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Chemotherapy plus radiotherapy *vs.* radiotherapy alone in high-risk endometrioid endometrial carcinoma

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Abstract. – OBJECTIVE: Adding chemotherapy to radiotherapy in patients with high-risk endometrioid endometrial cancer (EEC) remains controversial, particularly in stages I-II. We aimed to investigate the effect of treatment modalities on survival in high-risk EEC patients.

PATIENTS AND METHODS: Patients with high-risk EEC were evaluated retrospectively between 2010 and 2019. Patients who did not receive adjuvant treatment were excluded. We included seventy patients and formed two groups: patients who received radiotherapy (RT) alone and those who received chemotherapy and radiotherapy (CT and RT).

RESULTS: The median follow-up time was 60.3 months (8.0-143.5). 38.5% of the patients had relapsed. Recurrence-free survival (RFS) rates were 97. 1%, 68.3% , and 60.8% at 12-, 36-, and 60-month, respectively. Overall survival rates were 97.1%, 80.6%, and 72.6% at 12-, 36-, and 60-month, respectively. Hematological adverse events and neuropathy were more common in the CT and RT group than in the RT group. Multivariate Cox regression analysis for RFS revealed that the FIGO stage and treatment modalities were statistically independent factors (p=0.031 and p=0.040, respectively). Stage stratified log-rank test revealed that adding chemotherapy improved RFS in patients with stage III (p=0.020) but not in stage I-II disease (p=0.725). The number of chemotherapy cycles administered (≤4 *vs.* >4) did not affect survival in all patients and stage III disease (p=0.497, and p=0.436, respectively).

CONCLUSIONS: Adding chemotherapy to radiotherapy may be considered in high-risk stage III EEC. Further studies are needed to determine the optimal duration of chemotherapy.

Key Words:
High-risk endometrioid endometrial carcinoma, Chemotherapy, Radiotherapy, Survival.

Introduction

Endometrial cancer (EC) is the most common malignancy originating in female genital system accounting for 7% of new female cancer cases in the United States[1], and it is the second most common gynecological malignancy worldwide, considering both resource-abundant and resource-limited countries[2]. The incidence of EC is increasing due to various factors, such as the increasing prevalence of diabetes, obesity, and nulliparity[3-5]. More than 90% of EC cases occur in women over 50, and patients often suffer uterine bleeding[6,7]. More than two-thirds of patients with ECs have localized disease at diagnosis and a 5-year survival rate of over 95%[8]; however, patients representing advanced disease or distant metastasis have 5-year survival rates of about 69% and 18%, respectively[1]. Endometrioid EC (EEC) accounts for more than 75% EC cases[9].

External pelvic beam radiation therapy (EBRT) has been used to treat patients with high-risk EC for decades. Clinical studies comparing adjuvant chemotherapy to external beam radiation therapy alone found no difference in survival[10,11]. Due to the high risk of pelvic or distant recurrence with unimodal treatments, trials studying the efficacy of combining chemotherapy and radiotherapy were initiated in patients with different risk groups[12,13]. In 2016, a

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consensus conference proposed new risk groups for EC to guide adjuvant therapy use[14]. This consensus report recommended adding chemotherapy to EBRT for high-risk EEC, particularly patients without surgical nodal staging. Similarly, the National Comprehensive Cancer Network (NCCN) uterine cancer guideline recommended adjuvant EBRT and/or vaginal brachytherapy ± systemic chemotherapy for high-risk the International Federation of Gynecology and Obstetrics (FIGO) stage 1-3 EEC[15].

The addition of chemotherapy to radiotherapy in high-risk EC has been investigated in various randomized control trials[16-18]. However, although EEC has favorable survival outcomes compared to other histotypes, such as serous cancers, these studies evaluated all patients with different histotypes together. Therefore, it remains unclear whether the addition of chemotherapy improves survival in patients with EEC. Thus, we aimed to investigate the effect of treatment modalities on survival in real-life experiences in high-risk EEC patients.

Patients and Methods

Study Population and Data Collection

We designed the study in 2020; therefore, we used high-risk criteria in the consensus report in 2016: FIGO stage 1 grade 3 with myometrial invasion ≥1/2, and stage 2-3 disease for EECs[14]. Inclusion criteria were: ≥18 years old, high-risk stage 1-3 EEC, followed up in Bursa Uludag University Faculty of Medicine (Bursa, Turkey) between 2010 and 2019. Patients with low and intermediate-risk EEC, non-endometrioid EC, stage IV disease, missing clinical data, a history of heart failure, renal failure, liver failure, hormonal therapy, and patient without optimal surgical procedures were excluded from the study. Patients who received < 3 cycles of carboplatin and paclitaxel or other chemotherapy regimens were also excluded. Figure 1 demonstrates the patients' selection diagram. We retrospectively collected data about patients' demographic characteristics, type of surgical procedure, histopathological features, adjuvant treatment modalities, and attributes of patients with recurrence from the electronic records of our center. We used the final pathology reports of the patients for histopathological features.

Surgical Procedure and Adjuvant Treatment

In our institution, EC is treated surgically with a complete hysterectomy and bilateral salpingo-oophorectomy. Pelvic and paraaortic lymphadenectomy is performed in patients with grade 3 histology, cervical invasion, myometrial invasion ≥ 50%, and tumor size > 2 cm. Brachytherapy was delivered to all patients with stage 1B grade 3, stage 2, and stage 3 EEC. External radiotherapy was planned for the primary tumor site and pelvic lymph nodes with a total dose of 45 -50 gray (Gy) (1.8 Gy per fraction). Patients were irradiated by high dose rate (HDR) brachytherapy using an Ir192 source. Prescribed

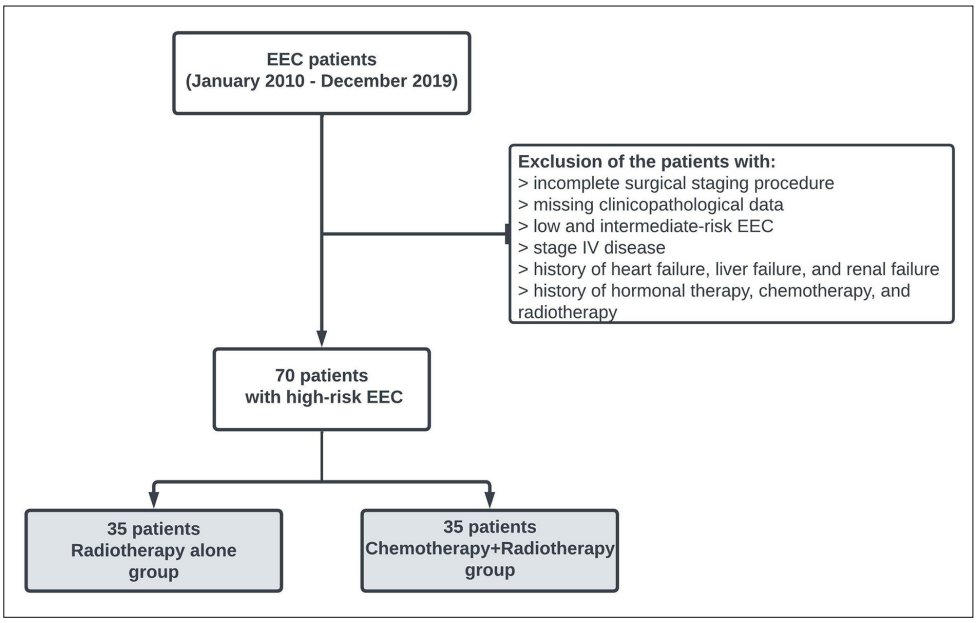

Figure 1. Patients flow diagram.

isodose was delivered to the upper 1/3 part of the vaginal mucosa at a depth of 5 mm. The dose was also calculated at the ICRU (International Commission on Radiation Units and Measurements) of the bladder and rectum, and the maximum dose in the vaginal mucosa. A total dose of 18-21 Gy with a fraction dose of 6-7 Gy was delivered to all patients. EEC patients in the chemotherapy and radiotherapy (CT and RT) group received adjuvant chemotherapy before or after (or both before and after) radiotherapy. Patients received intravenous carboplatin at a dose of 5 or 6 area under the curve and intravenous paclitaxel at a dose of 175 mg/m2 every 21 days for 4-6 cycles. Adjuvant therapy was initiated within four to eight weeks after surgery.

Outcomes

Recurrence-free survival (RFS) was defined as the time between the date of surgical staging and the date of (histologically or radiologically confirmed) recurrence or the date of death, irrespective of the cause. Overall survival (OS) was determined from the time of diagnosis until death for any reason. Adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0[19].

Statistical Analysis

Statistical analyses were performed using SPSS software Version 25.0 (IBM Corp., Armonk, NY, USA) . The Shapiro-Wilk test was used to assess whether the variables followed a normal distribution. Variables were reported as median (minimum-maximum) values and frequency values. According to the normality test results, Mann-Whitney's U test was used to compare the groups. Categorical variables were compared using the Chi-square test and Fisher's exact test. Kaplan-Meier analysis was employed for survival rates with comparisons made with the log-rank test. Multivariate Cox regression analysis for possible factors affecting RFS was performed using enter method with parameters with a p-value <0.25. A p-value of <0.05 was considered statistically significant.

Results

Postoperatively, 35 (50.0%) patients received radiotherapy alone, and 35 (50.0%) patients were treated with chemotherapy and radiotherapy. Table I shows the clinicopathological characteristics of the two groups. There was no significant difference between the two groups in other parameters except for the stage. The number of stage III patients was statistically significantly higher in the CT and RT group than in the radiotherapy alone (RT) group (p<0.001). The median number of chemotherapy cycles was 5 (range, 3-6). Table II shows adverse events observed during treatment for both groups. Hematological adverse events, including anemia, neutropenia, and thrombocytopenia, were both groups' most common adverse events. Hematological adverse events and neuropathy were significantly more common in the CT and RT group compared to the RT group (p<0.001, p=0.017, respectively). No chemotherapy or radiotherapy-related deaths or adverse events precluded further therapy were observed.

During a median follow-up time of 60.3 months (range 8.0-143.5), 27 (38.5%) patients had recurrences: 16 (45.7%) in the RT group, and 11 (31.4%) in the CT and RT group. Table III displays the recurrence sites of the patients. The patients who presented with distant recurrence were more common in the RT group but not statistically significant (p=0.192). RFS rates for all patients were 97.1%, 68.3%, and 60.8% at 12-, 36-, and 60-month, respectively. OS rates for all patients were 97.1%, 80.6%, and 72.6% at 12-, 36-, and 60-month, respectively.

The univariate and multivariate Cox regression analysis revealed that FIGO stage [hazard ratio (HR), 2.779; 95% confidence interval (CI), 1.096-7.046; p=0.031] and treatment modality (HR, 0.414; 95% CI, 0.178-0.959, p=0.040) were independent factors affecting RFS (Table IV). Due to the heterogeneous distribution for stage, further subgroup analyses were performed. In stage IB and II EEC, RFS rates were not different between treatment groups (p=0.725) (Figure 2A). However, in stage III disease, RFS was significantly longer in patients receiving chemotherapy and radiotherapy compared to those who received radiotherapy alone (p=0.020) (Figure 2B). Furthermore, statistically significant differences were not observed in RFS between patients receiving ≤4 cycles and >4 cycles of chemotherapy in all patients and patients with stage III EEC in the CT and RT group (p=0.497, p=0.436, respectively).

Discussion

Our study is a real-life data analysis comparing adjuvant chemotherapy and radiotherapy to radiotherapy alone in high-risk EEC patients. According

Table I. Clinicopathological features in the radiotherapy alone and chemotherapy and radiotherapy groups.

Characteristic		RT alone N = 35 (%)	CT&RT N = 35 (%)	*p*-value
Age	(Median) (Range, years)	62 (44-84)	60 (35-75)	0.506
ECOG PS	0 1/2	22 (62.8) 13 (37.2)	25 (71.5) 10 (28.5)	0.611
BMI	(Median) (Range, kg/m^2)	35.1 (23.1-44.9)	35.1 (20.4-68.5)	0.896
Parity	Nulliparous Parity ≥ 1	5 (14.3) 30 (85.7)	6 (17.1) 29 (82.9)	0.743
Surgery	TH & LD TH & LD + Omx	22 (62.8) 13(37.2)	19 (54.2) 16(45.8)	0.627
Stage	IB-II III	20 (57.1) 15(42.9)	5 (14.3) 30 (85.7)	**< 0.001**
Tumor size	(Median) (Range, cm)	4.0 (2.0-9.0)	4.0 (1.5-6.5)	0.972
Grade	1 & 2 3	20 (57.1) 15 (42.9)	26 (74.3) 9 (25.7)	0.208
MI	< 1/2 ≥ 1/2	10 (28.5) 25 (71.5)	13 (37.1) 22 (62.9)	0.611
LUSI	Absent Present	18 (51.4) 17(48.6)	18 (51.4) 17 (48.6)	1.00
LVSI	Absent Present	20 (57.1) 15 (42.9)	20 (57.1) 15 (42.9)	1.00

ECOG PS, Eastern Cooperative Oncology Group Performance Status, BMI, Body Mass Index; TH&LD, Total Hysterectomy, and Bilateral Pelvic Paroaortic Lymph Node Dissection; Omx, omentectomy; MI, Myometrial Invasion; LUSI, Lower Uterine Segment Involvement; LVSI, Lymphovascular Involvement. The bold front indicates a statistically significant difference.

to our findings, adding chemotherapy to radiotherapy provided a statistically significant survival benefit in patients with stage III EEC but not in high-risk stage IB-II EEC, supporting that chemotherapy is a rational treatment option for stage III disease.

In various randomized controlled trials (RCT), high-risk EC patients with endometrioid and non-endometrioid histology were evaluated, although their clinical courses were different[11,16-18,20,21]. In a pooled analysis of two ran-

Table II. Adverse events for both groups.

Adverse effects	RT alone		CT & RT		*p*-value
	Any grade N (%)	Grade 3 & 4 N (%)	Any grade N (%)	Grade 3 & 4 N (%)	
Hematological AE	8 (22.9)	2 (5.7)	30 (85.7)	9 (25.7)	**< 0.001**
Anemia	7 (20.0)	2 (5.7)	16 (45.7)	5 (14.3)	-
Thrombocytopenia	2 (5.7)	-	9 (25.7)	2 (5.7)	-
Neutropenia	1 (2.9)	-	10 (28.6)	4 (11.4)	-
Liver enzyme elevation	2 (5.7)	-	5 (14.3)	1 (2.9)	0.428
Acute kidney injury	1 (2.9)	-	2 (5.7)	-	1.000
Nausea/Vomiting	5 (14.3)	-	11 (31.4)	3 (8.6)	0.155
Neuropathy	1 (2.9)	-	9 (25.7)	2 (5.7)	**0.017**
Diarrhea	7 (20.0)	1 (2.9)	10 (28.6)	2 (5.7)	0.577
Dermatitis	3 (8.6)	-	2 (5.7)	-	1.000

**p*-values were calculated for any grade adverse events. The bold front indicates a statistically significant difference.

Table III. Recurrence sites after treatment modalities.

Recurrence sites	RT alone N (%)	CT & RT N (%)	*p*-value
Local	**3 (8.6)**	**3 (8.6)**	**1.000**
Vaginal	1 (2.9)	1 (2.9)	
Regional lymph nodes	2 (5.7)	2 (5.7)	
Distant	**13 (37.1)**	**8 (22.9)**	**0.192**
Abdominal cavity	4 (11.4)	4 (11.4)	
Distant lymph nodes	4 (11.4)	1 (2.9)	
Viscera & bone	5 (14.3)	3 (8.6)	

Table IV. Cox PH regression model estimates for the risk of clinical recurrence.

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age years	1.029	0.984-1.077	0.209	1.025	0.979-1.074	0.295
ECOG PS (R) *vs.* 1 & 2	1.058	0.490-2.283	0.886			
BMI kg/m²	0.978	0.909-1.052	0.544			
Parity nulliparous (R) *vs.* Parity ≥ 1	2.126	0.503-8.987	0.305			
Surgery TH&LD (R) *vs.* TH & LD+Omx	1.288	0.602-2.755	0.514			
Tumor size mm	0.917	0.704-1.194	0.520			
Grade 1 & 2 (R) *vs.* 3	1.103	0.495-2.459	0.810			
Myometrial invasion absent (R) *vs.* present	1.327	0.580-3.036	0.502			
LUSI absent (R) *vs.* present	1.309	0.612-2.798	0.487			
LVSI absent (R) *vs.* present	1.123	0.527-2.395	0.763			
FIGO stage IB & II(R) *vs.* III	1.794	0.758-4.247	0.184	2.779	1.096-7.046	**0.031**
Treatment RT (R) *vs.* CT&RT	0.616	0.285-1.329	0.217	0.414	0.178-0.959	**0.040**

ECOG PS, Eastern Cooperative Oncology Group Performance Status, BMI, Body Mass Index; TH&LD, Total Hysterectomy, and Bilateral Pelvic Paroaortic Lymph Node Dissection; Omx, omentectomy; LUSI, Lower Uterine Segment Involvement; LVSI, Lymphovascular Involvement. *Cox regression model is statistically significant (p=0.035). The bold front indicates a statistically significant difference.

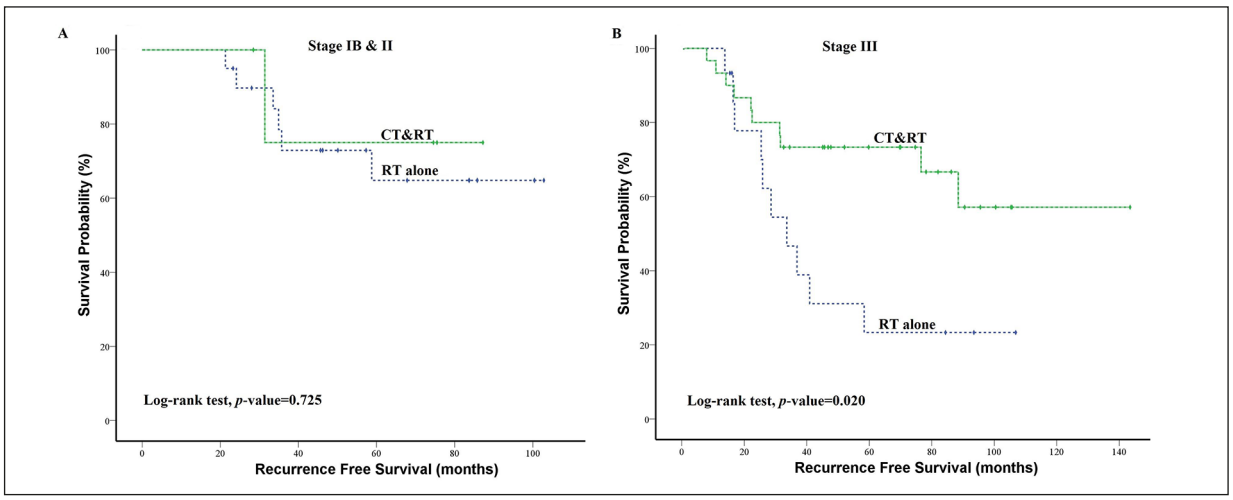

Figure 2. Kaplan-Meier curves of recurrence-free survival according to the treatments in patients with FIGO stage IB and II (**A**) and FIGO stage III disease (**B**).

domized trials, the addition of chemotherapy to radiotherapy in patients with stage high-risk I-III EC was reported to prolong progression-free survival (PFS) but not OS compared to radiotherapy alone[16]. In subgroup analysis, survival benefit in PFS was also observed in patients with EEC, but stratified analysis considering stages in this group was not reported. The PORTEC-3 is one of the most noteworthy trials comparing adjuvant therapies in patients with high-risk endometrial cancer[18]. This study's updated post-hoc survival analysis reported that treatment with chemoradiation improved failure-free survival (FFS) and OS, with the most significant benefit for the addition of chemotherapy seen in patients with stage III disease or serous cancers[22]. In patients with stage I-II EC and patients with non-serous histologies, adding chemotherapy was noted not to improve survival outcomes. However, the results of patients with stage III EEC were not reported. A meta-analysis including RCTs studying adding chemotherapy to radiotherapy versus radiotherapy alone in patients with high-risk stage I-II EC revealed that chemo-radiotherapy has no survival benefit over radiotherapy alone in terms of overall survival and failure-free survival[23]. Subgroup analysis for patients with EEC was not reported. Considering the overmentioned trials' results, it remains unclear whether adding chemotherapy to radiotherapy provides survival benefits in patients with the endometrioid subtype in all stages.

To our knowledge, there are limited retrospective studies regarding high-risk EEC in the literature. Van Weelden et al[24] reported that chemotherapy and radiotherapy improved survival compared with chemotherapy or radiotherapy alone in patients with stage III EEC, supporting our findings. Son et al[25] published a multicenter retrospective study including high-risk stage I-II EEC patients. They proclaimed that although administering adjuvant treatments (EBRT, brachytherapy, or chemotherapy) improved PFS and OS compared to observation, adding chemotherapy to radiotherapy did not provide any survival benefits in this population, supporting our findings. In addition to these studies, three large-scale National Cancer Database (NCDB) analyses[26-28] have been reported. In 2017, NCDB analysis of stage II EEC patients revealed that adding chemotherapy was not associated with OS advantage after propensity score matching[26]. In 2021, another NCDB research, including 1,120 stage III EEC patients, found that patients with lymphovascular space invasion had improved OS with chemotherapy and radiation compared to radiation alone[27]. Recently, Nasioudis et al[28] reported an NCDB analysis of stage I EEC patients claiming that the addition of chemotherapy did not improve survival in patients who received EBRT. Although radiotherapy administration and chemotherapy regimens were not reported in detail, and RFS analysis was not performed in the overmentioned NCDB analyses, these reports support that adding chemotherapy to radiotherapy may improve survival in stage III EEC, not in stage I and II disease. The prognostic groups were updated by changing stage IB and II EEC from the high-risk group to the high-intermediate risk group in ESGO/ESTRO/ESP guideline recommending chemotherapy not to be administered routinely in this group, which is consistent with our results[29].

In endometrial cancer, it has been reported that clinical characteristics such as age, body mass index, and histopathological features such as grade, ki67, lymphovascular invasion, ER receptor status, and squamous differentiation have prognostic values[8,30-33]. However, it was noted that only the FIGO stage and histotype might predict the benefit of chemotherapy in patients receiving adjuvant treatment and help the clinician in this sense[22,34,35].

Various chemotherapy schedules[36,37] were studied, including sequential or concurrent radiotherapy in RCTs in endometrial cancer, but optimal cycles of adjuvant chemotherapy were not determined[38]. Although Kim et al[39] claimed that $\geq$ 6 cycles of chemotherapy might be more beneficial than 3-5 cycles of chemotherapy for high-risk EEC patients, Mayama et al[40] reported that no statistical difference was found in terms of OS and RFS between patients receiving four cycles and those receiving six cycles of chemotherapy, consistent with our findings. We did not observe any treatment-related deaths or adverse events hindering further therapy. Although hematological adverse events and neuropathy were more common in the CR and RT group, adding chemotherapy appears to be a tolerable and manageable treatment option, as found in the PORTEC 3 trial[18]. RCTs and large-scale cohorts are needed to clarify the optimal duration of chemotherapy to decrease chemotherapy-related toxicity, particularly in patients receiving multimodal treatment.

The analysis of the molecular classification in the PORTEC 3 trial revealed that the molecular type of EC had substantial prognostic value and could predict the benefit of adjuvant therapy[41]. According to the molecular classification, EC is classified into four groups: POLE ultramutated, MSI hypermutated, copy-number low, and copy-number high. In

2020, the ESGO/ESTRO/ESP guideline presented a new prognostic risk group by integrating molecular classification[29]. The results of the ongoing PORTEC 4a trial may reveal how the molecular-integrated risk profile will affect our clinical approach[42].

The strengths of our study are that all patients received EBRT and brachytherapy, and those in the CT and RT group received at least three cycles of a standard chemotherapy regimen (carboplatin and paclitaxel), allowing comparison of the addition of chemotherapy to the treatment.

Limitations

On the other hand, our study had some limitations: a retrospective design, limited representation of stage I and II patients receiving chemotherapy, and inability to perform molecular profiling and OS analyses due to insufficient death. Although the integrated genomic-pathologic classification of EC is prognostic and predictive value, it is still not available in all centers, particularly in low and middle-income countries, as our center. Therefore, the updated consensus report also defined prognostic risk groups for patients with unknown molecular analysis[29].

Conclusions

Adding adjuvant chemotherapy to radiotherapy improved survival in high-risk stage III EEC patients. However, we did not observe any survival benefit in stage I-II disease. Chemotherapy may be considered in high-risk stage III EEC. Further studies are needed to determine the optimal duration of chemotherapy to avoid chemotherapy-related toxicities.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

A. B. Sahin and B. Ocak designed and managed the study. A. B. Sahin, B. Ocak, C.D. Abakay, B. Dakiki, B. Caner, and G. Islek extracted the data. A. B. Sahin and B. Ocak performed the analyses and wrote the manuscript. T. Evrensel, E. Cubukcu, and K. Ozerkan made contributions to the interpretation of data. C.D. Abakay, K. Ozerkan, A. Deligonul, B. Caner, B. Dakiki, and G. Islek provided comments on manuscript drafts. E. Cubukcu and T. Evrensel revised the article. All authors agreed to be accountable for the work.

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Availability of Data

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

Our studies followed the ethical guidelines established by the Institutional Research Committee and the Helsinki Declaration of 1964. The study was accepted by the Bursa Uludag University Faculty of Medicine (Approval number: 2021-5/21).

Informed Consent

Not applicable.

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