North Clin Istanb 2021;8(4):345–353
doi: 10.14744/nci.2020.47154

Original Article OBSTETRICS & GYNECOLOGY

Prognostic factors of endometrial cancer in elderly patient group and their effects on survival

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ABSTRACT

OBJECTIVE: The objective of the study was to investigate the prognostic factors of the elderly group and their effects on survival by examining the histopathological features, surgical treatment protocols, and treatment modalities of patients diagnosed with endometrial cancer (EC).

METHODS: The records of 397 EC patients who completed their treatment and follow-up at a single center between 2012 and 2019 were evaluated retrospectively. The patients were evaluated in two groups as <70 years old (n: 301; 75.8%) and >70 years old (n: 96; 24.2%). Following the evaluation of histopathological features and treatment protocols, independent risk factors influencing survival were investigated with the Cox regression model.

RESULTS: The incidence of non-endometrioid histology (16.3% vs. 32.3%, p: 0.001), high-grade tumors (50.5% vs. 69.8%; p: 0.001), and >50 myometrial invasion (19.6% vs. 36.5%, p: 0.003) in the >70 age group was more frequent than that in the <70 age group. The independent risk factors on overall survival in the >70 age group were determined as non-endometrioid histology (HR: 5.9; 95% CI: 1.4– 24.7) and lymph node metastasis (HR: 6.4; 95% CI: 1.6–25.0). In the <70 age group, non-endometrioid histology (HR: 11.3; 95% CI: 4.0–32.0) was identified as the only independent risk factor affecting 5-year survival.

CONCLUSION: EC, with non-endometrioid histology, which is observed at a higher rate in elderly patients despite equal surgery and adjuvant therapy, is the primary factor that affects survival.

Keywords: Elderly; endometrial cancer; non-endometrioid; prognosis.

Cite this article as: *Alemdaroglu S, Dogan Durdag G, Yilmaz Baran S, Yuksel Simsek S, Yetkinel S, Alkas Yaginc D, et al. Prognostic factors of endometrial cancer in elderly patient group and their effects on survival. North Clin Istanb 2021;8(4):345–353.*

Endometrial cancer (EC) is the most common gynecological cancer with 61,880 new diagnoses and 12,160 deaths in 2019 [1]. While more than 90% of patients are diagnosed after 50 years of age, the average age of diagnosis is 63 [2]. The 5-year survival rate of the EC, 66.9% of which is diagnosed at the local stage, was 95% at this stage, and the 5-year survival rate was reported as 81.2% when all stages were included [2, 3]. With increasing age, poorer prognosis has been reported in elderly patients with detection of more aggressive tumor histologies and high-grade tumors [4, 5].

The main treatment of EC is surgery. In the surgical approach with a hysterectomy and bilateral salpingo-oophorectomy, lymphadenectomy is recommended for

Received: Noverber 11, 2020 *Accepted:* December 04, 2020 *Online:* January 14, 2021

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high-risk patients [2]. Based on the findings obtained from the final pathological evaluation, patients are evaluated for adjuvant therapy. Adjuvant treatment options are distributed in a wide range such as external radiotherapy (ERT), brachytherapy (BRT), and/or chemotherapy (CT) according to the risk groups stated in the European Society for Medical Oncology (ESMO)-European Society of Gynaecological Oncology (ESGO)-European Society for Radiotherapy and Oncology (ESTRO) consensus report [2]. In EC, which is often associated with obesity, hypertension (HT), and diabetes mellitus and diagnosed at an advanced age, the medical condition of patients is determinative both during primary surgical treatment and adjuvant therapy.

While an increase in the incidence of EC was reported in the aging world population with the increase in life expectancy, it was found that elderly patients could not receive adequate surgical and adjuvant treatment, for both physician-related and patient-related reasons [6–11].

In this study, the histopathological features, surgical treatment protocols, and treatment modalities of elderly EC patients (>70 years old) who had completed surgical and adjuvant treatment at a single reference center were retrospectively analyzed. We aimed to investigate the prognostic factors of the elderly group and their effect on overall survival (OS).

MATERIALS AND METHODS

A total of 411 patients who were operated at our center between 2012 and 2019 with diagnosis of endometrial cancer were retrospectively reviewed using their data processing system records. The patients were examined in two groups as the >70 age group and the <70 age group. In addition, the characteristics of all patients were evaluated as a single group (entire cohort).

The pre-treatment body mass index (BMI: kg/m^2), additional systemic diseases, and smoking status of the patients were examined. Physical and gynecological examinations were performed, and laboratory findings were evaluated. While all patients were evaluated by ultrasonography during their gynecological examinations and later a chest X-ray, distant metastasis research was performed by computed tomography (CT) scan of the thorax and abdomen in high-risk patients.

Patients whose surgery information, pathology results, and follow-up information could not be obtained after diagnosis were excluded from the study.

Highlight key points

- Age is not an obstacle to receiving the necessary surgical and medical treatment in endometrial cancer.
- The incidence of non-endometrioid histology, high-grade tumors, and >50 MI in the >70 age group was more frequent than that in the <70 age group.
- Non-endometrioid histology and lymph node metastasis were determined as independent risk factors in the >70 age group.

Treatment Regimens

Hysterectomy and bilateral salpingo-oophorectomy were performed laparoscopically (LS) on all patients who were considered to be preoperatively on an early stage and did not present with distant organ metastasis, except for patients with a severe cardiopulmonary disease, which prevented them from remaining in the Trendelenburg position over a long period of time and patients whose uteri were too large to be removed from the vaginal route intact. The surgical procedure of the patients presented with advanced disease in the pre-operative evaluation was performed laparotomically (LT). Patients with endometrioid histology and lymphadenectomy were not performed in Stage 1–2 patients with a tumor diameter of smaller than 2 cm and <50% myometrial invasion (MI). All patients with non-endometrioid histology underwent bilateral pelvic paraaortic lymph node dissection (BPPLND). All surgical procedures were performed by the same gynecological oncology team.

At the end of the primary surgery, within the final pathological evaluation, histological type, grade, tumor diameter, lymphovascular invasion (LVSI), cervical glandular/stromal invasion, MI ratio (≤1/2, >1/2), pelvic and para-aortic lymph node metastasis rates, and the total number of removed lymph nodes were evaluated. Surgical staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 guidelines. The adjuvant treatment and follow-up decision of all patients was made by the multidisciplinary team according to the ESMO-ESGO-ESTRO consensus report by making a risk classification of the patients [2]. Accordingly, adjuvant radiotherapy (RT) and/or CT (carboplatin AUC 6–7.5 IV/paclitaxel 175 mg/m^2 IV, 6 cycles) was recommended for moderate-, moderate-high-, and high-risk patients. RT was performed as external pelvic RT±BRT. The order of treatment was customized according to the pathological and medical characteristics of the patients who needed adjuvant sandwich treatment.

Clinical Follow-up

Post-treatment follow-up of the patients was carried out at 3-month intervals during the first 2 years, at 6-month intervals between 2 and 4 years, and later, annually. In all follow-up visits, a complete physical examination, a detailed gynecological examination, and a complete blood count were performed. Imaging methods were performed when necessary. A biopsy was performed in suspicious cases.

The patients treated and followed by a multidisciplinary team.

This study was approved by the Baskent University Institutional Review Board on March 17, 2020 (Project no: KA 20/108).

Statistical Analysis

Statistical analysis was performed using the SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA). If continuous variables were normally distributed, they were described with mean±standard deviation values ($p>0.05$ in Kolmogorov–Smirnov test or Shapiro–Wilk [($n<30$)], and if the continuous variables were non-normally, they were described with median values. Comparisons between the groups were evaluated using Mann–Whitney U-test. The categorical variables between the groups were analyzed using Chi-squared test or Fisher's exact test. The association of OS was analyzed using the Cox proportional-hazards model. The Cox regression model with stepwise selection was used to identify the variables of the infused cell value. Thereafter, the treatment effect adjusted for these selected variables was calculated. The Cox model was also used to examine the interaction of treatment effect with subgroup status in an exploratory analysis.

RESULTS

Characteristics of the Study Population and Histopathological Results

A total of 397 patients diagnosed with EC who met the inclusion criteria were included in the study. Among these patients, 301 patients (75.8%) were <70 years old, while 96 patients (24.2%) were >70 years old. The median age was 63 (min: 33 and max: 89) in the entire group, 60 (min: 33 and max: 69) in the <70 age group, and 74 (min: 70 and max: 89) in the >70 age group. The most common comorbid disease in the entire group was HT (108 [27.2%]). There was no significant difference between the two subgroups in terms of additional systemic diseases ($p>0.193$). While the mean length of hospital stay was 5 days in all groups, the maximum length of stay was higher in the elderly group (21 vs. 28 days, p: 0.002). Non-endometrioid histology was detected in 20% of the entire group. The incidence of non-endometrioid histology (16.3% vs. 32.3%, p: 0.001), high-grade tumors (50.5% vs. 69.8%; p: 0.001), and >50 MI (19.6% vs. 36.5%, p: 0.003) was higher, and the tumor sizes were larger (3.5 vs. 4 cm; p: 0.026) in the >70 age group in comparison to the <70 age group. There was no significant difference between the groups in terms of LVSI, cervical glandular-stromal invasion, and pelvic and para-aortic lymph node metastases ($p>0.05$). The stages at the time of diagnosis were similar in both groups ($p>0.05$) (Table 1).

Surgical Characteristics and Adjuvant Treatment

About 53% of the patients were operated LT. There was no difference between the elderly group and the young group in terms of the two surgical methods LT versus LS (p: 336), whereas the transition from LS to LT was more common in the elderly group (n: 10 [6.3%] vs. n: 7 [15.9%]; $p<0.05$). In the elderly group, the transition from LS to LT was observed due to intense adhesions in three patients, anatomical variation in one patient, major vascular injury in one patient, and serous histology and common tumoral implants in two patients, while in the young group, it was due to intense adhesion in three patients, major vascular injury in three patients, and widespread tumoral implants in four patients. BPPLND was performed on 90% of the patients, and it was observed that a mean number of 62±24 lymph nodes were removed. There was no significant difference in the lymphadenectomy rates (88.7% vs. 93.8%; p: 0.153) between the two groups nor the number of lymph nodes removed in patients undergoing lymphadenectomy (62±23 vs. 60±26; p: 0.322). When the number of the extracted pelvic and para-aortic lymph nodes was evaluated separately, it was observed that there was no significant difference between the two groups (pelvic lymph node number; <70 age vs. >70 age; 32±11 vs. 30±12; p: 0.165, para-aortic lymph node number (Table 2); <70 age vs. >70 age; 29±14 vs. 26±15; p=0.609).

When the adjuvant treatments were examined individually in the general group, n: 106 (26.7%) patients were observed to receive CT, n: 61 (15.6%) received ERT, and n: 128 (32.7%) were observed to receive BRT.

Table 1. Patient and tumor characteristics

Characteristics	Entire group (n=397)	Age <70 years (n=301, 75.8%)	Age ≥70 years (n=96, 24.2%)	p
Age	63 (33–89)	60 (33–69)	74 (70–89)	0.000
BMI (kg/m^2)	35.2±8.2	34.8±7.9	36.8±9.1	0.246
Comorbidity (%)				
DM	9.8	9.9	11	0.193
HT	27.2	26.5	33	
DM+HT	23.9	22.8	30.8	
Cardiac disease	2.5	3.1	1.1	
KOAH	2.5	2	4.4	
Histology (%)				**0.001**
Endometrioid	79.8	83.7	67.7	
Non-endometrioid	20.2	16.3	32.3	
Tumor size (cm)	3.9 (0–19)	3.5 (0–19)	4 (0–12)	**0.026**
Grade (%)				**0.003**
1	39.8	43.5	28.1	
2–3	55.2	50.5	69.8	
Unknown	5.1	4.6	0.5	
LVSI (%)				0.085
Positive	34.2	31.8	44.2	
Negative	60.2	63.1	51	
Unknown	5.0	5.3	4.2	
Cervical glandular invasion (%)				0.504
Positive	4.8	4.3	6.2	
Negative	91.4	92.4	88.5	
Unknown	3.8	3.3	5.2	
Cervical stromal invasion (%)				0.652
Positive	10.6	10.3	11.5	
Negative	85.6	86.4	83.3	
Unknown	3.8	3.3	5.2	
Myometrial invasion (%)				**0.003**
≤1/2	74.3	78.4	61.4	
>1/2	23.7	19.6	36.5	
Unknown	2.0	2.0	2.1	
Pelvic LN metastasis (%)	12	11.2	14.4	0.419
Para-aortic LN metastasis (%)	10.6	9	15.6	0.081
FIGO stage at diagnosis (%)				0.61
IA	63.5	68.1	49.0	
IB	14.1	12.3	19.8	
II	5.5	5.3	6.2	
IIIA	2.0	1.7	3.1	
IIIB	0.3	0.3	0	
IIIC1	3.5	3.3	4.2	
IIIC2	8.6	7.0	13.5	
IVA	2.5	2.0	4.2	

BMI: Body mass index; DM: Diabetes mellitus; HT: Hypertension; LVSI: Lymphovascular invasion; LN: Lymph node.

TABLE 2. Surgical characteristics and adjuvant treatment

Characteristics	Entire group (n=397)	Age <70 years (n=301, 75.8%)	Age ≥70 years (n=96, 24.2%)	p
Surgical technique (%)				0.336
L/T	53.0	51.7	57.3	
L/S	47	48.3	42.7	
Laparo conversion (%)	8.4	6.3	15.9	**0.041**
Lymphadenectomy (%)	89.9	88.7	93.8	0.153
Total lymph node extracted	59 (46–76)	62±23	60±26	0.322
Adjuvant chemotherapy (%)				**0.008**
(–)	73.3	76.7	62.5	
(+)	26.7	23.3	37.5	
Adjuvant radiotherapy (%)				0.330
(–)	84.4	85.8	80.9	
(+)	15.6	14.4	19.1	
Adjuvant brachytherapy (%)				0.080
(–)	67.3	69.8	59.6	
(+)	32.7	30.2	40.4	

While there was no significant difference in terms of adjuvant RT (ERT and BRT) between the elderly and young groups, more patients were observed to receive adjuvant CT in the >70 age group (n: 36 [37.5%] vs. 70 [23.3%], p: 0.008).

Follow-up and Survival Analysis

The follow-up period of the whole group was 35±24 months, and there was no significant difference between the follow-up times of both groups (<70 age vs. >70 age; 36±25 months vs. 30±23 months; p: 0.51). With the Kaplan–Meier log-rank test, the 5-year OS period was determined as 88.3% for the entire group. It was determined as 76.4% in the >70 age group and 92.4% in the <70 age group (p: 0.0001) (Table 3). During the follow-up period, 30 deaths (7.7%) related to EC occurred. There were 16 deaths in the elderly group (4.1% of the entire group and 17.4% of >70 age group) and 14 deaths in the young group (3.6% of the entire group and 4.7% of <70 age group) (p: 0.000). When the parameters that affect survival were evaluated by univariate analysis, non-endometrioid histology, LVSI, MI, lymph node metastasis, and FIGO staging were observed to be effective on survival in both groups (p<0.005). There was no effect on cervical glandular invasion in the >70 age group, grade cervical stromal/glandular invasion in the <70 age group, and grade 5-year life span (p>0.05) (Table 4). When these factors, which appeared to be effective on survival in the univariate analyses, were evaluated with the Cox regression model, non-endometrioid histology (HR: 5.9; 95% CI: 1.4–24.7) and lymph node metastasis (HR: 6.4; 95% CI: 1.6–25.0) for the >70 age group and non-endometrioid histology (HR: 11.3; 95% CI: 4.0–32.0) for the <70 age group were identified as the independent risk factors affecting 5-year survival (Table 5).

DISCUSSION

In this study, although they were followed up by a multidisciplinary team for endometrial cancer, received similar surgical and adjuvant treatments, and had a similar FIGO stages, the 5-year OS of the patients over the age of 70 was lower than that of the younger group. The independent risk factors determining the OS for the >70 age group were found as lymph node metastasis and non-endometrioid histology.

In the literature, there are studies accepting different age groups between 60 and 75 as the cutoff point for elderly groups [5, 12–14]. As the 2016–2018 data reported by Turkey's statistical agency (Turkish Statistical Institute – TUIK) about life expectancy was 81 years for women, 70 years of age were determined as

Table 3. Survival rates

	Estimate mean[a]	Std. error	95% confidence interval Lower bound	Upper bound	1. year survivor %	3. year survivor %	5. year survivor %	p
OS*	86.8	1.3	84.2	89.5	95.4	90.2	88.3	–
DFS*	86.6	1.5	83.5	89.6	95.6	91.6	89.4	–
Age group								**0.0001**
>70 OS	77.8	3.6	70.8		84.8	93.4	81.2	76.4
<70 OS	89.8	1.3	87.2		92.4	96.0	96.0	92.4

OS: Overall survival; DFS: Disease free survival.

Table 4. Parameters affecting overall survival in univariate analysis

	Entire group (n=397)				Age group <70				Age group ≥70			
Histology												
Endometrioid	98.1	97.0	95.7	**0.0001**	98.0	97.1	96.2	**0.0001**	96.7	94.1	87.8	**0.0001**
Non-endometrioid	83.4	63.2	59.3		83.6	72.6	72.6		83.0	48.6	39.3	
Grade												
I	98.1	95.3	95.3	**0.007**	97.7	95.2	95.2	0.163	95.8	95.8	95.8	**0.045**
II–III	94.6	88.3	83.3		94.5	94.5	90.0		93.2	81.5	74.3	
LVSI												
Positive	97.9	95.5	94.6	**0.0001**	97.3	96.2	95.0	**0.015**	97.7	92.8	92.8	**0.001**
Negative	90.5	82.5	79.5		92.7	88.0	88.0		85.3	71.5	63.7	
Cervical glandular invasion												
Positive	86.9	71.8	47.9	**0.0001**	91.7	91.7	91.7	0.789	100	100	100	0.723
Negative	96.4	93.3	92.1		96.2	94.1	93.2		94.8	84.8	82.7	
Cervical stromal invasion												
Positive	86.0	59.1	55.4	**0.0001**	93.1	84.4	84.4	0.278	62.5	25.0	0.0	**0.0001**
Negative	96.4	93.3	92.1		96.2	94.1	93.2		94.8	84.8	82.7	
Myometrial invasion												
≤1/2	96.2	93.1	90.9	**0.0001**	97.6	97.6	92.2	**0.042**	95.8	91.0	87.2	**0.012**
>1/2	86.7	79.0	75.8		88.0	84.2	84.2		84.3	70.8	63.3	
Lymph node metastasis												
Positive	81.6	66.6	63.1	**0.0001**	84.8	78.3	78.3	**0.001**	68.8	47.1	39.3	**0.0001**
Negative	96.7	92.9	91.6		96.5	94.7	93.8		97.0	87.3	79.7	
FIGO stage												
I	97.7	95.6	94.8	**0.0001**	97.0	96.1	95.2	**0.0001**	98.3	96.6	94.0	**0.0001**
II	94.7	74.8	66.5		92.3	92.3	92.3		80.0	20.0	0.0	
III–IV	86.4	69.3	66.7		88.4	78.6	78.6		78.4	54.0	0.0	

the limit in our study [15]. Of the 397 patients included in the study, no significant difference was found in terms of additional systemic diseases and BMI in the comparison of the patients over 70 years old (n=96,

Table 5. Independent risk factors affecting 5-year overall survival by evaluating the factors that have an effect on survive in univariate analysis in both groups in Cox regression analysis

	B	SE	Wald	df	p	Hazard ratio	95.0% CI for hazard ratio	
							Lower	Upper
<70 years								
Non-endometrioid	2.433	0.528	21.193	1	0.0001	11.389	4.043	32.082
>70 years								
Non-endometrioid	1.790	0.723	6.125	1	0.013	5.991	1.451	24.732
Lymph node metastasis	1.861	0.694	7.200	1	0.007	6.430	1.651	25.032

24.2%) to younger patients (n=301, 75.8%). Although chronological age alone is not an objective finding of the aging process and vulnerability to oncological diseases, the increase in the incidence of chronic diseases and decreased performance of patients with increasing age are among the most important steps in the choice of surgery and adjuvant treatment [16, 17].

With increasing age, more patients present with non-endometrioid histology and high-grade tumors [5]. In our study, in accordance with the literature, elderly patient group was observed to more frequently have tumors with non-endometrioid histology (32.3% vs. 16.3%, p: 0.001), high-grade tumors (69.8% vs. 50.5%, p: 0.003), and more than 50% MI (36.5% vs. 19.6%, p: 0.003). In the study of Günakan et al. [18] evaluating endometrial disorders at the age of 65 and over, non-endometrioid histology was found in 36.8% of patients diagnosed with EC. In the literature, in similarity to our results, undifferentiated tumors were detected at a higher rate in the non-endometrioid histology of elderly patient groups [19, 20]. Even though more LVSI, cervical glandular/stromal invasion, and pelvic/para-aortic lymph node involvement rates were expected due to the aggressive tumor structure ($p>0.05$) in EC with non-endometrioid histology, there was no significant difference in our study ($p>0.05$). According to the final pathology results, when the FIGO stages of both groups were evaluated, the situation was similar (p: 0.61). This may be explained by the early and rapid diagnosis and treatment of the patients.

When the surgical treatment characteristics of both groups were evaluated, it was observed that all patients who were admitted to our center received surgical treatment, and there was no significant difference in surgical technique selection (LS vs. LT) ($p>0.05$). In EC, for which the primary treatment is the surgical approach, it is important for the elderly group to receive adequate surgical treatment with minimally invasive techniques with lesser morbidity rates that may affect long-term survival [21]. Many studies have shown that minimally invasive techniques are associated with fewer post-operative complications, shorter hospital stays and have no effect on mortality, recurrence, or survival [21, 22]. Nevertheless, minimally invasive techniques were observed to be used less frequently in the elderly group for no specific reason [20], but this difference seemed to disappear as shown in our study with experienced teams at tertiary centers [23].

At our clinic, a systemic lymphadenectomy decision is made according to the histological type, FIGO grade, tumor diameter, and MI depth, which are among the Mayo criteria [24]. There was no significant difference between the lymphadenectomy rates and the total number of lymph nodes removed in both groups ($p>0.05$). While lymphadenectomy is an important part of routine surgery in advanced stage EC, its role in early-stage EC is controversial [25]. The controversy about the indications, anatomical limits, therapeutic location, and systemic treatment is ongoing [26]. In a study by Seagle et al. [27] evaluating 152,702 patients, the authors detected that hazard of death decreased by 1–14% for each additional five lymph nodes removed in endometrioid and serous EC. In multivariate analyses performed in a study evaluating 63,372 early-stage endometrioid-type EC patients over 50 years of age, lymphadenectomy was presented as an independent predictor of OS for Grade 1 and Grade 2 patients with HR rates of 0.893 and 0.827, respectively ($p<0.0001$) [28]. However, Frost et al. [25] were not able to demon-

strate the effect of lymphadenectomy on PFS and OS in their study. Regardless of the discussion on lymphadenectomy, the fact that both patient groups received surgical treatment equally increased the effect of the final pathology results and adjuvant therapy on survival.

In the comparison of the two groups in terms of adjuvant therapies, it was observed that the >70 age group with a higher rate of non-endometrioid histology received a higher rate of CT (37.5% vs. 23.3%, p: 0.008), but no significant difference was observed between the two groups in terms of ERT and BRT (p>0.05). In the study of Fiorentino et al. [29] evaluating patients over 65 years of age receiving ERT and BRT, it was reported that RT was well tolerated and had a low toxicity profile, independent from comorbidities. Torgeson et al. [19], however, reported that elderly patient group received a lower rate of adjuvant RT (48% vs. 34%, p<0.001) in comparison to the younger group, and this negatively affected OS. While CT was shown to have an acceptable toxicity profile in patients with gynecological cancer over the age of 75 [30], only 37.5% of patients were reported to receive adjuvant treatment, although 46.3% were recommended adjuvant therapy [16]. In our study, it was observed that the group of elderly patients with high-risk non-endometrioid histology, Grade 2–3 histology, and more MI invasion received more CT as recommended.

In univariate analyses, histology, grade, MI, LVSI, cervical stromal invasion, lymph node metastasis, and FIGO staging were observed to correlate with survival in accordance with the literature [2]. Non-endometrioid histology, and lymph node metastasis were determined as independent risk factors in the >70 age group, and non-endometrioid histology was an independent risk factor in the <70 age group on survival. This indicates that the main factor affecting the survival rate of patients who receive surgical and adjuvant treatments is non-endometrioid histology for the elderly and the young, and additionally, lymph node metastasis for the elderly.

In our study, the data of a patient group who received surgery and adjuvant treatment from the same gynecological oncology team at a single center are presented retrospectively. While this situation causes a limitation in comparison to studies that are multicenter and contain more patients, it creates a homogeneous case in terms of treatment and follow-up. Thus, compared to many studies in the literature, elderly and younger patients had received equal surgical and adjuvant therapy in this study.

Conclusion

Age is not observed as an obstacle at tertiary centers in terms of receiving adequate surgery and adjuvant treatment for patients diagnosed with EC. Non-endometrioid histology is observed as the determinant parameter on the survival of elderly patient group who received treatment under equal conditions. However, to identify different factors, randomized controlled trials are needed for patients in the elderly group, who are not adequately represented in studies.

Acknowledgments: We thank Cagla Sariturk for assistance with the statistical analysis in the study.

Ethics Committee Approval: The Baskent University Institutional Review Board Ethics Committee granted approval for this study (date: 17.03.2020, number: KA 20/108).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – SA, SYS, GDD, SYB, SY, DAY; Design – SA, OCG; Supervision – HC; Fundings – HC; Materials – HC; Data collection and/or processing – HC, SA, SYS; Analysis and/or interpretation – SA, HC; Literature review – SA, HC; Writing – SA, HC; Critical review – SA, OCG, HC.

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