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ORIGINAL RESEARCH

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Determination of the impact of prognostic factors on disease-free and overall survival in patients with endometrial cancer; oncological outcomes and retrospective analysis of 1028 cases

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Abstract

Background: Endometrial cancer (EC) incidence is increasing. This study determined prognostic factors for disease-free survival (DFS) and overall survival (OS) in EC patients from a single tertiary center over 22 years. **Methods**: 1028 patients who underwent surgery for EC between 2000–2022 were evaluated retrospectively using International Federation of Gynecology and Obstetrics (FIGO) 2009 staging. Statistical analysis included Kaplan-Meier survival analysis and Cox proportional hazards regression modeling. **Results**: 899 (87.7%) patients had endometrioid histology. Grade distribution: 475 (46.2%) grade 1, 371 (36.1%) grade 2, 170 (16.75%) grade 3. FIGO staging: 833 (81.0%) stage I, 71 (7%) stage II, 87 (9%) stage III, 31 (3.0%) stage IV. 368 (35.8%) patients had ≥50% myometrial invasion, 130 (12.7%) cervical involvement, 384 (37.53%) lymphovascular space invasion (LVSI), 80 (7.8%) lymph node metastases. Risk classification: 520 (50.6%) low risk, 195 (19.0%) intermediate risk, 121 (11.8%) high-intermediate risk, 190 (18.6%) high risk. Lower OS and DFS rates were significantly associated with non-endometrioid histology, advanced stage, high grade, high risk classification, ≥50% myometrial invasion, cervical involvement, lymph node metastases, and LVSI (all $p < 0.001$). In multivariate analysis, independent DFS prognostic factors were FIGO stage (hazard ratios (HR): 4.37 for stage II, HR: 8.68 for stage III, both $p < 0.001$) and tumor grade (HR: 2.26 for grade 2, $p = 0.039$; HR: 4.52 for grade 3, $p < 0.001$). Independent OS prognostic factors were risk classification (HR: 2.12 for intermediate-high risk, $p = 0.031$; HR: 2.75 for high risk, $p = 0.003$) and tumor grade (HR: 1.86 for grade 2, $p = 0.024$; HR: 2.71 for grade 3, $p = 0.002$). Median follow-up was 84 months. **Conclusions**: FIGO staging, tumor grade, histopathological type, risk classification, myometrial invasion depth, cervical involvement, LVSI, and lymph node metastases significantly affected survival outcomes. These findings support comprehensive surgical staging and histopathological assessment for prognostic stratification.

Keywords

Endometrial cancer; Prognostic factor; Disease-free survival; Overall survival; FIGO staging; Lymph node management

1. Introduction

Endometrial cancer (EC), one of the most common malignancies of the female reproductive system, was the fourth most common cancer among women in the United States and was the sixth most common cause of cancer death in 2021 [1]. According to European Cancer Information System (ECIS) data, the incidence of EC has been increasing in Europe in recent decades due to hormonal factors, prevalence of obesity, and advances in cancer detection and diagnosis [2, 3]. However, the incidence of EC varies between countries as a result of differences in risk factors. EC, whose incidence has increased in Turkey, constitutes 6% of all cancers, and the lifetime risk of EC is 2.5% in women [4].

Although EC occurs predominantly in postmenopausal women, it can also manifest in premenopausal patients, particularly those with hereditary cancer syndromes [5]. Risk factors for EC other than age have been reported as obesity, diabetes mellitus, family history of EC or Lynch syndrome, tamoxifen use, exogenous estrogen exposure, prolonged menstrual history, sedentary lifestyle, and poor dietary habits [6–10]. The initial symptom in most women

with EC is bleeding, and early diagnosis is quite simple [11]. Because more than 50% of women diagnosed with EC are diagnosed at an early stage, they can often be treated through surgical intervention. The standard treatment approach, particularly for early-stage EC, involves total hysterectomy with bilateral salpingo-oophorectomy and systematic pelvic and para-aortic lymphadenectomy when indicated [12]. Although 5-year overall survival (OS) is reported to be over 90%, recurrence develops in 15% of early-stage patients, and approximately 75% of recurrences occur within the first three years [4]. Therefore, determining the risk of recurrence is very important for effective treatment management. Numerous prognostic biomarkers have been proposed for disease-free survival (DFS), recurrence, and OS in EC. The histological grade of EC is a strong prognostic factor, and higher-grade tumors are associated with worse prognosis and increased risk of recurrence [13]. Another important prognostic factor is the FIGO stage of the tumor, which defines how far the tumor has spread. The International Federation of Gynecology and Obstetrics (FIGO) staging system, most recently updated in 2023, incorporates various factors including tumor size, depth of myometrial invasion (MI), local spread, presence of metastasis, and importantly, molecular classification features [14]. The integration of molecular classification into endometrial cancer management represents a paradigm shift in the field. The Cancer Genome Atlas (TCGA) research network identified four distinct molecular subtypes of endometrial cancer with significantly different prognostic implications: POLE ultramutated (POLEmut), microsatellite instability-high/mismatch repair deficient (MSI-H/MMRd), copy-number low/no specific molecular profile (CNL/NSMP), and copy-number high/p53 abnormal (CNH/p53abn) [15, 16]. Patients with POLEmut tumors demonstrate excellent prognosis with significantly lower recurrence rates and higher overall survival compared to other subtypes, potentially benefiting from de-escalation of adjuvant therapy. Conversely, p53abn tumors carry the worst prognosis and most likely benefit from aggressive adjuvant treatment approaches. The MSI-H/MMRd subtype shows intermediate prognosis with potential for enhanced response to immunotherapy, while NSMP tumors demonstrate heterogeneous behavior ranging from favorable to intermediate outcomes [17, 18]. Advanced FIGO stages (III or IV) according to the updated 2023 classification system, which now incorporates molecular features, demonstrate significantly worse recurrence and OS outcomes compared to early-stage disease [19]. Lymphovascular space invasion (LVSI) refers to the presence of tumor cells within lymphatic or vascular channels, representing a critical prognostic factor. Substantial LVSI, defined as involvement of five or more vessels according to World Health Organization (WHO) 2021 criteria, indicates significantly higher risk of lymph node metastasis and distant recurrence. Deep myometrial invasion, defined as involvement of 50% or more of the myometrial thickness, along with tumor diameter exceeding 2 cm, indicates elevated risk of lymph node metastasis and systemic spread. These risk factors collectively contribute to a worse prognosis and influence treatment decision-making [20, 21]. Contemporary risk stratification systems classify patients with EC into low, intermediate, intermediate-high, and high-risk categories, with treatment approaches tailored accordingly based on these comprehensive risk assessments [22]. The European Society of Gynaecological Oncology, European Society for Radiotherapy and Oncology, and European Society of Pathology (ESGO-ESTRO-ESP) 2021 guidelines have further refined these risk categories by incorporating molecular classification results when available [23]. Recent research efforts have focused on identifying novel prognostic markers that may enhance risk stratification beyond traditional clinicopathological factors. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score has emerged as a promising inflammation-based prognostic marker in various malignancies, including gynecologic cancers. This composite biomarker reflects both nutritional and inflammatory status, with higher scores associated with better prognosis across multiple cancer types [24]. Although molecular testing was not routinely available during the study period of our cohort, the prognostic significance of molecular subtypes has been well established in recent literature and represents an important consideration for future risk stratification strategies. Additionally, contemporary surgical approaches have evolved significantly, with minimally invasive techniques becoming the standard of care for appropriate candidates. Recent studies have demonstrated that laparoscopic and robotic-assisted approaches offer equivalent oncological outcomes to traditional open surgery while providing superior short-term benefits including reduced blood loss, shorter hospital stays and improved cosmetic results. Some centers have reported that Pfannenstiel incisions may represent a safe and cosmetically favorable option in early-stage endometrial cancer when open surgery is required, though this was not the primary focus of surgical technique evaluation in our study [25].

Multiple reports have identified numerous clinicopathological factors affecting the prognosis and recurrence risk of EC. However, debate continues regarding the relative importance and optimal integration of these various prognostic factors. Furthermore, the impact of lymph node management strategies, including the extent of lymphadenectomy and the emerging role of sentinel lymph node biopsy, on survival outcomes requires continued investigation [26–28]. Therefore, this study aimed to comprehensively determine the clinicopathological factors affecting DFS and OS in a large cohort of patients with EC diagnosed and treated at our institution, with particular emphasis on lymph node management strategies and their impact on survival outcomes.

2. Materials and methods

2.1 Study design and patient population

This retrospective study was conducted between January 2000 and June 2022 at Istanbul University Cerrahpaşa Medical Faculty, Department of Gynecological Oncology, in patients who underwent surgery due to EC. Ethical approval was obtained from the Cerrahpaşa Medical Faculty Ethics Committee (approval number: E-83043809-804.01-514105, dated 19 October 2022). The study protocol was prepared in accordance with the Declaration of Helsinki.

2.2 Inclusion and exclusion criteria

Inclusion criteria comprised patients who (1) underwent primary surgical treatment for histologically confirmed endometrial carcinoma at our institution; (2) had complete medical records, including preoperative imaging, surgical reports, and pathological findings; (3) had adequate follow-up data for survival analysis; and (4) were staged according to the FIGO 2009 classification system.

Exclusion criteria included patients with: (1) other known concurrent malignancies at the time of diagnosis; (2) previous history of systemic chemotherapy or pelvic radiotherapy; (3) incomplete pathological reports lacking essential prognostic information including tumor size, myometrial invasion depth, tumor grade, cervical involvement, LVSI assessment, or lymph node evaluation; (4) inadequate follow-up data (less than 6 months unless death occurred); and (5) patients who did not undergo primary surgical treatment at our institution.

After applying these criteria, a total of 1028 patients with endometrial carcinoma were included in the final analysis.

2.3 Data collection and variables

Patient demographic data, preoperative imaging results, tumor marker values, and intraoperative exploration findings were systematically extracted from medical records and evaluated retrospectively in conjunction with comprehensive pathological report results. The following variables were collected and analyzed:

Patient characteristics: age at diagnosis, body mass index, menopausal status, comorbidities, and family history of cancer.

Tumor characteristics: histological type, tumor grade, FIGO stage, tumor size, depth of myometrial invasion, cervical involvement, lymphovascular space invasion, and presence of lymph node metastases.

Surgical details: type of surgical procedure, extent of lymphadenectomy, number of lymph nodes removed, surgical approach, and intraoperative complications.

Treatment information: use of adjuvant radiotherapy, chemotherapy, or hormone therapy.

2.4 Staging and pathological assessment

All patients were staged according to the FIGO 2009 staging system for endometrial carcinoma. Experienced gynecologic pathologists performed pathological assessments according to standardized protocols. Myometrial invasion was categorized as either $<$50% or $\geq$50% of the myometrial thickness, with patients having exactly 50% invasion classified in the $\geq$50% group according to standard clinical practice. Cervical involvement was defined as invasion of cervical stromal tissue, with endocervical glandular involvement alone considered as stage I disease. Lymphovascular space invasion (LVSI) was assessed and categorized as either absent or present. Lymph node assessment included documentation of the total number of lymph nodes removed, the method of lymph node sampling (sentinel lymph node biopsy or systematic lymphadenectomy), and the presence of metastatic disease. Patients were classified into risk groups according to established criteria:

- Low risk: grade 1–2 endometrioid adenocarcinoma, $<$50% myometrial invasion, tumor size $<$2 cm, no LVSI.

- Intermediate risk: grade 1–2 endometrioid adenocarcinoma with any single risk factor ($\geq$50% myometrial invasion, tumor size $\geq$2 cm, or LVSI).

- High-intermediate risk: grade 1–2 endometrioid adenocarcinoma with multiple risk factors or grade 3 endometrioid adenocarcinoma with $<$50% myometrial invasion.

- High risk: grade 3 endometrioid adenocarcinoma with $\geq$50% myometrial invasion or non-endometrioid histology.

Disease-free survival (DFS) was defined as the time from completion of primary treatment to the first documented recurrence of disease or death from any cause, whichever occurred first. For patients with FIGO Stage IVB disease (distant metastases at diagnosis), progression-free survival (PFS) was used instead of DFS, defined as the time from initiation of treatment to disease progression or death. Overall survival (OS) was defined as the time from completion of primary treatment to death from any cause. Patients who were alive at the last follow-up were censored at that time point. The follow-up protocol included clinical examinations and imaging studies every 3–4 months for the first 2 years, every 6 months for years 3–5, and annually thereafter. The median follow-up time was 84 months (range: 6–264 months). Missing data were handled using complete case analysis for the primary survival endpoints. For patients with incomplete survival status information, extensive efforts were made to contact patients or their families through telephone calls and review of national death registry data when available. Patients lost to follow-up were censored at their last known contact date. The impact of missing data on survival estimates was assessed through sensitivity analyses.

2.5 Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed using Student's t-test or the Mann-Whitney U test, depending on data distribution. Survival analysis was conducted using the Kaplan-Meier method, with survival curves compared using the log-rank test. Univariate Cox proportional hazards regression was performed to identify factors associated with DFS and OS. Variables with p-values < 0.10 in univariate analysis were included in multivariate Cox regression models using backward stepwise selection. The proportional hazards assumption was tested using Schoenfeld residuals. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated for all variables in the final multivariate models. Statistical significance was defined as $p < 0.05$ for all analyses. p-values were calculated using the likelihood ratio test for Cox regression models.

All data were double-entered and cross-verified to ensure accuracy. Two independent gynecologic pathologists reviewed pathological slides in cases where initial reports lacked sufficient detail for risk stratification. Survival data were validated through multiple sources, including hospital records, outpatient clinic visits, and, when necessary, contact with patients' primary care physicians.

3. Results

3.1 Demographic and clinico-pathological findings

The clinico-pathological characteristics for the 1028 patients included in the study are shown in Table 1. The average age of the patients included in the study was 59 years (range: 29–91), with 82.4% of the patients being postmenopausal at the time of diagnosis. Histological distribution revealed that 899 patients (87.7%) had endometrioid adenocarcinoma, while 126 patients (12.3%) had non-endometrioid histologies including serous carcinoma (n = 45, 4.4%), clear cell carcinoma (n = 28, 2.7%), mixed carcinoma (n = 31, 3.0%), carcinosarcoma (n = 18, 1.8%), and other rare histological types (n = 7, 0.7%). The tumor grade distribution showed that 475 patients (46.2%) had grade 1 tumors, 371 patients (36.1%) had grade 2 tumors, and 170 patients (16.75%) had grade 3 tumors. According to the 2009 FIGO staging classification system, 833 patients (81.0%) were presented with stage I disease, 71 patients (7%) with stage II, 87 patients (9.0%) with stage III, and 31 patients (3.0%) with stage IV disease. Myometrial invasion assessment revealed that 656 patients (64.0%) had <50% myometrial invasion, while 368 patients (35.8%) had ≥50% myometrial invasion. Cervical involvement was identified in 130 patients (12.7%), while 897 patients (87.3%) had no cervical stromal involvement. Lymphovascular space invasion (LVSI) was present in 384 patients (37.53%). LVSI was absent in 644 patients (62.6%). Risk group classification categorized 520 patients (50.6%) as low risk, 195 patients (19.0%) as intermediate risk, 121 patients (11.8%) as high-intermediate risk, and 190 patients (18.6%) as high risk. Lymph node evaluation was performed in 836 patients (81.3%), while 192 patients (18.7%) did not undergo lymph node assessment due to medical comorbidities or early-stage low-risk disease. Among patients who underwent lymph node evaluation, the median number of lymph nodes removed was 18 (range: 1–67). Lymph node sampling strategy varied according to the time period and institutional protocols:

Lymph node sampling (1–10 nodes): 249 patients (29.8% of those with lymph node evaluation).

- Systematic lymphadenectomy (≥11 nodes): 587 patients (70.2% of those with lymph node evaluation).

- Sentinel lymph node biopsy: 64 patients (7.6% of those with lymph node evaluation, primarily in recent years).

Lymph node metastases were identified in 80 patients (9.6% of those with lymph node evaluation, 7.8% of the total cohort). Among patients with positive lymph nodes, 34 patients (42.0%) had involvement of a single lymph node, 10 patients (12.0%) had involvement of two lymph nodes, and 36 patients (46.0%) had involvement of three or more lymph nodes.

3.2 Disease-free survival and overall survival findings

The median follow-up time was 84 months (range: 6–264 months). During the follow-up period, 156 patients (15.2%) experienced disease recurrence, and 142 patients (13.8%) died from any cause.

Although the death information of the patients can be ac-

TABLE 1. Clinico-pathological characteristics of the participants.

Variables	N	%
Histology		
Endometrioid	899	87.7%
Non-endometrioid	126	12.3%
Stage		
I	833	81%
II	71	7%
III	87	9%
IV	31	3%
Grade		
1	475	46.2%
2	371	36.1%
3	170	16.75%
Lymphovascular invasion		
No	639	62.47%
Yes	384	37.53%
Myometrial invasion		
<50%	656	64%
≥50%	368	35.8%
Cervical involvement		
No	897	87.3%
Yes	130	12.7%
Risk groups		
Low	520	50.6%
Intermediate	195	19%
High-intermediate	121	11.8%
High	190	18.6%
Lymph node metastasis		
No	948	92.2%
Yes	80	7.8%
Number of lymph node metastases (n: 80)		
1	34	42.0%
2	10	12.0%
≥3	36	46.0%
Total number of removed lymph nodes		
1–5	106	12.7%
6–10	144	17.2%
11–15	142	17%
16–20	145	17.3%
21 and over	300	35.8%
Total number of lymph nodes removed		
Lymph sampling (between 1–10 lymphs)	249	29.8%
Lymphadenectomy (11 and above)	587	70.2%
Method of removal of lymph nodes		
Bilateral sentinel lymph node biopsy	64	9.6%
Lymphadenectomy (11 and above)	472	71.4%
Lymph sampling (1–10)	125	19%

cessed from the death notification system, there was a difference between the DFS and OS numbers due to the inability to obtain information about the general survival status of some patients. Disease-free survival analysis was explained in detail. Overall cohort DFS rates were 5-year DFS 91.2% (95% CI: 89.4–93.0%) and 10-year DFS 89.1% (95% CI: 86.9–91.3%), and median DFS was not reached. The disease-free survival (DFS) rates for the endometrioid type are as follows: 5-year DFS, 92.8%; 10-year DFS, 90.9%; and median DFS: not reached. The disease-free survival (DFS) rates for the non-endometrioid group were as follows: 5-year DFS, 81.4%; 10-year DFS, 77.8%; median DFS: not reached ($p < 0.001$). We provided a detailed analysis of disease-free survival by FIGO stage.

Stage I: 5-year DFS 94.2%, 10-year DFS 92.8%, median DFS not reached.

Stage II: 5-year DFS 88.7%, 10-year DFS 85.9%, median DFS not reached.

Stage III: 5-year DFS 72.0%, 10-year DFS 66.7%, median DFS 156 months.

Stage IV: 5-year DFS 58.1%, 10-year DFS 46.8%, median DFS 48 months ($p < 0.001$).

We provided a detailed analysis of disease-free survival by tumor grade:

Grade 1: 5-year DFS 96.8%, 10-year DFS 94.7%, median DFS not reached.

Grade 2: 5-year DFS 89.2%, 10-year DFS 87.1%, median DFS not reached.

Grade 3: 5-year DFS 78.0%, 10-year DFS 72.5%, median DFS not reached ($p < 0.001$).

We provided a detailed analysis of disease-free survival by myometrial invasion:

<50%: 5-year DFS 94.8%, 10-year DFS 93.2%, median DFS not reached.

≥50%: 5-year DFS 84.2%, 10-year DFS 80.4%, median DFS not reached ($p < 0.001$).

We provided a detailed analysis of disease-free survival by lymph node status:

Negative: 5-year DFS 93.1%, 10-year DFS 91.0%, median DFS not reached.

Positive: 5-year DFS 71.3%, 10-year DFS 65.0%, median DFS 142 months ($p < 0.001$).

The overall survival analysis was explained in detail.

Overall survival rates for the cohort were as follows: 5-year OS, 87.8% (95% CI: 85.7–89.9%); 10-year OS, 82.4% (95% CI: 79.8–85.0%); and median OS: not reached.

We provided a detailed analysis of OS by histological type: endometrioid: 5-year OS 89.4%, 10-year OS 84.7%, median OS not reached, and non-endometrioid: 5-year OS 76.7%, 10-year OS 68.2%, median OS not reached ($p < 0.001$). We provided a detailed analysis of OS in the FIGO stage:

Stage I: 5-year OS 91.2%, 10-year OS 86.8%, median OS not reached.

Stage II: 5-year OS 84.5%, 10-year OS 78.9%, median OS not reached.

Stage III: 5-year OS 68.8%, 10-year OS 58.1%, median OS 168 months.

Stage IV: 5-year OS 48.4%, 10-year OS 32.3%, median OS 42 months ($p < 0.001$).

We provided a detailed analysis of OS by risk group:

Low risk: 5-year OS 94.2%, 10-year OS 90.8%, median OS not reached.

Intermediate risk: 5-year OS 88.7%, 10-year OS 82.1%, median OS not reached.

High-intermediate risk: 5-year OS 81.0%, 10-year OS 73.6%, median OS not reached.

High risk: 5-year OS 72.4%, 10-year OS 61.5%, median OS 186 months ($p < 0.001$).

Among patients who underwent lymph node evaluation, the extent of lymphadenectomy showed significant associations with survival outcomes:

- Lymph node sampling (1–10 nodes): 5-year DFS 89.6%, 10-year DFS 86.2%.

- Systematic lymphadenectomy (≥11 nodes): 5-year DFS 91.8%, 10-year DFS 89.4%.

- Sentinel lymph node biopsy: 5-year DFS 96.9%, 10-year DFS 96.9% ($p = 0.032$).

- Lymph node sampling (1–10 nodes): 5-year OS 85.3%, 10-year OS 78.1%.

- Systematic lymphadenectomy (≥11 nodes): 5-year OS 88.9%, 10-year OS 83.7%.

- Sentinel lymph node biopsy: 5-year OS 98.4%, 10-year OS 94.1% ($p < 0.001$).

The superior outcomes observed with sentinel lymph node biopsy likely reflect both patient selection bias (which has been performed primarily recently for low-risk patients) and improvements in surgical techniques.

Multivariate analyses were implemented and are shown below. Independent prognostic factors for DFS (Cox regression):

- FIGO Stage II *vs*. I: HR 4.37 (95% CI: 2.18–8.77), $p < 0.001$.

- FIGO Stage III *vs*. I: HR 8.68 (95% CI: 3.73–20.22), $p < 0.001$.

- FIGO Stage IV *vs*. I: HR 12.45 (95% CI: 4.89–31.67), $p < 0.001$.

- Grade 2 *vs*. 1: HR 2.26 (95% CI: 1.04–4.91), $p = 0.039$.

- Grade 3 *vs*. 1: HR 4.52 (95% CI: 2.01–10.19), $p < 0.001$.

The independent prognostic factors for overall survival (OS) were identified using Cox regression analysis:

- High-intermediate risk *vs*. low risk: HR 2.12 (95% CI: 1.07–4.17), $p = 0.031$.

- High risk *vs*. low risk: HR 2.75 (95% CI: 1.42–5.34), $p = 0.003$.

- Grade 2 *vs*. 1: HR 1.86 (95% CI: 1.09–3.20), $p = 0.024$.

- Grade 3 *vs*. 1: HR 2.71 (95% CI: 1.43–5.14), $p = 0.002$.

Variables such as LVSI, cervical involvement, and the depth of myometrial invasion were important in the initial analysis; however, they were not included in the final models because they are already incorporated into the FIGO staging system and risk group classification, which demonstrated stronger independent prognostic value (Figs. 1,2,3, Table 2). Among the 1028 patients, 342 (33.3%) received adjuvant treatment: 198 patients (19.3%) received radiotherapy alone, 89 patients (8.7%) received chemotherapy alone, and 55 patients (5.3%) received combined chemoradiotherapy. The decision for adjuvant treatment was based on present risk factors and international guidelines during the study period.

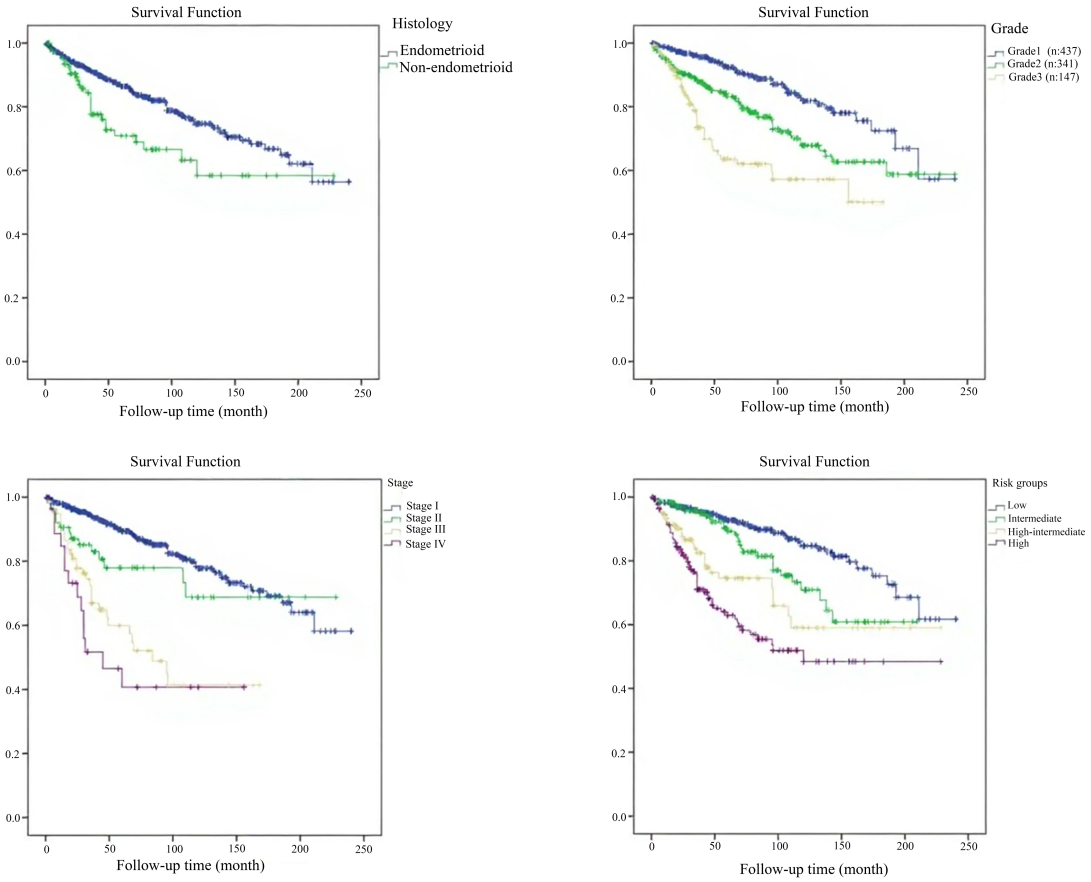

FIGURE 1. Overall survival for histology, stage, grade and risk groups.

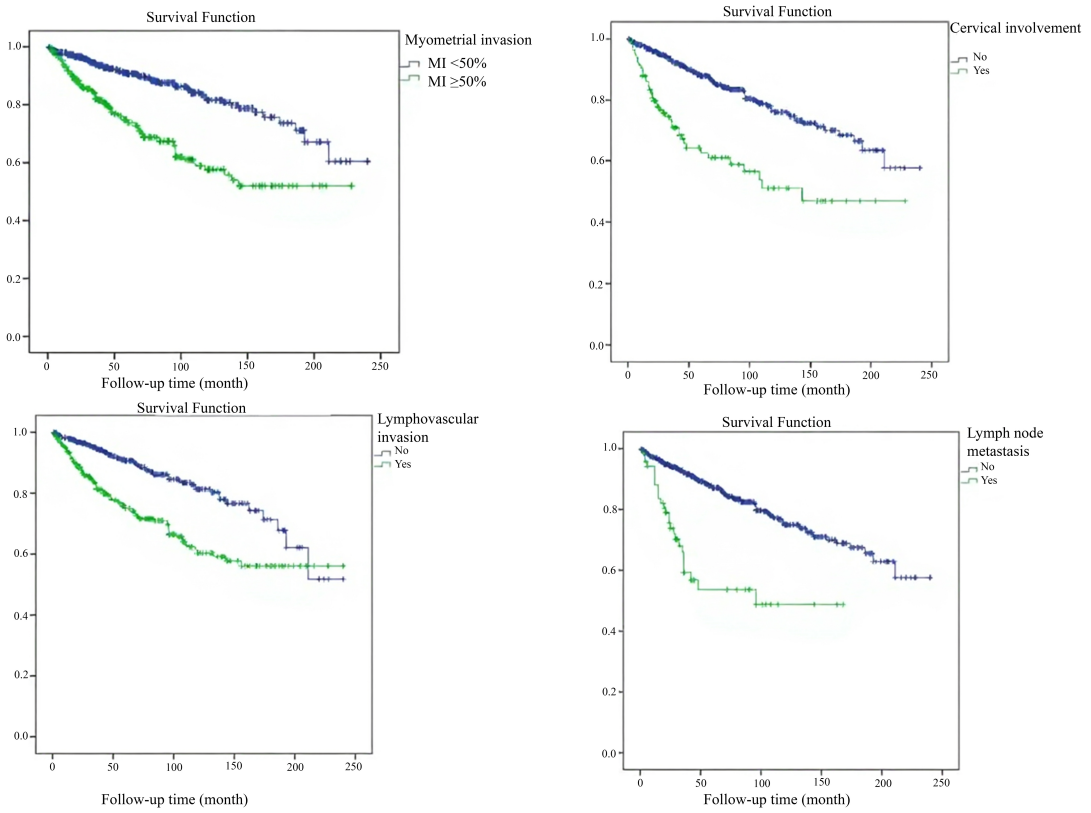

FIGURE 2. Overall survival for myometrial invasion, cervical invasion, lymphovascular invasion and lymph node metastasis.

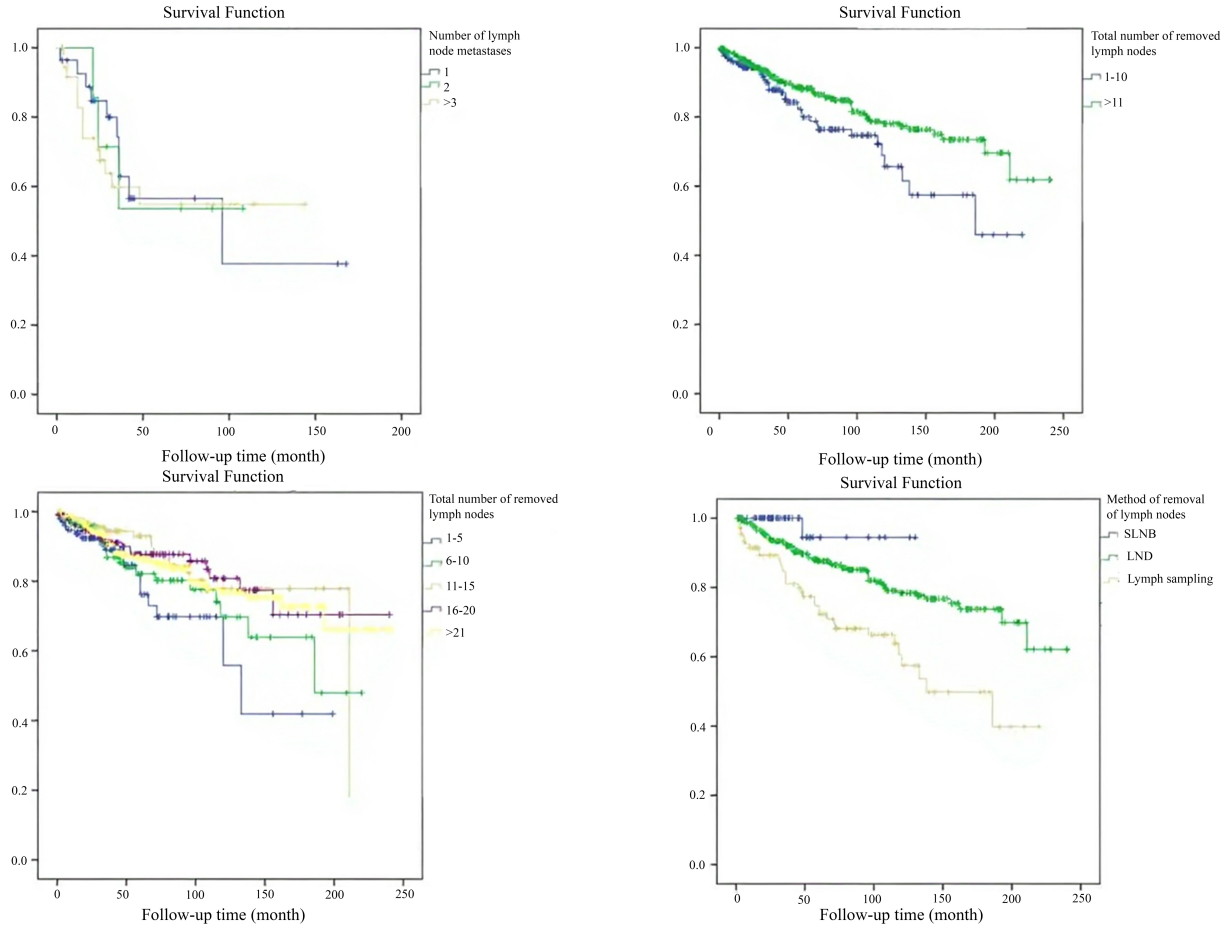

FIGURE 3. Overall survival for number of lymph node metastases, total number of removed lymph nodes and method of removal of lymph nodes. SLNB, Sentinel Lymph Node Biopsy; LND, Lymph Node Dissection.

TABLE 2. Independent prognostic factors for disease-free survival and overall survival.

	B	*p*	HR	95% CI	
				Low	High
Disease-free survival					
Stage					
I	0.240	0.658	1.271	0.439	3.684
II	1.476	<0.001	4.374	2.182	8.765
III	2.162	<0.001	8.688	3.733	20.218
Grade					
1	0.815	0.039	2.259	1.040	4.905
2	1.508	<0.001	4.519	2.005	10.185
Overall survival					
Risk groups		0.015			
Intermediate	0.211	0.506	1.234	0.663	2.297
Intermediate-high	0.749	0.031	2.115	1.072	4.174
High	1.013	0.003	2.754	1.420	5.341
Grade					
1	0.622	0.024	1.863	1.085	3.197
2	0.996	0.002	2.708	1.427	5.138

CI, confidence intervals; HR, hazard ratios.

4. Discussion

This comprehensive retrospective analysis of 1028 endometrial cancer patients represents one of the largest single-institution studies examining prognostic factors and survival outcomes over a 22-year period. Our findings confirm the prognostic significance of established clinicopathological factors while providing valuable insights into lymph node management strategies and their impact on survival outcomes in endometrial cancer. The most significant finding of our study relates to the comprehensive analysis of lymph node management strategies and their association with survival outcomes. While traditional prognostic factors such as FIGO stage, tumor grade, histological type, and myometrial invasion depth demonstrated expected associations with survival, the detailed evaluation of lymphadenectomy extent and methodology provides novel insights into optimal surgical management approaches. Our analysis revealed that systematic lymphadenectomy ($\geq$11 lymph nodes removed) was associated with superior survival outcomes compared to limited lymph node sampling, with 5-year disease-free survival rates of 91.8% versus 89.6%, respectively (p = 0.032). More notably, patients who underwent sentinel lymph node biopsy demonstrated exceptional outcomes with 5-year disease-free survival of 96.9% and 5-year overall survival of 98.4%. However, these superior outcomes likely reflect both patient selection bias, as sentinel lymph node biopsy was primarily performed in recent years for carefully selected low-risk patients, and the evolution of surgical techniques and perioperative care over the study period. The prognostic impact of lymph node metastases was profound, with patients having positive lymph nodes demonstrating significantly worse outcomes (5-year DFS: 71.3% *vs*. 93.1% for node-negative patients, $p < 0.001$). Among patients with lymph node metastases, the number of involved lymph nodes showed a trend toward worse prognosis, with patients having three or more involved lymph nodes experiencing the poorest outcomes, consistent with established literature on lymph node burden as a prognostic factor. Although molecular testing was not routinely available during our study period (2000–2022), the prognostic significance of molecular subtypes identified by The Cancer Genome Atlas (TCGA) has been well established in recent literature and represents a critical consideration for future risk stratification strategies. The TCGA classification divides endometrial cancers into four distinct molecular subtypes with significantly different prognostic implications: POLE ultramutated (POLEmut), microsatellite instability-high/mismatch repair deficient (MSI-H/MMRd), copy-number low/no specific molecular profile (CNL/NSMP), and copy-number high/p53 abnormal (CNH/p53abn) [16]. Patients with POLEmut tumors demonstrate excellent prognosis with significantly lower recurrence rates and higher overall survival compared to other subtypes, potentially benefiting from de-escalation of adjuvant therapy. The updated FIGO 2023 staging system now incorporates molecular classification, with POLEmut tumors receiving a specific substage (IAm POLEmut) regardless of other risk factors, reflecting their favorable prognosis [19]. Conversely, p53abn tumors carry the worst prognosis and are upstaged in the FIGO 2023 system (IICm p53abn), recognizing their aggressive behavior and need for intensive treatment approaches. The integration of molecular classification into routine clinical practice represents a paradigm shift toward personalized medicine in endometrial cancer management [29–33]. Future studies incorporating molecular data could significantly refine the risk stratification demonstrated in our cohort, potentially identifying patients who might benefit from treatment de-escalation or intensification based on their molecular profile rather than traditional histopathological features alone. Recent research has identified several novel prognostic markers that may enhance risk stratification beyond traditional clinicopathological factors. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score has emerged as a promising inflammation-based prognostic marker in various malignancies, including gynecologic cancers. This composite biomarker, calculated as (hemoglobin $\times$ albumin $\times$ lymphocyte count)/platelet count, reflects both nutritional and inflammatory status, with higher scores associated with better prognosis across multiple cancer types [24, 34]. Although HALP score data were not available for our historical cohort, this marker represents a cost-effective and easily obtainable prognostic tool that could be integrated into future risk assessment models. The HALP score has demonstrated significant prognostic value in ovarian cancer staging with an area under the curve of 0.671 ($p < 0.05$), suggesting potential utility in endometrial cancer prognostication as well [24, 34]. Other emerging biomarkers include various inflammatory indices such as the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index, all of which reflect the complex interplay between cancer progression and host immune response. These markers, combined with traditional prognostic factors and molecular classification, may enable more precise individualized prognostic modeling in the future. The surgical management of endometrial cancer has evolved significantly during our study period, with a marked shift toward minimally invasive approaches. While our analysis focused primarily on oncological outcomes rather than surgical technique comparison, it is important to acknowledge the contemporary evidence supporting minimally invasive surgery as the standard of care for appropriate candidates. Recent studies have consistently demonstrated that laparoscopic and robotic-assisted approaches offer equivalent oncological outcomes to traditional open surgery while providing superior short-term benefits including reduced blood loss, shorter hospital stays, fewer postoperative complications, and improved cosmetic results [35]. The adoption of minimally invasive techniques has increased dramatically, with recent data showing that 82.2% of endometrial cancer cases now utilize minimally invasive approaches compared to 45.8% in earlier periods.

Contemporary surgical considerations also include the evolution of incision techniques when open surgery is required. Recent studies have demonstrated that Pfannenstiel incisions may represent a safe and cosmetically favorable option in early-stage endometrial cancer, offering improved aesthetic outcomes compared to traditional midline incisions while maintaining adequate surgical exposure for appropriate cases [36]. While surgical technique was not the primary

focus of our study, these evolving practices represent important considerations for patient counseling and surgical planning in the current era. Our findings regarding lymph node management strategies align with evolving evidence supporting the adoption of sentinel lymph node biopsy as the standard approach for lymph node assessment in endometrial cancer. The superior outcomes observed with sentinel lymph node biopsy in our cohort, while influenced by patient selection and temporal factors, reflect the broader trend toward less morbid surgical approaches that maintain oncological safety. Sentinel lymph node biopsy has demonstrated high detection rates (>90% in experienced centers) and excellent negative predictive value for identifying lymph node metastases while significantly reducing the risk of lymphedema and other complications associated with complete lymphadenectomy [37]. The technique has been endorsed by major gynecologic oncology societies and is increasingly adopted as the standard of care for lymph node assessment in early-stage endometrial cancer. The integration of molecular classification with sentinel lymph node biopsy results may further refine surgical decision-making. For example, patients with POLEmut tumors may be candidates for even less extensive surgical staging given their excellent prognosis, while those with p53abn tumors may require more comprehensive staging and aggressive adjuvant treatment regardless of lymph node status. Our risk group classification system, based on traditional clinicopathological factors, demonstrated significant prognostic discrimination with clear separation of survival curves between risk categories. However, the integration of molecular classification into contemporary risk stratification systems, as reflected in the ESGO-ESTRO-ESP 2021 guidelines and the updated FIGO 2023 staging system, represents a significant advancement in precision medicine for endometrial cancer. The current study's findings support the continued importance of comprehensive histopathological assessment while highlighting the need for integration of molecular testing into routine practice. The combination of traditional prognostic factors with molecular classification promises to enable more precise treatment selection, potentially allowing for de-escalation of therapy in favorable molecular subtypes and intensification in high-risk molecular profiles. While detailed analysis of adjuvant treatment impact was beyond the scope of this study, our preliminary findings suggest that patients receiving adjuvant therapy, despite having higher-risk disease characteristics, achieved outcomes comparable to or better than expected based on their risk profiles. This observation supports the continued use of risk-adapted adjuvant treatment strategies while highlighting the need for more sophisticated risk stratification tools that incorporate molecular features. Contemporary adjuvant treatment approaches increasingly consider molecular classification results, with emerging evidence supporting immunotherapy for MSI-H/MMRd tumors and targeted therapies for specific molecular subtypes. The integration of molecular testing results with traditional risk factors promises to enable more personalized adjuvant treatment selection in the future. Several limitations of our study merit acknowledgment. The retrospective design and extended study period (2000–2022) introduce potential biases related to evolving surgical techniques, staging protocols, and treatment approaches. The lack of molecular testing data represents a significant limitation given the current importance of molecular classification in endometrial cancer management. Additionally, the superior outcomes observed with sentinel lymph node biopsy likely reflect patient selection bias and temporal improvements in care rather than technique superiority alone. Future research should focus on integrating molecular classification with traditional prognostic factors to develop more sophisticated risk prediction models. Prospective studies evaluating the impact of molecular classification on treatment selection and outcomes are needed to validate the clinical utility of these emerging biomarkers. Additionally, investigation of novel prognostic markers such as the HALP score and other inflammatory indices may provide additional tools for risk stratification and treatment personalization.

5. Conclusions

This comprehensive analysis confirms the prognostic significance of established clinicopathological factors in endometrial cancer while providing valuable insights into lymph node management strategies. The findings support the continued importance of comprehensive surgical staging and histopathological assessment while highlighting the evolving landscape of molecular classification and personalized medicine in endometrial cancer management. The superior outcomes associated with systematic lymphadenectomy compared to limited sampling support the importance of adequate lymph node assessment, while the excellent results observed with sentinel lymph node biopsy reflect the potential for maintaining oncological safety while reducing surgical morbidity. The integration of molecular classification into future risk stratification models promises to enable more precise treatment selection and improved patient outcomes. As the field continues to evolve toward personalized medicine approaches, the combination of traditional prognostic factors, molecular classification, and novel biomarkers such as inflammatory indices will likely enable more sophisticated risk prediction and treatment selection. This evolution represents an exciting opportunity to improve outcomes while minimizing treatment-related morbidity for patients with endometrial cancer.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

AI—conceptualization; formal analysis and investigation; writing–original draft preparation; supervision. AG—methodology. TB—writing–review and editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Since the study was retrospective and observational, the Clinical Research Ethics Committee of Cerrahpaşa Medical Faculty waived the need for written informed consent. Ethical approval was received from the Cerrahpaşa Medical Faculty Ethics Committee (approval number: E-83043809-804.01-514105, dated 19 October 2022). The study protocol was prepared in accordance with the Declaration of Helsinki.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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