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Adjuvant radiotherapy for FIGO 2023 stage IC endometrial carcinoma

FIGO 2023 evre IC endometriyal karsinomda adjuvan radyoterapi

Alper Kahvecioğlu[1], Sezin Yüce Sarı[1], Melis Gültekin[1], Ecem Yiğit[1], Zafer Arık[2], Alp Usubütün[3], Utku Akgör[4], Derman Başaran[4], Nejat Özgül[4], Ferah Yıldız[1]

[1]*Hacettepe University Faculty of Medicine, Department of Radiation Oncology, Ankara, Türkiye*
[2]*Hacettepe University Faculty of Medicine, Department of Medical Oncology, Ankara, Türkiye*
[3]*Hacettepe University Faculty of Medicine, Department of Pathology, Ankara, Türkiye*
[4]*Hacettepe University Faculty of Medicine, Department of Gynecologic Oncology, Ankara, Türkiye*

Abstract

Objective: Within the International Federation of Gynecology and Obstetrics (FIGO) 2023 staging framework, stage IC endometrial carcinoma denotes tumors with aggressive histology confined to the endometrium, without myometrial invasion. This study evaluated treatment outcomes and survival following adjuvant radiotherapy (RT).

Materials and Methods: Twenty-eight patients diagnosed with FIGO 2023 stage IC endometrial carcinoma who were treated with adjuvant RT were retrospectively analyzed.

Results: The most common histologic subtype was serous carcinoma (39%), followed by clear cell carcinoma (25%), high-grade endometrioid carcinoma (25%), carcinosarcoma (7%), and undifferentiated carcinoma (4%). Half of the patients received RT alone, while the remainder received combined RT and chemotherapy. Vaginal brachytherapy was the predominant adjuvant RT technique (86%). The median duration of observation was 59 months. The 2- and 5-year overall survival (OS) rates were 96% and 87; locoregional recurrence-free survival (LRRFS) rates were 96% and 82; and distant metastasis-free survival (DMFS) rates were 92% and 80%, respectively. The presence of malignant peritoneal cytology during surgical staging predicted significantly poorer 5-year OS (93% vs. 33%), LRRFS (86% vs. 33%), and DMFS (90% vs. 0%). Within this limited cohort, the addition of chemotherapy to adjuvant RT did not confer a clear survival advantage. No severe treatment-related toxicities were observed.

Conclusion: While patients with FIGO 2023 stage IC endometrial carcinoma typically achieve favorable outcomes after adjuvant RT, malignant peritoneal cytology remains an adverse prognostic factor. In this subgroup, escalation of adjuvant therapy, such as combination chemotherapy, may be appropriate.

Keywords: Endometrial cancer, FIGO 2023, malignant peritoneal cytology, radiotherapy, stage IC

Öz

Amaç: Uluslararası Jinekoloji ve Obstetrik Federasyonu (FIGO) 2023 evreleme sistemine göre evre IC endometriyal karsinom, miyometriyal invazyon olmaksızın endometriuma sınırlı agresif histolojiye sahip tümörleri tanımlar. Bu çalışma, adjuvan radyoterapi (RT) sonrası tedavi sonuçlarını ve sağkalımı değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: FIGO 2023 evre IC endometriyal karsinom tanısı almış ve adjuvan RT ile tedavi edilmiş 28 hasta retrospektif olarak analiz edildi.

Bulgular: En sık görülen histolojik alt tip seröz karsinomdu (%39), bunu berrak hücreli karsinom (%25), yüksek dereceli endometrioid karsinom (%25), karsinosarkom (%7) ve diferansiye olmayan karsinom (%4) izledi. Hastaların yarısı yalnızca RT alırken, diğer yarısı RT ile kemoterapi kombinasyonu ile

PRECIS: In our analysis of International Federation of Gynecology and Obstetrics 2023 stage IC endometrial carcinoma, malignant peritoneal cytology emerged as a significant adverse prognostic factor, even among patients who received adjuvant radiotherapy.

Corresponding Author/Sorumlu Yazar: Assoc. Prof. Sezin Yüce Sarı,
Hacettepe University Faculty of Medicine, Department of Radiation Oncology, Ankara, Türkiye
E-mail: sezin_yuce@hotmail.com **ORCID ID:** orcid.org/0000-0003-2395-6868

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tedavi edildi. En yaygın RT tekniği vajinal brakiterapiydi (%86). Ortanca izlem süresi 59 aydı. İki ve beş yıllık genel sağkalım (GS) oranları sırasıyla %96 ve %87, lokal bölgesel rekürrenssiz sağkalım (LBRS) oranları %96 ve %82, uzak metastazsız sağkalım (UMS) oranları ise %92 ve %80 olarak bulundu. Cerrahi evreleme sırasında malign peritoneal sitoloji saptanan hastalarda 5 yıllık GS (%93'e karşı %33), LBRS (%86'ya karşı %33) ve UMS (%90'a karşı %0) anlamlı derecede düşüktü. Bu sınırlı kohortta, RT'ye kemoterapi eklenmesi belirgin bir sağkalım avantajı sağlamadı. Ciddi tedaviye bağlı toksisite gözlenmedi.

Sonuç: FIGO 2023 evre IC endometriyal karsinomlu hastalar genellikle adjuvan RT sonrasında iyi prognoz gösterse de, malign peritoneal sitoloji olumsuz bir prognostik faktör olmaya devam etmektedir. Bu alt grupta kemoterapi eklenmesi gibi adjuvan tedavi intensifikasyonu uygun olabilir.

Anahtar Kelimeler: Endometriyal kanser, FIGO 2023, malign peritoneal sitoloji, radyoterapi, evre IC

Introduction

Endometrial carcinoma is the most frequent gynecologic malignancy in developed nations and the second most prevalent in lower-income regions[1]. Over time, treatment has evolved into a highly personalized approach, particularly with the identification of novel molecular markers that are closely related to prognosis[2,3]. These advancements have led to changes in current treatment guidelines by categorizing factors that influence treatment decisions as clinicopathological or molecular features[4,5]. Despite the availability of guideline recommendations supported by high-level evidence for most patients with endometrial carcinoma, the optimal treatment approach for those with aggressive histological subtypes without myometrial invasion (MI) remains unclear.

Endometrial carcinoma confined to a polyp or to the endometrial lining is a rare condition that can pose challenges in deciding on adjuvant treatment[6]. Based on the 2020 European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines, non-endometrioid carcinomas without MI are categorized as intermediate risk, and postoperative vaginal brachytherapy (VBT) is typically recommended to reduce the likelihood of vaginal relapse[4]. However, since such cases are infrequent, they have rarely been included in randomized trials, resulting in a limited evidence base compared with that for conventional intermediate-risk endometrioid carcinomas. The 2023 revision of the International Federation of Gynecology and Obstetrics (FIGO) classification redefined these tumors (aggressive histologies such as high-grade endometrioid and non-endometrioid carcinomas without MI) as stage IC disease[7]. This recent change emphasizes the need for updated clinical data reflecting real-world outcomes. Accordingly, this study aimed to investigate the oncologic outcomes and prognostic determinants in patients with FIGO 2023 stage IC endometrial carcinoma who underwent adjuvant radiotherapy (RT), with or without additional chemotherapy.

Materials and Methods

A retrospective cohort analysis was performed using data from 1,297 women with histologically confirmed endometrial carcinoma who received adjuvant RT at our institution between 1994 and 2023. Patients were eligible if they had aggressive histologic subtypes (grade 3 endometrioid or non-endometrioid) limited to the endometrial lining or to a polyp, corresponding to FIGO 2023 stage IC disease[7].

Adjuvant treatment decisions for all patients were made at the weekly gynecologic oncology tumor board, with participation by gynecologic oncologists, medical oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine specialists, all of whom possess expertise in gynecologic oncology. All patients received an initial treatment consisting of total hysterectomy and bilateral salpingo-oophorectomy with or without lymph node dissection (LND). Peritoneal exploration and pelvic washings were performed according to institutional standards; surgical reports were reviewed to document the extent of exploration. All patients received RT, predominantly with high-dose-rate intracavitary VBT. In cases where LND was not performed, external beam radiotherapy (EBRT) was preferred. Systemic chemotherapy, most frequently as six cycles of carboplatin (AUC5) and paclitaxel (175 mg/m^2), was optionally administered entirely before RT, in a "sandwich" schedule (three cycles before and three cycles after RT), or in a sequential schedule. No concurrent chemoradiation was administered. The decision to administer chemotherapy largely depended on clinical practice at that time. No patients received concurrent chemotherapy.

Post-treatment surveillance included physical and gynecologic examinations every three months during the first two years, then at six-month intervals for the next three years, and annually thereafter. Each visit included assessments by both gynecologic and radiation oncologists, as well as routine laboratory tests. Imaging was performed when recurrence was clinically suspected.

Ethical approval was obtained from the Hacettepe University Health Sciences Research Ethics Board (date: 1305.03.2024, number: 2024/05-25).

Statistical Analysis

Data analyses were conducted using SPSS version 23.0 (IBM, Armonk, NY, USA). Survival outcomes, including overall survival (OS), locoregional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS), were estimated with the Kaplan-Meier method, and group comparisons were made using the log-rank test. Locoregional recurrence refers to failures within the vagina, pelvic nodes, or para-aortic nodes, whereas distant metastasis (DM) encompasses hematogenous or peritoneal dissemination. Time-to-event intervals were measured

from the date of surgery to the first event or last follow-up. The prognostic relevance of clinicopathologic variables, such as age, LND status, number of dissected nodes, peritoneal cytology, histologic subtype, tumor location, p53 status, hormone receptor status, and adjuvant treatment type, was evaluated by univariate analysis. Because of the limited sample size and low event count, multivariate Cox regression was not performed; statistical significance was defined as $p<0.05$.

Results

The study population consisted of 28 patients. Table 1 summarizes patient, tumor, and treatment characteristics. The most common histology was serous carcinoma (n=11, 39%), and the most common RT technique was VBT alone (n=24, 86%). Four patients who did not undergo LND received EBRT. While three of these patients received EBRT alone, the fourth patient experienced a rapid local recurrence (LR) extending to the distal vagina during adjuvant chemotherapy and subsequently underwent EBRT followed by VBT. VBT was delivered at a median dose of 27.5 Gy (range, 21-28 Gy) in 3-5 fractions, while EBRT was administered at a median dose of 50.4 Gy (range, 45-50.4 Gy) in 25-28 fractions. Adjuvant chemotherapy was administered to 50% (n=14) of patients. The Median number of chemotherapy cycles was 6 (range, 3-6). Five patients (36%) received the entire chemotherapy course prior to RT, seven (50%) received chemotherapy via a sandwich approach, and two (14%) received chemotherapy after RT.

The median duration of observation was 59 months (range: 4-188 months), with 26 patients (93%) having a follow-up exceeding two years. Throughout the follow-up period, seven patients (25%) experienced disease relapse, and the details of these cases are outlined in Table 2. The rate of LR and DM was 10.7% (n=3) and 21.4% (n=6), respectively. Of the three local recurrences observed, two occurred during follow-up after completion of adjuvant RT, whereas one developed while the patient was still receiving adjuvant chemotherapy and was subsequently treated with RT.

The 2- and 5-year rates for OS, LRRFS, and DMFS were 96% and 87%, 96% and 82%, and 92% and 80%, respectively. Table 3 provides a summary of the univariate analysis outcomes. Survival rates tended to be higher among patients who were under 62 years of age, had endometrioid-type tumors, were hormone receptor positive, or were treated with chemotherapy, although these trends did not reach statistical significance. Malignant peritoneal cytology was the sole factor significantly associated with poorer survival; patients with malignant cytology had markedly worse outcomes than those with benign cytology (Figure 1).

The therapy was well tolerated overall, with no instances of acute treatment-related toxicity of grade 3 or higher reported. For RT-related late toxicity, 6 (21%) patients experienced vaginal stenosis and 10 (36%) experienced vaginal dryness; all events were grade 1-2. Of the 14 patients who received systemic therapy, six (43%) experienced late peripheral neuropathy of grade ≤2, which was the only chemotherapy-related toxicity observed.

Table 1. Summary of patient demographics, tumor features, and treatment details

Characteristic	No (%)
Age (median)	62 years (range, 39-77 years)
Surgery	
TH+BSO	4 (14)
TH+BSO+LND	24 (86)
Extent of LND	
Pelvic	6 (25)
Pelvic and Para-aortic	18 (75)
Number of removed lymph nodes, median	33 (range, 2-86)
Peritoneal cytology	
Positive	3 (11)
Negative	25 (89)
Histology	
Serous carcinoma	11 (39)
Clear cell carcinoma	7 (25)
Endometrioid type carcinoma (grade 3)	7 (25)
Carcinosarcoma	2 (7)

Table 1. Continued

Characteristic	No (%)
Undifferentiated carcinoma	1 (4)
Tumor localization	
Limited to a polyp	17 (61)
Confined to endometrium	11 (39)
LVSI	
Present	0 (0)
Absent	21 (75)
Unknown	7 (25)
p53 staining pattern by immunohistochemistry	
Wild-type	5 (18)
Mutated	16 (57)
Unknown	7 (25)
Adjuvant treatment	
RT	14 (50)
RT+CT	14 (50)
RT technique	
VBT alone	24 (86)
EBRT alone	3 (11)
EBRT+VBT	1 (3)
CT sequence	
Prior to RT	5 (36)
Sandwich approach	7 (50)
After RT	2 (14)

BSO: Bilateral salpingo-oophorectomy, CT: Chemotherapy, EBRT: External beam radiotherapy, LND: Lymph node dissection, LVSI: Lymphovascular space invasion, RT: Radiotherapy, TH: Total histerectomy, VBT: Vaginal brachytherapy

Table 2. Characteristics of 7 patients with recurrence

Patient no.	Age (years)	Histology	Peritoneal cytology	p53	LVSI	Treatment	Recurrence type	Recurrence interval (months)	Salvage treatment	Last status
1	57	CS	(+)	WT	(-)	CT→EBRT+VBT	LR+DM (peritoneum)	14	CT	DoD
2	54	SC	(-)	Mut.	(-)	CT→VBT→CT	LR+DM (peritoneum)	114	CT	DoD
3	62	EC	(-)	N/A	(-)	VBT	LR	56	SBRT	AWD
4	70	SC	(-)	Mut.	(-)	VBT	DM (liver)	51	Surgery+CT	ANED
5	69	SC	(-)	Mut.	N/A	VBT	DM (peritoneum)	37	CT	DoD
6	71	EC	(+)	Mut.	(-)	VBT	DM (liver)	27	CT	AWD
7	70	CCC	(+)	N/A	(-)	VBT	DM (peritoneum)	21	CT	DoD

ANED: Alive with no evidence of disease, AWD: Alive with disease, CCC: Clear cell carcinoma, CS: Carcinosarcoma, CT: Chemotherapy, DoD: Died of disease, DM: Distant metastasis, EBRT: External beam radiotherapy, EC: Endometrioid carcinoma, LR: Local recurrence, LVSI: Lymphovascular space invasion, Mut.: Mutated, N/A: Not available, no.: Number, RT: Radiotherapy, SBRT: Stereotactic body radiotherapy, SC: Serous carcinoma, VBT: Vaginal brachytherapy, WT: Wild type

Table 3. Findings from the univariate analysis

	5y OS (%)	p	5y LRRFS (%)	p	5y DMFS (%)	p
Age (years)						
<62 (n=14)	92	0.91	92	0.65	92	0.38
≥62 (n=14)	84		73		69	
LND						
Yes (n=24)	85	0.58	78	0.56	78	0.33
No (n=4)	100		100		100	
N of removed LNs						
<33 (n=14)	75	0.41	69	0.55	70	0.48
≥33 (n=14)	93		86		86	
Peritoneal cytology						
Positive (n=3)	33	<0.05	33	<0.05	0	<0.05
Negative (n=25)	93		86		90	
Histology						
Endometrioid (n=7)	100	0.67	67	0.65	83	0.95
Non-endometrioid (n=21)	81		84		79	
Tumor localization						
Limited to polyp (n=17)	80	0.70	79	0.75	73	0.89
Confined to endometrium (n=11)	100		75		88	
p53						
Abnormal staining (n=16)	89	0.49	90	0.43	77	0.63
Wild-type staining (n=5)	75		75		75	
Unknown (n=7)	86		73		83	
ER						
Positive (n=12)	100	0.23	100	0.23	90	0.07
Negative (n=6)	80		80		53	
Unknown (n=10)	79		71		81	
PR						
Positive (n=9)	100	0.99	100	0.86	100	0.22
Negative (n=8)	86		86		54	
Unknown (n=11)	79		71		81	
Treatment						
RT (n=14)	81	0.76	67	0.47	66	0.21
RT+CT (n=14)	92		92		92	
EBRT						
Yes (n=4)	75	0.18	83	0.86	83	0.97
No (n=24)	88		81		80	

CT: Chemotherapy, DMFS: Distant metastasis-free survival, EBRT: External beam radiotherapy, ER: Estrogen receptor, LN: Lymph node, LND: Lymph node dissection, LRRFS: Locoregional recurrence-free survival, N: Number, OS: Overall survival, PR: Progesterone receptor, RT: Radiotherapy

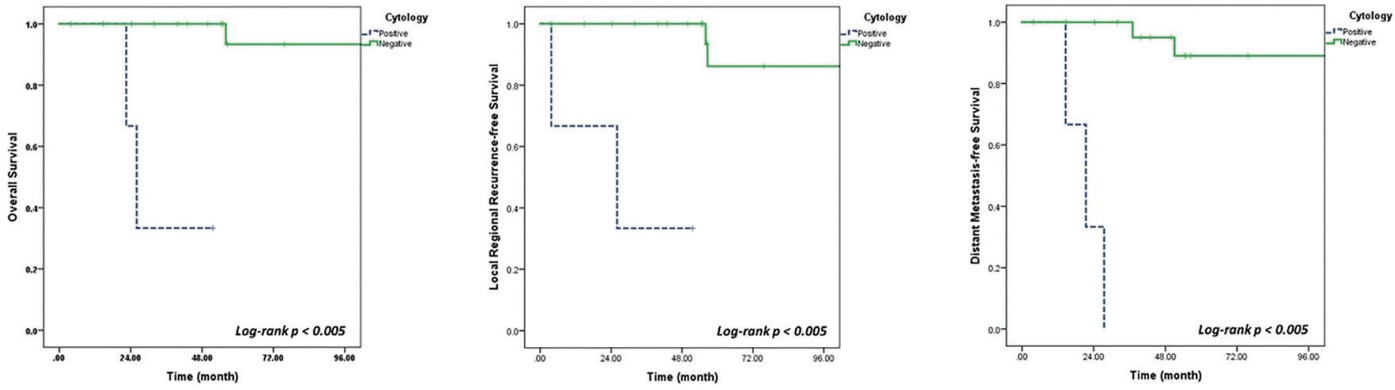

Figure 1. Kaplan-Meier survival curves according to the result of peritoneal cytology

Discussion

This study presents one of the few institutional experiences focusing exclusively on patients with FIGO 2023 stage IC endometrial carcinoma, an uncommon subset characterized by aggressive histology without MI. Our findings demonstrate that adjuvant RT achieves excellent locoregional control with minimal toxicity, while malignant peritoneal cytology remains a strong predictor of poor survival outcomes across all endpoints. Because of the rarity of this entity, prospective data are scarce, and existing evidence largely derives from small retrospective cohorts with heterogeneous designs. Previous series have reported inconsistent outcomes regarding the benefit of chemotherapy or RT in non-myoinvasive, high-grade disease. In the study by Thomas et al.[8], 42 patients diagnosed with stage I endometrial serous carcinoma were evaluated, of whom 15 had tumors without MI. Over a median follow-up of 39 months, none of the patients without MI developed a recurrence, regardless of whether adjuvant treatment was given, and all were alive at 5 years. In contrast, Kelly et al.[9], reported improved survival following adjuvant chemotherapy in a small cohort of 33 patients with serous endometrial carcinoma without MI. Notably, among their Stage I population, no vaginal cuff failures occurred in women treated with VBT; recurrences occurred in approximately one-fifth of those who did not receive it. By comparison, another retrospective study involving 84 women with FIGO 2009 stage I serous or clear cell carcinoma reported that approximately one quarter had tumors confined to the endometrium and that the cohort had a 5-year OS of 84%[10]. In that series, adjuvant chemotherapy did not translate into improved clinical outcomes. A larger population-based investigation encompassing 1,709 women with serous carcinoma confined to the endometrium provided further insight into the role of adjuvant therapy[11]. Roughly half of the patients (51%) underwent postoperative treatment with RT and/or chemotherapy, whereas the remaining 49% were managed by observation alone. That study demonstrated a clear survival advantage for those receiving adjuvant chemotherapy, either alone or in combination with RT, compared with observation. In our cohort, predominant use of a VBT-centered approach resulted in excellent vaginal control, reinforcing its role as an effective modality for local disease management.

Despite inconsistent findings reported across retrospective series, the majority of these analyses focused exclusively on patients with serous or clear-cell histologies, thereby overlooking other aggressive subtypes included in the current FIGO 2023 classification[8,9,11-15]. Although combining distinct histologic entities may not be ideal from a biological standpoint, it should be emphasized that the updated FIGO 2023 classification designates grade-3 endometrioid tumors as aggressive subtypes, aligning them with other high-grade epithelial variants[7]. Hence, more comprehensive studies that collectively evaluate these aggressive histological types are needed. In a recent study by Dallaire Nantel et al.[16], 24% (6 of 25) of patients with grade 3 endometrioid, serous, clear cell, mixed, or carcinosarcoma histology confined to the endometrium or a polyp were treated with VBT, while 76% did not receive adjuvant therapy. In this study, the 3-year progression-free survival and OS rates were very high, being 93% and 100%, respectively. Therefore, researchers indicated that postsurgical follow-up is a safe approach in these cases. In contrast, Chang-Halpenny et al.[17] reported a 5-year OS of 80.6% when 80% of the 46 patients with either serous or clear cell carcinoma confined to the endometrium did not receive any adjuvant treatment. Therefore, other prognostic factors should be considered when deciding whether to administer adjuvant treatment in these cases. Given the results of these studies, one can conclude that adjuvant treatment should be administered to patients with aggressive histologies even if the tumor does not have MI. However, it remains unclear whether this adjuvant treatment should be RT, chemotherapy, or both. Our findings demonstrated satisfactory oncologic outcomes with RT; consequently, vaginal recurrence occurred in only 10.7% of patients. On the other hand, the addition of chemotherapy did not provide a statistically significant survival benefit in this small cohort. However, it should be noted that the 5-year rates of OS, LRRFS, and DMFS in patients that

received chemotherapy were higher than those in patients that received RT alone. This is most likely due to the limited number of individuals and events.

The complexity of determining adjuvant treatment in this uncommon and diverse patient population is further compounded by uncertainty in prognostic factors. As a result, physicians frequently resort to using prognostic factors identified in the literature for broader categories of endometrial cancer patients when addressing this specific subgroup. Although malignant peritoneal cytology is consistently overlooked in staging systems and remains a topic of debate because of conflicting research outcomes, emerging evidence indicates its potential prognostic significance, even among patients with tumors lacking MI[17-21]. Chang-Halpenny et al.[17] demonstrated that malignant peritoneal cytology was associated with an increased risk of recurrence in patients with early-stage serous or clear-cell carcinoma that was limited to or originated from an endometrial polyp. Similarly, in a multi-institutional study involving 33 women with serous endometrial carcinoma confined to a polyp, malignant peritoneal cytology was significantly associated with an increased risk of disease recurrence[18]. In our study, malignant peritoneal cytology emerged as a strong adverse prognostic factor across all survival outcomes. Adjuvant chemotherapy was administered to 33% of patients with malignant cytology; however, likely because of the small sample size, we could not determine the impact of adding chemotherapy on the prognosis of these patients. In light of findings from studies emphasizing the prognostic significance of malignant peritoneal cytology in patients with endometrial cancer, we firmly advocate for its inclusion as a crucial factor when deciding on adjuvant treatment.

Study Limitations

While this study attempts to collectively assess various histologies classified as stage IC according to FIGO 2023, it is crucial to acknowledge its limitations. Firstly, as this is a retrospective analysis including cases treated over nearly three decades (1994-2023), restaging according to the FIGO 2023 system carries inherent limitations. Differences in surgical staging procedures, pathological evaluation, and documentation during this long period may have introduced heterogeneity and a potential risk of understaging. Additionally, the small patient cohort significantly limits the generalizability of our findings. The inherent uncertainty regarding unrecorded factors that might have influenced adjuvant treatment decisions such as comorbidities or institutional preferences, also represents a notable limitation. Moreover, recent advances in molecular classification have reshaped the understanding of endometrial carcinoma biology and prognosis. Findings from The Cancer Genome Atlas indicate that distinct molecular subgroups confer prognostic information that surpasses that provided by traditional histopathologic factors[2,3]. However, molecular stratification was not feasible in our cohort due to the retrospective nature of the study and the lack of available molecular data. Prospective, multicenter investigations incorporating molecular classification are essential to substantiate our observations and refine adjuvant treatment approaches for FIGO 2023 stage IC disease. These factors underscore the need for larger, prospective, and molecularly characterized studies to validate our findings and strengthen evidence-based decision-making in this rare context.

Conclusion

In conclusion, patients diagnosed with FIGO 2023 stage IC endometrial carcinoma who undergo adjuvant RT generally exhibit favorable prognoses. However, our findings underscore the prognostic significance of malignant peritoneal cytology, which remains clinically relevant despite its exclusion from the current staging system. Although overall outcomes are favorable, the presence of malignant peritoneal cytology correlates with poorer survival and may warrant more intensive therapeutic approaches. Future research should focus on evaluating treatment intensification strategies and elucidating the molecular pathways underlying malignant peritoneal cytology. Such efforts will be crucial for optimizing therapeutic decision-making and improving outcomes in this uncommon but clinically important subset of patients.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Hacettepe University Health Sciences Research Ethics Board (date: 1305.03.2024, number: 2024/05-25).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., S.Y.S., M.G., E.Y., Z.A., A.U., U.A., D.B., N.Ö., F.Y., Concept: A.K., S.Y.S., M.G., E.Y., Z.A., A.U., U.A., D.B., N.Ö., F.Y., Design: A.K., S.Y.S., M.G., E.Y., Z.A., A.U., U.A., D.B., N.Ö., F.Y., Data Collection or Processing: A.K., E.Y., Analysis or Interpretation: A.K., Literature Search: A.K., S.Y.S., M.G., Z.A., A.U., U.A., D.B., N.Ö., F.Y., Writing: A.K., S.Y.S., M.G., F.Y.

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