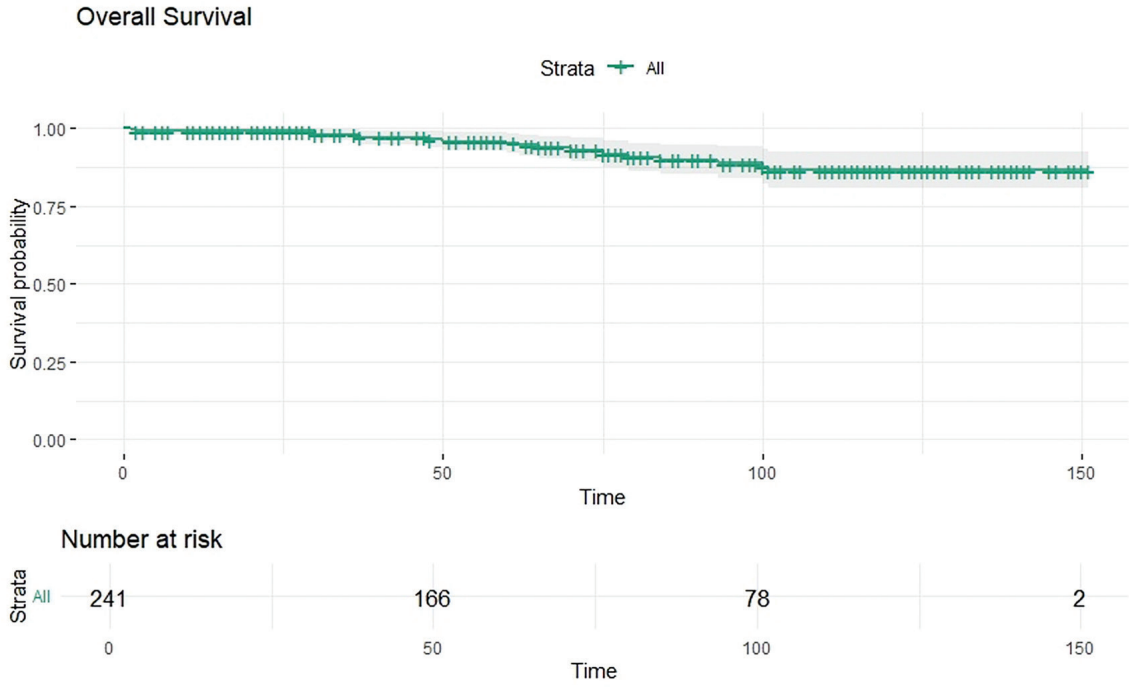

Figure 1. Kaplan-Meier curve for overall survival. The plot illustrates the overall survival probability of the study cohort (n=241) over time. The shaded area represents the 95% confidence interval, and the risk table below shows the number of patients at risk at different time points

factors have been implicated in prognosis, including LVSI. LVSI is increasingly recognized as a key adverse prognostic factor in EC and has been incorporated into contemporary risk stratification systems and the updated FIGO 2023 staging framework. Recent large-scale studies and meta-analyses have demonstrated that LVSI is strongly associated with lymph node metastasis, disease recurrence, and cancer-related mortality, particularly in early-stage, high-grade tumors and in advanced-stage disease[20,21]. In the present cohort, although LVSI was identified in 17.0% of patients, it did not emerge as an independent predictor of overall or DFS in multivariate analyses. This finding should be interpreted in the context of the study population, which consisted exclusively of FIGO 2009 stage I-II endometrioid carcinomas with a low overall event rate, as well as the strong collinearity observed between LVSI and established adverse pathological features such as high histological grade and deep myometrial invasion. When these interrelated variables were analyzed simultaneously, histological grade remained the dominant independent determinant of prognosis. Moreover,

Figure 2. Kaplan-Meier curves for overall survival by endometrial cancer stage. Overall survival probabilities are shown according to disease stage (stage 1a, stage 1b, stage 2). The shaded areas represent 95% confidence intervals. The risk table below indicates the number of patients at risk at different time points. Comparison across groups revealed no statistically significant difference (log-rank test, p=0.12)

Table 5. Cox regression analysis of factors associated with disease-free survival

	Univariate analysis				Multivariate analysis			
	HR	95% CI		p-value	HR	95% CI		p-value
		Lower limit	Upper limit			Lower limit	Upper limit	
CA-125	1.001	0.985	1.018	0.880	0.998	0.979	1.017	0.824
Myometrial invasion	0.618	0.069	5.549	0.668	0.476	0.050	4.541	0.519
Stage	0.421	0.051	3.499	0.423	1.313	0.217	7.936	0.767
LVI	0.422	0.111	1.6	0.205	1.906	0.167	21.710	0.603
Grade	0.227	0.038	1.359	0.104	0.456	0.060	3.438	**0.046**
Chemotherapy	0.16	0.043	0.619	**0.008**	0.245	0.038	1.567	0.137
External radiotherapy	0.3	0.09	1.01	0.052	0.426	0.051	3.548	0.430
Brachytherapy	0.538	0.143	2.031	0.361	0.778	0.160	3.793	0.756

CI: Confidence interval, HR: Hazard ratio, LVI: Lymphovascular invasion, Statistically significant p values are indicated in bold

the absence of molecular classification in this retrospective cohort represents an important limitation, as emerging evidence indicates that the prognostic impact of LVSI varies across molecular subgroups, with greater relevance in p53-abnormal and no specific molecular profile tumors, and limited significance in POLE-mutated cancers[22,23]. Therefore, the lack of independent prognostic significance of LVSI in our analysis should not be interpreted as contradictory to current staging paradigms but rather as reflective of cohort-specific characteristics and methodological constraints.

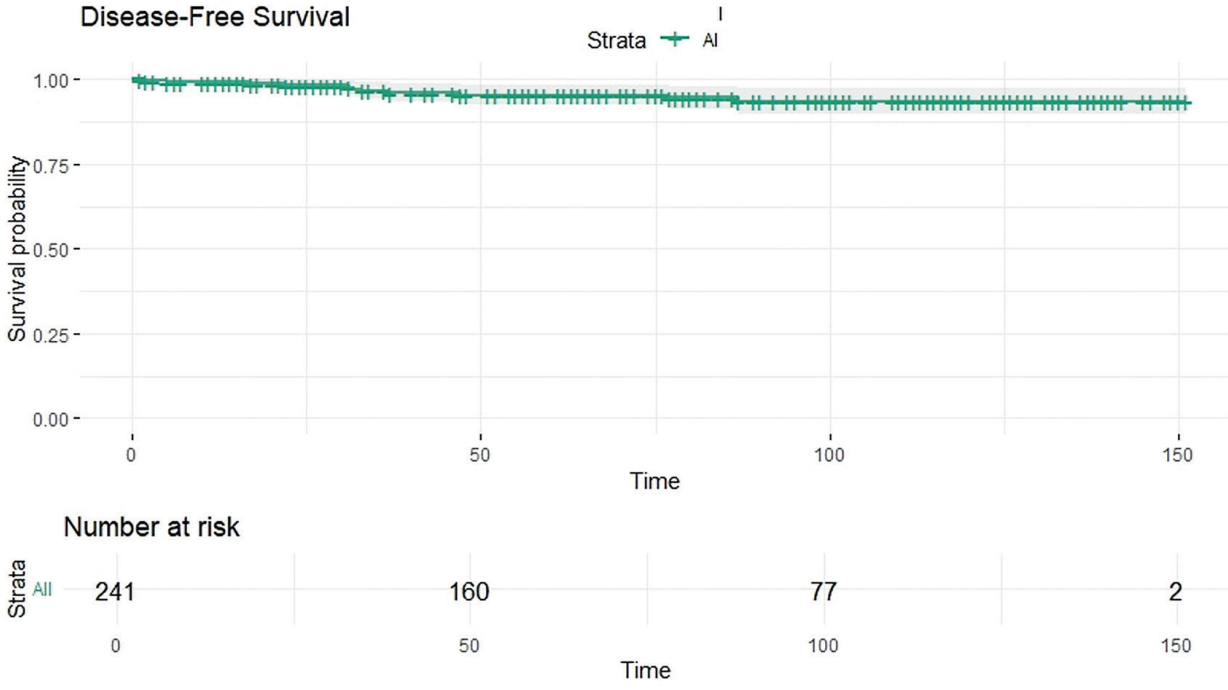

Figure 3. Kaplan-Meier curve for disease-free survival. The plot demonstrates the disease-free survival probability of the study cohort (n=241) over time. The shaded area represents the 95% confidence interval, and the risk table indicates the number of patients at risk at corresponding time points

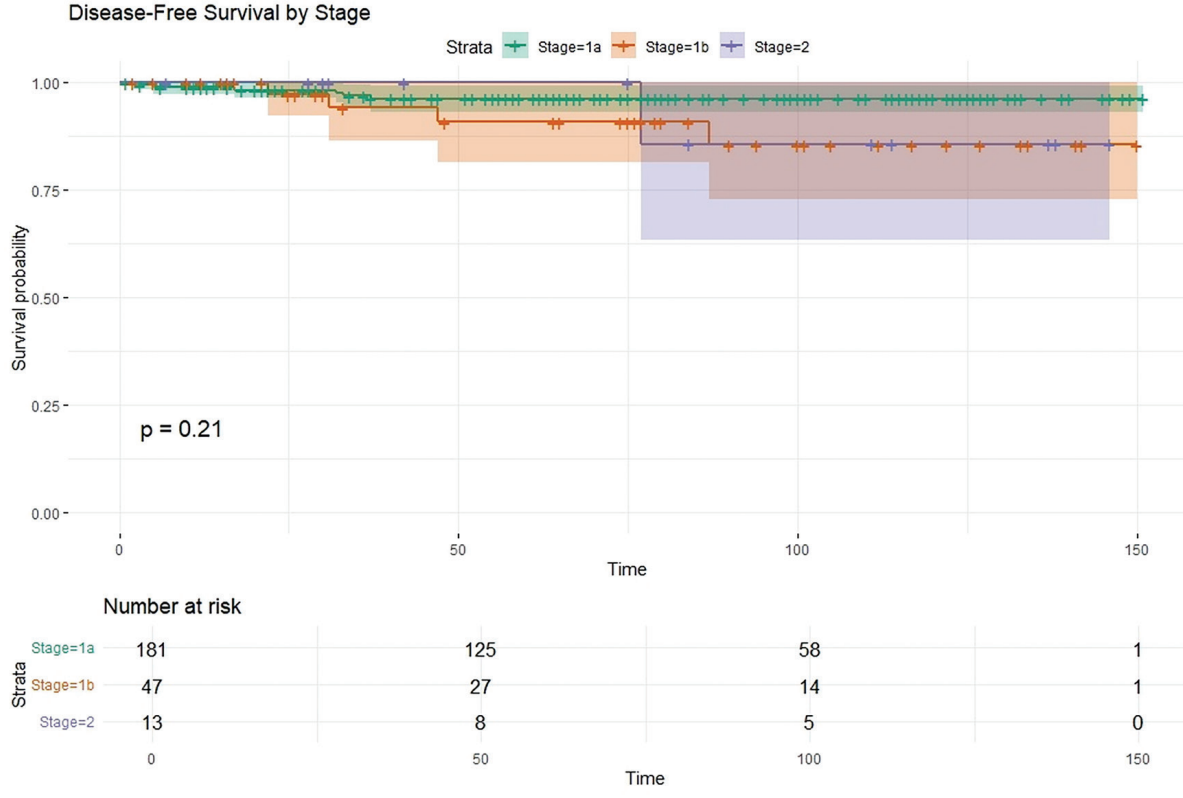

Figure 4. Kaplan-Meier curves of disease-free survival according to endometrial cancer stage. Patients with stage 1a, stage 1b, and stage 2 disease were compared. Shaded areas represent 95% confidence intervals. The number of patients at risk at each time point is shown below the graph. Differences between groups were assessed using the log-rank test and were not statistically significant (p=0.21)

In recent years, the prognostic assessment of EC has undergone a paradigm shift from reliance on traditional clinicopathological parameters toward an integrated molecular framework. While histological grade, depth of myometrial invasion, and LVSI have long constituted the cornerstone of risk stratification, contemporary classification systems increasingly incorporate molecular and immunohistochemical markers to capture tumor biology more precisely. However, this transition has occurred gradually in real-world practice, and a substantial proportion of patients treated during the past decade were managed in the absence of systematic molecular profiling. In this context, the present study reflects a transitional, pre-molecular clinical setting and provides robust long-term outcome data based on well-established pathological prognostic factors. Importantly, these conventional parameters remain clinically relevant, as they continue to guide management decisions in settings where molecular testing is unavailable or incomplete, and serve as the foundation upon which modern molecular risk stratification has been built. Future studies integrating LVSI with molecular classification are warranted to refine individualized risk assessment and optimize adjuvant treatment strategies in early-stage EC.

The prognostic significance of the serum CA-125 level has been extensively debated in the literature. Some investigators have proposed that elevated preoperative CA-125 may reflect occult extrauterine disease or aggressive tumor biology, and several studies have correlated higher CA-125 levels with poorer survival[24,25]. In our cohort, patients who died had significantly higher CA-125 levels compared with survivors, and univariate analysis confirmed CA-125 as a predictor of OS. However, its prognostic value was attenuated in multivariate analysis, suggesting that CA-125 may function more as a surrogate marker of high-grade disease or advanced stage rather than as an independent determinant, particularly once grade and stage are accounted for. This interpretation is consistent with the observations of Todo et al.[26], who noted that while CA-125 elevation was associated with worse outcomes, its predictive capacity diminished once grade and stage were included in multivariable models.

Another important observation from our study is the lack of significant survival benefit from adjuvant radiotherapy or chemotherapy in early-stage disease. Approximately one-third of our patients received adjuvant radiotherapy, and less than 10% received chemotherapy; however, neither modality independently influenced OS or DFS. This finding resonates with results from randomized trials such as ASTEC/EN.5 and GOG-99, which demonstrated that adjuvant radiotherapy improves locoregional control but does not confer an OS advantage in early-stage, low-to-intermediate-risk EC[27,28]. Similarly, the addition of chemotherapy in early-stage, high-intermediate-risk patients has yielded inconsistent results, with no clear survival benefit demonstrated in most studies. Our findings therefore support the growing consensus that adjuvant therapy should be individualized and primarily reserved for patients with substantial risk factors such as high-grade histology, deep myometrial invasion, or LVSI.

In contrast to grade, variables such as age, BMI, menopausal status, tumor size, and depth of myometrial invasion did not emerge as independent predictors of survival in our multivariate analysis. While obesity and comorbid metabolic disorders are well-established risk factors for the development of EC, their impact on prognosis after diagnosis remains less certain. Several studies have reported that extreme obesity may be associated with poorer survival, possibly due to technical challenges in surgical staging or increased perioperative morbidity[29]. Our analysis revealed greater body weight among deceased patients, but this association did not remain significant after adjustment, likely reflecting the overwhelming influence of tumor biology rather than host factors in determining outcomes once the disease is established.

The role of the extent of surgery, particularly lymphadenectomy, in early-stage EC has been controversial. While systematic pelvic and para-aortic lymphadenectomy provides valuable staging information, multiple randomized controlled trials, including ASTEC and Benedetti Panici et al.[31], have shown no survival benefit in terms of OS or DFS[30]. In our cohort, nearly half of the patients underwent lymphadenectomy, but the extent of surgery was not associated with survival outcomes. This finding reinforces the position of major guidelines, including the European Society for Medical Oncology and National Comprehensive Cancer Network, which recommend selective rather than routine lymphadenectomy, particularly when intraoperative assessment and preoperative imaging suggest low-risk disease.

The pattern of recurrence in our series is also noteworthy. Despite excellent overall outcomes, 11 women experienced disease relapse, which most frequently occurred in the pelvis and abdomen. This distribution aligns with published data, in which locoregional recurrence predominates in early-stage EC, whereas distant failures are more common in high-grade tumors[32]. Interestingly, in our analysis, adjuvant chemotherapy was associated with higher recurrence rates according to univariate testing. This likely reflects treatment selection bias, as chemotherapy was preferentially administered to patients with high-risk features who inherently carried a greater risk of relapse.

Our study has several strengths. It is based on a relatively large, single-institution cohort with long-term follow-up, comprehensive clinicopathological documentation, and standardized treatment protocols implemented by a dedicated gynecologic oncology team. These features allow reliable assessment of prognostic variables in a relatively homogeneous patient population. Moreover, the inclusion

of multiple survival endpoints (OS and DFS) and rigorous multivariate modelling enhanced the robustness of our conclusions.

Study Limitations

Nevertheless, limitations must be acknowledged. The retrospective design carries inherent risks of selection bias and missing data, although our exclusion of incomplete records helped minimize this issue. The study was conducted in a single tertiary referral center, which may limit its generalizability to broader populations with different demographic and healthcare characteristics. Molecular data, including assessments of recently recognized prognostic classifiers such as POLE mutations, p53 status, and mismatch repair deficiency (as introduced by The Cancer Genome Atlas, TCGA), were not available, which represents an important limitation given their emerging role in FIGO 2023 risk group stratification and their potential to modify the prognostic impact of conventional pathological factors, including LVSI[33]. Furthermore, the lack of systematic availability of immunohistochemical markers, such as p53 and mismatch repair proteins, which are increasingly incorporated into routine diagnostic practice, reflects evolving standards during the long study period and underscores that the findings should be interpreted in the context of pre-molecular, transitional real-world clinical settings. In addition, peritoneal cytology data was not uniformly available throughout the study period, which limited its inclusion in prognostic modeling. Future prospective studies integrating molecular classification with traditional clinicopathological parameters are essential to refine risk-adapted treatment strategies and improve individualized patient care.

Conclusion

In conclusion, our findings confirm that early-stage EC generally has an excellent prognosis, with long-term survival rates exceeding 90%. Among the clinicopathological variables assessed, histological grade emerged as the most consistent and independent determinant of both OS and DFS. Traditional risk factors, such as age, body weight, stage, and extent of surgical staging, were less predictive once grade was accounted for. These results underscore the need for careful pathological evaluation of tumor grade in all patients and suggest that adjuvant treatment decisions should be tailored primarily according to histological aggressiveness rather than stage alone. Future studies incorporating molecular profiling may further refine prognostic assessment and guide personalized therapy in this common gynecologic malignancy.

Ethics

Ethics Committee Approval: Institutional approval for the study protocol was obtained from the İnönü University Scientific Research and Publication Ethics Committee (decision number: 2022/3087, date: 26.04.2022).
Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: R.M., N.Z.Ç., Design: R.M., N.Z.Ç., E.Y., Data Collection or Processing: R.M., N.Z.Ç., Analysis or Interpretation: Ş.Y., Literature Search: N.Z.Ç., Writing: N.Z.Ç., E.Y., Ş.Y.
Conflict of Interest: Ercan Yılmaz MD is editor-in-chief in Turkish Journal of Obstetrics and Gynecology. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.
Financial Disclosure: The authors declared that this study received no financial support.

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