RESEARCH ARTICLE / *Araştırma Makalesi*

Survival, Failure Patterns, and Toxicity Outcomes in Endometrial Cancer Patients Receiving Adjuvant Radiotherapy

Adjuvan Radyoterapi Uygulanan Endometrium Kanseri Hastalarında Sağkalım, Nüks Paternleri ve Toksisite Sonuçları

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Abstract

Introduction	This study aimed to investigate the survival outcomes, recurrence patterns, and treatment-related toxicities of endometrial cancer (EC) patients who underwent adjuvant radiotherapy.
Materials and Methods	Between January 2012 and December 2021, one hundred fourteen patients who underwent adjuvant radiotherapy with the diagnosis of endometrial cancer were retrospectively analyzed. Cases were evaluated for overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS), cancer-specific survival (CSS), and distant metastasis-free survival (DMFS).
Results	Median follow-up was 63 months (8 -135). At 5 years OS, DFS, LRFS, CSS, and DMFS were 85.5%, 90.5%, 98.9%, 94.1%, and 90.5%, respectively. Univariate analysis of lymphovascular space invasion (LVSI) is statistically significant for DFS, DMFS, and CSS, respectively (p=0.019, p=0.019, p=0.021) and histology, tumor grade, stage were statistically significant for LRFS, respectively (p=0.031, p=0.010, p=0.049). Grade 1 and 2 acute gastrointestinal toxicity were observed in 40 patients (35.1%). Grade 1 acute genitourinary toxicity was observed in 35 patients (30.7%). Grade 3 late genitourinary and gastrointestinal toxicity was observed in 0.9% and 1.8%, respectively
Conclusion	Histology, grade, LVSI, and stage didn't significantly affect overall survival, but LVSI and stage were the most influential prognostic factors on relapse patterns. Adjuvant radiotherapy is safe and well tolerated by patients with endometrial cancer with acceptable toxicity.
Keywords	Endometrial Cancer, Adjuvant Radiotherapy, Survival, Treatment-related toxicity

Öz

Amaç	*Bu çalışma, adjuvan radyoterapi uygulanan endometrium kanseri (EK) hastalarının sağkalım sonuçlarını, nüks paternlerini ve tedaviye bağlı toksisiteleri araştırmayı amaçladı.*
Yöntem ve Gereçler	*Ocak 2012-Aralık 2021 tarihleri arasında endometrium kanser tanısı ile adjuvan radyoterapi uygulanan 114 hasta retrospektif olarak incelendi. Vakalar, genel sağkalım (GS), hastalıksız sağkalım (HSK), lokal rekürrenssiz sağkalım (LRSK), kansere spesifik sağkalım (KSS) ve uzak metastazsız sağkalım (UMSK) açısından değerlendirildi.*
Bulgular	*Medyan takip süresi 63 aydı (8 -135). 5 yıllık GS, HSK, LRSK, KSS ve UMSK, sırasıyla, %85.5, %90.5, %98.9, %94.1 ve %90.5 idi. Tek değişkenli analizde, lenfovasküler alan invazyonu (LVAI) ile HSK, UMSK ve KSS arasında istatistiksel olarak anlamlı bir ilişki vardı (sırasıyla, p=0.019, p=0.019, p=0.021). LRSK ile histoloji, tümör derecesi, evre arasında anlamlı ilişki vardı. (sırasıyla, p=0.031, p=0.010, p=0.049). 40 hastada (%35.1), grade 1 ve 2 akut gastrointestinal toksisite gözlendi. 35 hastada (%30.7), grade 1 akut genitoüriner toksisite gözlendi. Grade 3 geç genitoüriner ve gastrointestinal toksisite sırasıyla %0.9 ve %1.8 oranında gözlendi.*
Sonuç	*Histoloji, grade, LVAI ve evre genel sağkalımı üzerinde anlamlı etkisi olmamasına karşın, LVAI ve evre nüks açısından en etkili prognostik faktörlerdi. Adjuvan radyoterapi güvenli ve kabul edilebilir toksisite ile endometrium kanserli hastalar tarafından iyi tolere edilmektedir.*
Anahtar Kelimeler	*Endometrium Kanseri, Adjuvan Radyoterapi, Sağkalım, Tedaviye bağlı toksisite*

INTRODUCTION

Endometrial cancer (EC) is the sixth most common malignancy worldwide.[1] The first symptom of ECs is often abnormal or postmenopausal uterine bleeding. Endometrioid carcinoma is usually associated with unopposed estrogenic stimulation and endometrial hyperplasia.[2] Endometrial cancer histologic subtypes are classified as endometrioid and non-endometrioid. Endometrioid types accounts for the majority of endometrial cancers and most commonly occur is generally hormone-dependent, and have a more favorable prognosis. Grade 3 endometrioid cancers are more complex and generally have a less favorable prognosis. Non-endometrioid cancers include more aggressive subtypes such as serous cancers, clear cell cancers, and carcinosarcomas.[3]

The primary treatment for EC is surgery, and the International Federation of Gynecology and Obstetrics (FIGO) advocates surgical staging, including pelvic and para-aortic lymphadenectomy and total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy. Adjuvant radiotherapy (RT), including external beam pelvic radiotherapy (EBRT) and/or vaginal brachytherapy (VBT), proves a good prognosis and is generally recommended based on risk stratification.[4,5]

Adjuvant therapy indications depend on age, grade, histological type, myometrial invasion depth, and lymphovascular space invasion (LVSI) presence.[4] LVSI is a strong prognostic factor for pelvic recurrence, distant metastasis, and decreased overall survival.[6] Early diagnosis of EC generally improves outcomes, whereas 5-year OS is worse in patients with advanced disease, ranging from 57% to 66% (FIGO stage III) and 20% to 26% (FIGO stage IV). 5-year DFS is estimated at 90% in patients without lymph node metastasis, 60–70% in those with pelvic lymph node metastasis, and 30–40% in those with para-aortic lymph node metastasis.[7, 8]

This study aims to examine the survival outcomes, recurrence patterns, and toxicities of patients with EC diagnosed with adjuvant radiotherapy.

MATERIALS and METHODS

In this study, the data of patients who underwent adjuvant radiotherapy with the diagnosis of endometrial cancer between January 2012 and December 2021 in the Radiation Oncology unit of Sakarya Training and Research Hospital were retrospectively analyzed. The study included 114 patients who met the criteria. Patients excluded from the study were those who received radiotherapy with palliative or definitive intent and those with incomplete data This study was approved by Sakarya University Institutional Review Board (E-71522473-050.01.04-241720-167)

Demographic characteristics and age of the patients, myometrial invasion depth of the tumor, lymphovascular space invasion and tumor size, RT technique and doses were analyzed. Outcomes were overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS), cancer-specific survival (CSS) and distant metastasis-free survival (DMFS).

Patient and Tumor Characteristics

In total, one hundred fourteen patients were included. Ninety-nine patients (86.8%) were with endometrioid type histology. Sixty-six patients (57.9%) were at Stage I (29 in Stage IA and 37 in Stage IB), 25 patients (21.9%) were in Stage II and 23 patients (20.2%) were at Stage III (six in Stage IIIA, one in Stage IIIB, seven in Stage IIIC1 and nine in Stage IIIC2). The patient and tumor characteristics are shown in Table 1.

Surgery

Ten patients (8.8%) underwent TAH and BSO without lymphadenectomy, 33 patients (28.9%) underwent pelvic lymphadenectomy in addition to TAH and BSO and 71 patients (62.3%) underwent pelvic and para-aortic lymphadenectomy and peritoneal washing in addition to TAH and BSO.

Table 1. The patient and tumor characteristics	
Characteristics	**Number of patients (%)**
Age, years (median, range)	64 (30-81)
<60	38 (33.3)
60-70	44 (37.7)
>70	32 (30)
Histology	
Endometrioid	99 (86.8)
Non-endometrioid	15 (13.2)
Grade	
Grade1-2	75 (65.8)
Grade3	34 (29.8)
Unknown	5 (4.4)
Tumor Size, cm (median, range)	5 (1-11)
Lymphovascular space invasion	
Yes	33 (29)
No	65 (57)
Unknown	16 (14)
Stage	
I	66 (57.9)
II	25 (21.9)
III	23 (20.2)
Lymph node presence	
Positive	14 (12.3)
Negative	100 (87.7)

Radiotherapy

Planning CT scans of the patients were taken in a 2.5 mm section thickness, in the supine position. RT was performed using the three-dimensional conformal radiotherapy (3D-CRT) or volümetric-modulated arc therapy (VMAT) technique for all patients. EBRT was given at a dose of 50.4 Gy in 1.8 Gy fractions in 29 patients (25.4%), 45 Gy in 1.8 Gy fractions in 83 patients (72.8%) and 46 Gy in 2 Gy fractions in 2 patients (2%). The median total dose of radiotherapy was 45 Gy and the median fraction size was 1.8 Gy. Nine patients (7.9%) with para-aortic lymph node metastases were also irradiated to the para-aortic field. After EBRT, HDR brachytherapy was applied to the vaginal cuff in 87 patients (76.3%). For brachytherapy, the dose was 5 to 7 Gy (median, 6 Gy) administered in 2 to 4 fractions (median, 3 fractions).

Chemotherapy

Chemotherapy was administered to 28 patients (24.6%) with stage 3 disease or non-endometrioid histology. Chemotherapy was administered as 6 cycles of paclitaxel and carboplatin before radiotherapy.

Statistical Analysis

Statistical analysis was performed by using the SPSS 21.0 software package. Survival analysis was performed using the Kaplan and Meier method. Univariate analysis was performed using the log-rank test. OS, DFS, LRFS, CSS and DMFS were calculated starting from the date of the biopsy. $p < 0.05$ was considered statistically significant.

Follow-up

Patients were followed up with general clinical examination, pelvic examination, laboratory tests, and imaging studies every 3 to 6 months in the first two years of their follow-up, and every 6 to 12 months thereafter.

RESULTS

Median follow-up was 63 months (8 -135). The median age was 64 years (30 to 81 years). Tumor size, histology, age, presence of lymph nodes, tumor grade, LVSI, myometrial invasion depth, tumor localization, and chemotherapy application were analyzed by univariate analysis in terms of OS, DFS, LRFS, CSS, DMFS. Statistically significant data are shown in Table 2.

Outcome and pattern of failure

At the last control, 90 patients (78.9%) were alive, 24 patients (21.1%) died (8 patients (7%) died due to endometrial cancer). Local recurrence was observed in 2 patients (1.8%) and distant metastases were observed in 11 patients (9.6%). The most common isolated organ metastasis was lung metastasis in 3 patients (27.3%) and liver metastasis in 3 patients (27.3%). Other organ metastases were present in 5 patients (37.2%).

Table 2. Univariate analysis affecting OS, DFS, LRFS, DMFS, and CSS

Patient characteristics	OS	DFS	LRFS	DMFS	CSS
	Univariate analysis	Univariate analysis	Univariate analysis	Univariate analysis	Univariate analysis
	p	p	p	p	p
Histology	0.688	0.657	0.031	0.518	0.848
Grade	0.194	0.669	0.010	0.642	0.525
LVSI	0.766	0.019	0.518	0.019	0.021
Stage	0.246	0.007	0.049	0.020	0.135

LVSI, lymphovascular space invasion; OS, overall survival; DFS, disease-free survival; LRFS, local recurrence-free survival, CSS, cancer-specific survival; DMFS, distant metastasis-free survival.

Overall Survival and Disease-Free Survival

For all patients, the OS at 5 years was 85.5% and the DFS at 5 years 90.5%. 5-year OS and DFS patients are shown in Figure 1.

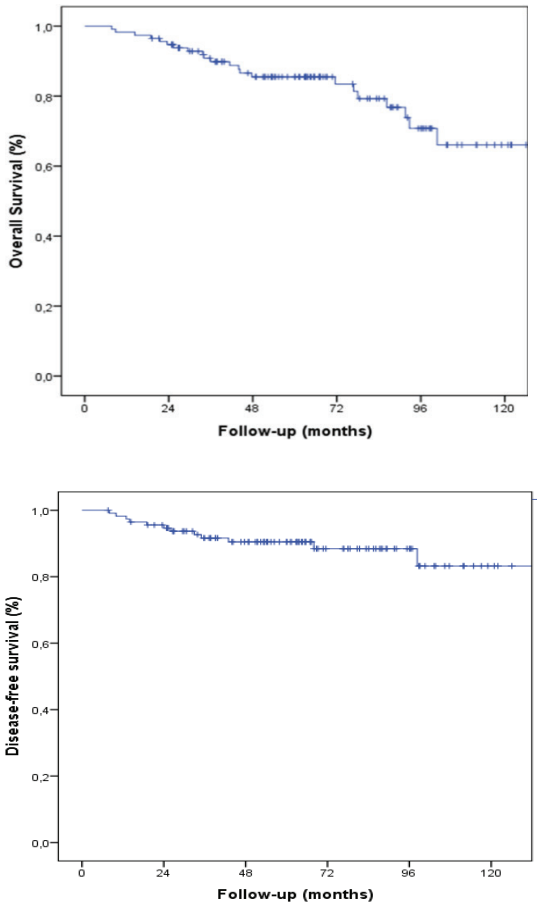

Figure 1: Overall survival and disease-free survival at 5 years

When the univariate analysis of tumor size, histology, age, presence of lymph nodes, tumor grade, LVSI, myometrial invasion depth, tumor localization, and chemotherapy application is examined in terms of OS and DFS; there wasn't any significant relationship with these factors for OS. There was a significant relationship between LVSI and stage, for DFS (respectively p=0.019 and 0.007); there was no significant relationship between histology, and grade. (Respectively p=0.657, 0.669).

Local Relapse-Free Survival, Cancer-Specific Survival, and Distant Metastasis-Free Survival

The LRFS for all patients at 5 years was 98.9%, the CSS at 5 years were and 94.1% and the DMSF at 5 years was and 90.5%.

When the univariate analysis of tumor size, histology, age, presence of lymph nodes, tumor grade, LVSI, myometrial invasion depth, tumor localization, and chemotherapy application is examined in terms of LRFS and CSS, DMFS; histology, tumor grade, stage was statistically significant prognostic factor for LRFS, (respectively p=0.031, p=0.010, p=0.049). LVSI was statistically significant for DMFS and CSS, (respectively p=0.019, p=0.021).

Toxicity

Acute Toxicity

Acute gastrointestinal toxicity was observed in 50 patients (35.1%). Grade 1 and 2 acute gastrointestinal toxicity were observed in 36 patients (31.6%) and 4 patients (3.5%), res-

pectively. Grade 1 acute genitourinary toxicity was observed in 35 patients (30.7%).

Late Toxicity

Grade 1-2 late gastrointestinal toxicity was observed in 6 patients (5.3%). Grade 3 late toxicity was observed as 0.9% genitourinary and 1.8% gastrointestinal.

DISCUSSION

We retrospectively reviewed single-center data of EC patients who underwent adjuvant RT and analyzed data on survival outcomes, pattern of failure, and treatment-related toxicities of patients.

Many studies, in EC; showed that age, stage, histology, tumor grade, lymphovascular involvement, and myometrial invasion are important prognostic factors.[9-11] Two important nomograms are available to predict survival. The first consists of five criteria: age at diagnosis, negative lymph nodes, FIGO stage, final histological grade, and histological subtype.[12] Secondly, age, tumor grade, and lymphovascular area involvement were shown to be highly predictive in the PORTEC 1 and PORTEC 2 trials.[13] Similarly, in this study, we found that histology, LVSI, grade, and stage for endometrial cancer adversely affect survival. However, we could not find a significant effect of age and myometrial invasion on survival. When evaluated according to histological type, in studies conducted that the endometrioid type has a better prognosis. The non-endometrioid types are more aggressive.[14,15] In our study, endometrioid histology was more common (86.8%), which supports the literature, and non-endometrioid histopathology was statistically significant for LRFS as a poor prognostic factor. (p=0.031).

In studies conducted, the rate of LVSI varies between 12% and 34%.[16-18] The presence of vascular invasion has been a strong prognostic factor in studies of various malignant tumors, including endometrial carcinoma. Vascular invasion is considered an early step in the metastatic process and is important for the progression of malignant tumors.[19] Rasool et al. examined 176 patients with endometrial cancer and found that LVSI was not predictive of recurrence or poor outcome.[20] In contrast, Gaducci et al. found that LVSI was associated with distant, hematogenous insufficiency.[21] Similarly, in our study, the rate of LVSI was 28.9%, and DFS and CSS were found to be significantly lower in patients with LVSI involvement, respectively (p=0.019, p=0.021).

A three-tiered grading system (as suggested by FIGO) was used to evaluate tumor grade, where the solid growth pattern was up to 5% for Grade 1 tumors, 6 to 50% for Grade 2 tumors, and more than 50% for Grade 3 tumors. Grade 1 and 2 tumors are usually classified as low grade and fall under the type I classification and typically have a good prognosis; grade 3 tumors are classified as high grade and fall under the type II classification and tend to be more aggressive with a poorer prognosis.[22] In our study, grade 1-2 tumors were seen in 65.8% and grade 3 tumors in 29.8%. Supporting the literature, grade 3 tumors as a poor prognostic factor were found to be statistically significant in terms of LRFS (p=0.010).

5-year overall survival in EC by FIGO surgical stage; IA(90.3%), IB (80.85%), II (80.5%), IIIA (68.5%), IIIB (53.1%), IIIC1 (58.3%), IIIC2 (51.2%, IVA (22%) and IVB (21.1%).[23] In our study, 5-year OS stage I (88.2%), stage II (92.4%) and stage III (67.6%) (p=0.246), 5-year CSS, stage I (98.8%), stage II (92.4%) and stage III (86.9%), (p=0.135), 5-year DFS and DMFS, stage I (96.8%), stage II (81%) and stage III (83%), (p=0.007, p=0.020), respectively, 5-year LRFS, stage I (100%), stage II (95.8%) and stage III (100%), (p=0.049). In our study, OS and CSS were higher in stage II patients compared to stage III patients, while LRFS, DFS, and DMFS were significantly lower, unlike the literature. According to our results, the presence of a tumor invading the stromal connective tissue of the cervix can be considered as a poor prognostic factor in terms of distant metastasis and local recurrence. Ferriss JS et al. found that deep cervical stromal invasion was an independent predictor of

death in stage II endometrial cancers.[24] When a subgroup analysis is performed for stage III, it can be understood whether this difference is due to lymph node involvement or neighboring organ invasion. However, subgroup analysis could not be performed due to the small number of stage 3 patients in our study.

Overall, randomized prospective studies have not demonstrated OS benefit, although adjuvant RT can significantly reduce the risk of local recurrence for early-stage endometrial cancer. Because of the high risk of death from comorbidities in this elderly population, most trials were not powered for OS. Acute side effects of adjuvant radiotherapy may include fatigue, cystitis, diarrhea, skin irritation, and vaginitis.[25] In addition, adjuvant therapy for the whole pelvis may be associated with toxicities such as urinary incontinence and fecal leakage, adversely affecting long-term quality of life.[26] In our study, similar to the literature, 5-year OS was lower than CSS, DFS, LRFS, and DMFS, respectively. (85.5%, 94.1%. 90.5%, 98.9%, and 90.5%). In our study, Grade 1 and 2 acute gastrointestinal toxicity was observed in 40 patients (35.1%), and Grade 1 acute genitourinary toxicity was observed in 35 patients (30.7%). Grade 3 late toxicity was observed in 0.9% genitourinary and 1.8% gastrointestinal.

Our study has some limitations. Most importantly, it is a retrospective study. It also includes all stages and histopathology of endometrial cancer. In addition, our study's small number of patients didn't allow us to perform subgroup analysis. The results of clinical studies with larger patient groups will contribute to the creation of the most appropriate multidisciplinary strategy according to histological subtype and stage.

CONCLUSION

OS was lower than CSS in patients with endometrial cancer due to comorbidities, and there was no significant result in terms of risk factors in univariate analysis. However, the presence of LVSI was found to be a poor prognostic factor for CSS in univariate analysis. Treatment-related toxicity was tolerable and the grade 3 toxicity rate was very low. This study demonstrated that adjuvant RT is a safe and effective treatment option for patients with endometrial cancer.

Conflict of Interest

There is no conflict of interest to declare for this paper.

Authorship contributions: Concept –HH, SGA; Design – HH, SGA; Data collection and/or processing – HH; Data analysis and/or interpretation – HH, SGA; Literature search – HH, SGA; Writing – HH, SGA; Critical review – HH, SGA.

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