Experimental
&
Clinical Article

Effect of "Time to Surgery" on the Endometrial Cancer Prognosis

Engin CELIK[1], Harika YUMRU CELIKSOY[2], Hamdullah SOZEN[2], Hale GOKSEVER CELIK[1], Semen ONDER[3], Mehmet Yavuz SALIHOGLU[2], Samet TOPUZ[2]

Istanbul, Turkey

ABSTRACT

OBJECTIVE: Endometrial cancer is the most common gynecological cancer in developed countries. Our study aims to determine the effect of the time between diagnosis and surgery of endometrial cancer on the prognosis of the disease.

STUDY DESIGN: Patients who were diagnosed with epithelial type endometrial cancer and did not receive preoperative chemotherapy, radiotherapy, or hormonal therapy were included in the study.

RESULTS: Two hundred eighty-five patients were included in the study. We divided the patients into two groups regarding before and after 8 weeks from diagnosis to surgery. Clinical characteristics of the patients were comparable between the groups, except for comorbid conditions and body mass index. Using cox-regression analysis, time to operation did not have a significant effect on both recurrence and cancer-associated death risk. The log-rank test analysis also showed that there was no significant difference in progression-free survival and disease-specific survival between the patients. There was no significant difference between the groups in terms of progression-free survival and disease-specific survival for cases with endometrioid type grade 1-2 tumors. There was also no significant difference between the groups regarding progression-free survival and disease-specific survival in the patients with tumors of endometrioid type grade 3 and non-endometrioid histology.

CONCLUSION: Time delay between diagnosis to surgery of the patients with endometrial cancer has no prognostic importance for recurrence and survival outcomes.

Keywords: Disease-specific survival, Endometrial cancer, Pandemic, Progression-free survival, Time to operation

Gynecol Obstet Reprod Med 2022;28(1):89-97

[1] *University of Health Sciences, Istanbul Kanuni Sultan Suleyman Training and Research Hospital Department of Obstetrics and Gynecology Istanbul, Turkey*

[2] *Istanbul University Istanbul Faculty of Medicine Department of Gynecological Oncology Istanbul, Turkey*

[3] *Istanbul University Istanbul Faculty of Medicine Department of Pathology Istanbul, Turkey*

Address of Correspondence: *Hale Goksever Celik*
University of Health Sciences Istanbul Kanuni Sultan Suleyman Training and Research Hospital, Turgut Ozal Boulevard, No:1, 343030 Kucukcekmece-Istanbul, Turkey
hgoksever@yahoo.com

Submitted for Publication: 27.03.2021 Revised for Publication: 29.03.2021
Accepted for Publication: 16.06.2021 Online Published: 02.09.2021

ORCID IDs of the authors: *EC: 0000-0001-7646-6091*
HYC: 0000-0002-6452-7317 *HS: 0000-0002-0568-5307*
HGC: 0000-0002-5162-3262 *SO: 0000-0002-1384-630X*
MYS: 0000-0002-1097-0727 *ST: 0000-0002-9069-0185*

Quick Response Code:	Access this article online
	Website: www.gorm.com.tr e- mail: info@gorm.com.tr
	DOI:10.21613/GORM.2021.1202

How to cite this article: *Celik E. Yumru Celiksoy H. Sozen H. Goksever Celik H. Onder S. Yavuz Salihoglu M. Topuz S. Effect of "Time To Surgery" On The Endometrial Cancer Prognosis. Gynecol Obstet Reprod Med. 2022;28(1):89-97*

Introduction

Endometrial cancer is the most common gynecological cancer in developed countries. Since the disease usually manifests as abnormal uterine bleeding or postmenopausal bleeding, it is diagnosed in the early stages by endometrial biopsy (1). Endometrial cancer, having a proven positive effect on survival if surgery is performed by a gynecologist oncologist, is surgically staged (2).

Endometrial cancer patients are usually found to be elder and obese people with several comorbidities. Preoperative workup and preparation for surgery of this group of patients would take time. Recently postponing surgeries are recommended by international and national societies due to the COVID-19 pandemic (3). Delaying the surgery may have a negative effect on the patient's psychological condition (4). However, there is insufficient evidence regarding the impact of the time from cancer diagnosis to surgery on survival (5).

Our study aims to determine the effect of the time between diagnosis and surgery of endometrial cancer on the International Federation of Gynecology and Obstetrics (FIGO) stage of cancer and the prognosis of the disease.

Material and Method

In our retrospective cohort study, patients who were operated on for endometrial cancer between January 2006 and December 2017 in the Department of Gynecological Oncology at Istanbul Faculty of Medicine Hospital were retrospectively evaluated.

All procedures performed in our study were in accordance with the ethical standards of the institutional research committee (2018/681, Ethics Committee of Istanbul University) and with the Helsinki declaration. We collected the patients' data from the hospital records and we did not document any personal information. All patients were called to confirm their current recurrence and survival status.

We included all patients who had been operated on for EC for 12 years. Hysterectomy with or without bilateral adnexectomy, pelvic and/or paraaortic lymphadenectomy, and omentectomy were performed on these patients according to the disease severity.

Patients who were diagnosed with epithelial type endometrial cancer and did not receive preoperative chemotherapy, radiotherapy, or hormonal therapy were included in the study.

Histopathological examinations were performed by experienced gynecological pathologists.

Progression-free survival (PFS) was defined as the length of time from operation date to the date of the first recurrence. Disease-specific survival (DSS) referred to the period beginning at the time of operation to the time of the death from EC.

The demographical and clinical characteristics of the patients including age, body mass index (BMI), parity (nulliparity and multiparity), menopausal status (premenopausal and postmenopausal), smoking, personal medical histories such as hypertension and diabetes mellitus, time to surgery, follow-up time, PFS, and DSS were reviewed. Surgical and pathological details including histology, International Federation of Gynecology and Obstetrics (FIGO) stage and grade of tumor, tumor size, lymphovascular space invasion (LVSI), myometrial invasion, and metastasis to lymph nodes, omentum, and adnexal structures were recorded. The patients were stratified in terms of histological types, FIGO stage, and risk group according to the World Health Organization (WHO), FIGO, and European Society of Gynecologic Oncology (ESGO), respectively.

We divided the patients into two groups regarding time to operation. Since it was stated that endometrial cancer surgery could be delayed for 8 weeks during the covid 19 pandemic, the groups were divided into two considering this period (6). All parameters were compared between these two groups. The patients were also sub-analyzed in terms of demographical, clinical, surgical, and postoperative characteristics based on having different histologic types and grade endometrial cancer.

Statistical analysis

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) statistics 22.0 version for Windows. Means were presented with standard deviation (SD) while the number of cases and percentages (%) were used for nominal variables. The difference in mean values and characteristics between groups were analyzed with independent samples t-test and chi-square test. The possible factors identified with univariate analysis were further analyzed using the Cox regression analysis and hazard ratios (HR) and 95% confidence interval (CI) in the patients having surgery before and after eight weeks were estimated. The Kaplan-Meier survival estimates were calculated to create the patients' survival curves and the differences of these survival curves were assessed with the log-rank test. $p<0.05$ was considered as statistically significant.

Results

A total of 789 patients underwent an operation for endometrial cancer for 12 years. Among them, 285 patients who met the eligibility criteria were included in the study. Table I represents the demographical and clinical characteristics of the whole population in the study. The mean age of the study population was 60 years while the mean BMI was 35.2±7.7 kg/m^2. Most of the patients (82.8%) were postmenopausal and the most common complaint is postmenopausal bleeding (75.1%).

When evaluated the surgical characteristics of the patients as shown in Table II, the mean tumor diameter was 3.5±2.0 cm and most of the patients were found to have grade 1 tumor (57.9%) and FIGO stage 1 tumor (82.8%). Of those, 87.4% of the patients (n=249) had endometrioid type histology and it was observed that pelvic lymphadenectomy was performed in 77.9% of the patients (n=222). The mean duration between the diagnosis of endometrial cancer and surgery was found to be 10.0±6.7 weeks. Postoperative follow-up without any additional therapy was the most commonly recommended approach in our population (165 patients, 57.9%). While recurrence was detected in 33 patients (11.6%) during the follow-up period, 27 patients (9.5%) died due to cancer.

When the patients in the different groups regarding time to the operation were compared, there was no statistical significance in terms of age, parity, menopausal status, and complaint during the consultation (Table I). However, comorbid conditions were more commonly diagnosed in the patients operated on after 8 weeks (20.2% vs 32.7%, p=0.20) and these patients had higher BMI (33.7±6.5 kg/m^2 vs 36.3±8.3 kg/m^2, p=0.003).

Surgical and postoperative characteristics were also compared between the patients who operated at different times (Table II). Tumor characteristics did not differ significantly regarding tumor size, grade, FIGO stage, LVSI, myometrial invasion, histology, cervical invasion, metastatic, and risk status.

Table I: *Demographical and clinical characteristics of the patients*

Characteristics	All population	Group 1 (n=114) (time to operation<8 weeks)	Group 2 (n=171) (time to operation≥8 weeks)	p^a
	mean±SD (min-max) or number (%)			
Age	60.0±10.3	60.6±10.0	59.6±10.5	0.436
Parity				
Nullipar	46 (16.1)	15 (13.2)	31 (18.1)	0.264
Multipar	239 (83.9)	99 (86.8)	140 (81.9)	
Body mass index (kg/m²)	35.2±7.7	33.7±6.5	36.3±8.3	**0.003**
Menopausal status				
Premenopausal	49 (17.2)	17 (14.9)	32 (18.7)	0.405
Postmenopausal	236 (82.8)	97 (85.1)	139 (81.3)	
Comorbidity				
Absent	206 (72.3)	91 (79.8)	115 (67.3)	**0.020**
Present	79 (27.7)	23 (20.2)	56 (32.7)	
Complaint				
Check-up	22 (7.7)	87 (76.3)	127 (74.3)	0.960
Abnormal uterine bleeding	47 (16.5)	18 (15.8)	29 (17)	
Postmenopausal bleeding	214 (75.1)	1 (0.9)	1 (0.6)	
Pelvic pain	2 (0.7)	8 (7)	14 (8.2)	

SD: Standard deviation, a: Independent sample t-test and Chi-square test were applied

Table II: *Surgical and postoperative characteristics of the patients*

Characteristics	All population	Group 1 (n=114) (time to operation<8 weeks)	Group 2 (n=171) (time to operation≥8 weeks)	p^a
	mean±SD (min-max) or number (%)			
Tumor size (cm)	3.5±2.0	3.3±2.0	3.6±2.1	0.132
Grade				
1	165 (57.9)	67 (58.8)	98 (57.3)	0.681
2	67 (23.5)	24 (21.1)	43 (25.1)	
3	53 (18.6)	23 (20.2)	30 (17.5)	
Stage				
1	236 (82.8)	98 (86)	138 (80.7)	0.718
2	19 (6.7)	6 (5.3)	13 (7.6)	
3	18 (6.3)	6 (5.3)	12 (7)	
4	12 (4.2)	4 (3.5)	8 (4.7)	
Lymphovascular space invasion				
Absent	235 (82.5)	93 (81.6)	142 (83)	0.751
Present	50 (17.5)	21 (18.4)	29 (17)	
Myometrial invasion				
<50%	198 (69.5)	80 (70.2)	118 (69)	0.834
≥50%	87 (30.5)	34 (29.8)	53 (31)	
Histology				
Endometrioid	249 (87.4)	98 (86)	151 (88.3)	0.560
Non-endometrioid	36 (12.6)	16 (14)	20 (11.7)	
Time to operation (weeks)	10.0±6.7			
Recurrence				
Absent	252 (88.4)	98 (86)	154 (90.1)	0.290
Present	33 (11.6)	16 (14)	17 (9.9)	
Death				
Absent	231 (81.1)	88 (77.2)	143 (83.6)	0.215
Present due to cancer	27 (9.5)	15 (13.2)	12 (7)	
Present due to another reason	27 (9.5)	11 (9.6)	16 (9.4)	
Postoperative additional therapy				
Follow-up	165 (57.9)	64 (56.1)	101 (59.1)	0.665
Brachytherapy	42 (14.7)	19 (16.7)	23 (13.5)	
Radiotherapy	34 (11.9)	16 (14)	18 (10.5)	
Chemobrachytherapy	9 (3.2)	4 (3.5)	5 (2.9)	
Chemoradiotherapy	23 (8.1)	6 (5.3)	17 (9.9)	
Chemotherapy	12 (4.2)	5 (4.4)	7 (4.1)	

SD: Standard deviation, a: Independent sample t-test and Chi-square test were applied

When the patients were further analyzed based on their histologic type and grade, there was also a significant difference in terms of body mass index and comorbid conditions in the endometrioid histologic type and grade 1-2 endometrial cancer, as shown in Table III. Patients operated after 8 weeks were found to have higher BMI and more common comorbid conditions (p=0.031 and p=0.034, respectively). When tumor characteristics were evaluated, tumor size was statistically significantly larger in the group operated after 8 weeks (2.8±1.5 cm vs 3.3±1.7 cm; p=0.037). There was no statistically significant difference between the groups regarding FIGO stage, LVSI, myometrial invasion, lymph node metastasis, and cervix invasion (Table IV).

Patients with endometrioid grade 3 and non-endometrioid histology were divided into two groups as operated before and after 8 weeks. Age, BMI, comorbidity, and complaints during the consultation were comparable between the groups (Table V). When tumor characteristics were evaluated, no statistically significant difference was found between the groups in terms of tumor size, FIGO stage, myometrial invasion, and metastasis status (Table VI).

When significant predictors for PFS and DSS were detected using cox-regression univariate and multivariate analysis, time to operation did not have a significant effect on both recurrence (HR: 1.21% 95 CI 0.61-2.42) and cancer-associated death risk (HR: 0.58 95% CI 0.27-1.25) (Table VII and VIII). On the other hand, age, histology type, grade, and FIGO stage were determined as predictors for PFS and DSS as the result of univariate analysis. After entering these significant variables in univariate analysis into multivariate analysis, all of them remained as independent predictors for PFS while only grade and stage were significant predictors for DSS.

The univariate effect of time to operation on the survival of patients with endometrial cancer was investigated using the log-rank test. The Kaplan-Meier survival estimates were calculated and were plotted in Figure 1-3. The log-rank test analysis also showed that there was no significant difference in PFS and DSS between the patients who operated before and after 8 weeks (Log-rank p=0.586, chisq=0.296, 1df, and Log-rank p=0.161, chisq=1.966, 1df, respectively) (Figure 1). There was no significant difference between the groups in terms of PFS (Log-rank p=0.954, chisq=0.003, 1df) and DSS (Log-rank p=0.295, chisq=1.097, 1df) for cases with endometrioid type grade 1-2 tumors (Figure 2). There was also no significant difference between the groups regarding PFS (Log-rank p=0.388, chisq=0.745, 1df) and DSS (Log-rank p=0.845, chisq=0.038, 1df) in the patients with tumors of endometrioid type grade 3 and non-endometrioid histology (Figure 3).

Discussion

Our aim in this retrospective cohort study is to investigate the importance of time to operate in patients with EC. We compared the demographical and clinical characteristics, survival outcomes of the patients in the early and late operated groups. The key finding of our study was that time elapsed between the diagnosis of endometrial cancer and operation had no statistically significant effect, except for the increase in tumor diameter. Progression-free survival and DSS were not affected significantly by the postponement of the operation. In addition, time to operation did not remain as an independent prognostic factor for EC in univariate and multivariate analysis.

There are papers in the literature having contradictory results. As far as we are aware, the first study in the literature

Table III: *Comparison of the patients with endometrioid and grade 1,2 endometrial cancer divided according to being operated at different times regarding their demographical and clinical characteristics*

Characteristics	***mean±SD (min-max) or number (%)***		
	Group 1 (n=91) (time to operation<8 weeks)	***Group 2 (n=139) (time to operation≥8 weeks)***	***p[a]***
Age	59.2±9.9	58.4±10.5	0.564
Parity			
Nullipar	10 (11)	27 (19.4)	0.089
Multipar	81 (89)	112 (80.6)	
Body mass index (kg/m²)	34.2±6.8	36.4±8.2	**0.031**
Menopausal status			
Premenopausal	16 (17.6)	29 (20.9)	0.540
Postmenopausal	75 (82.4)	110 (79.1)	
Comorbidity			
Absent	72 (79.1)	92 (66.2)	**0.034**
Present	19 (20.9)	47 (33.8)	
Complaint			
Check-up	6 (6.6)	12 (8.6)	0.939
Abnormal uterine bleeding	17 (18.7)	26 (18.7)	
Postmenopausal bleeding	67 (73.6)	100 (71.9)	
Pelvic pain	1 (1.1)	1 (0.7)	

SD: Standard deviation. a: Independent sample t-test and Chi-square test were applied

Table IV: *Comparison of the patients with endometrioid and grade 1,2 endometrial cancer divided according to being operated at different times regarding their surgical and postoperative characteristics of the patients*

Characteristics	**mean±SD (min-max) or number (%)**		
	Group 1 (n=91) (time to operation<8 weeks)	**Group 2 (n=139) (time to operation≥8 weeks)**	***p*[a]**
Tumor size (cm)	2.8±1.5	3.3±1.7	**0.037**
Stage			
1	85 (93.4)	122 (87.8)	0.425
2	3 (3.3)	11 (7.9)	
3	3 (3.3)	5 (3.6)	
4	0 (0)	1 (0.7)	
Lymphovascular space invasion			
Absent	84 (92.3)	131 (94.2)	0.561
Present	7 (7.7)	8 (5.8)	
Myometrial invasion			
<50%	69 (75.8)	105 (75.5)	0.961
≥50%	22 (24.2)	34 (24.5)	
Recurrence			
Absent	86 (94.5)	134 (96.4)	0.490
Present	5 (5.5)	5 (3.6)	
Death			
Absent	78 (85.7)	125 (89.9)	0.359
Present due to cancer	4 (4.4)	2 (1.4)	
Present due to another reason	9 (9.9)	12 (8.6)	
Postoperative additional therapy			
Follow-up	61 (67)	98 (70.5)	0.952
Brachytherapy	17 (18.7)	21 (15.1)	
Radiotherapy	10 (11)	13 (9.4)	
Chemobrachytherapy	1 (1.1)	2 (1.4)	
Chemoradiotherapy	1 (1.1)	3 (2.2)	
Chemotherapy	1 (1.1)	2 (1.4)	

SD: Standard deviation, a: Independent sample t-test and Chi-square test were applied

Table V: *Comparison of the patients with endometrioid grade 3 and non-endometrioid endometrial cancer divided according to being operated at different times regarding their demographical and clinical characteristics*

Characteristics	***mean±SD (min-max) or number (%)***		
	Group 1 (n=23) (time to operation<8 weeks)	***Group 2 (n=30) (time to operation≥8 weeks)***	***p*[a]**
Age	66.0±9.0	65.2±9.4	0.745
Parity			
Nullipar	5 (21.7)	4 (13.3)	0.419
Multipar	18 (78.3)	26 (86.7)	
Body mass index (kg/m²)	31.6±4.7	35.0±8.3	0.085
Menopausal status			
Premenopausal	1 (4.3)	3 (10)	0.440
Postmenopausal	22 (95.7)	27 (90)	
Comorbidity			
Absent	19 (82.6)	22 (73.3)	0.424
Present	4 (17.4)	8 (26.7)	
Complaint			
Check-up	1 (4.3)	0	0.595
Abnormal uterine bleeding	1 (4.3)	3 (10)	
Postmenopausal bleeding	20 (87)	26 (86.7)	
Pelvic pain	1 (4.3)	1 (3.3)	

SD: Standard deviation, a: Independent sample t-test and Chi-square test were applied

Table VI: *Comparison of the patients with endometrioid grade 3 and non-endometrioid endometrial cancer divided according to being operated at different times regarding their surgical and postoperative characteristics of the patients*

Characteristics	***mean±SD (min-max) or number (%)***		
	Group 1 (n=23) (time to operation<8 weeks)	***Group 2 (n=30) (time to operation≥8 weeks)***	***p[a]***
Tumor size (cm)	5.0±2.7	5.4±2.8	0.655
Stage			
1	13 (56.5)	14 (46.7)	0.623
2	3 (13)	2 (6.7)	
3	3 (13)	7 (23.3)	
4	4 (17.5)	7 (23.3)	
Lymphovascular space invasion			
Absent	9 (39.1)	9 (30)	0.487
Present	14 (60.9)	21 (70)	
Myometrial invasion			
<50%	11 (47.8)	12 (40)	0.569
≥50%	12 (52.2)	18 (60)	
Recurrence			
Absent	12 (52.2)	18 (60)	0.569
Present	11 (47.8)	12 (40)	
Death			
Absent	10 (43.5)	16 (53.3)	0.550
Present due to cancer	11 (47.8)	10 (33.3)	
Present due to another reason	2 (8.7)	4 (13.3)	
Postoperative additional therapy			
Follow-up	3 (13)	1 (3.3)	0.464
Brachytherapy	2 (8.7)	2 (6.7)	
Radiotherapy	6 (26.1)	5 (16.7)	
Chemobrachytherapy	3 (13)	3 (10)	
Chemoradiotherapy	5 (21.7)	14 (46.7)	
Chemotherapy	4 (17.4)	5 (16.7)	

SD: Standard deviation, a: Independent sample t-test and Chi-square test were applied

Table VII: *Risk factors for progression-free survival in endometrial cancer*

Factor	**Univariate analysis**			**Multivariate analysis**		
	HR	**95% CI**	***p[a]***	**HR**	**95% CI**	***p[a]***
Age (years)	0.26	0.12-0.57	0.001	0.38	0.17-0.85	**0.019**
Histology	0.06	0.03-0.12	<0.001	0.37	0.13-1.01	0.053
Grade	0.05	0.03-0.11	<0.001	0.20	0.06-0.61	**0.005**
Stage	0.11	0.06-0.23	<0.001	0.29	0.13-0.64	**0.002**
Time to operation (weeks)	1.21	0.61-2.42	0.587	0.99	0.48-2.04	0.989

HR: Hazard ratio, CI: Confidence interval, a: Cox regression test was applied

Table VIII: *Risk factors for disease-specific survival in endometrial cancer*

Factor	**Univariate analysis**			**Multivariate analysis**		
	HR	**95% CI**	***p[a]***	**HR**	**95% CI**	***p[a]***
Age (years)	2.79	1.25-6.21	0.012	2.06	0.86-4.94	0.105
Histology	19.36	8.91-42.06	<0.001	2.78	0.94-8.23	0.066
Grade	28.04	11.23-70.02	<0.001	4.30	1.11-16.74	**0.035**
Stage	3.69	2.70-5.05	<0.001	2.80	1.81-4.34	**<0.001**
Time to operation (weeks)	0.58	0.27-1.25	0.166	0.45	0.20-1.03	0.059

HR: Hazard ratio, CI: Confidence interval

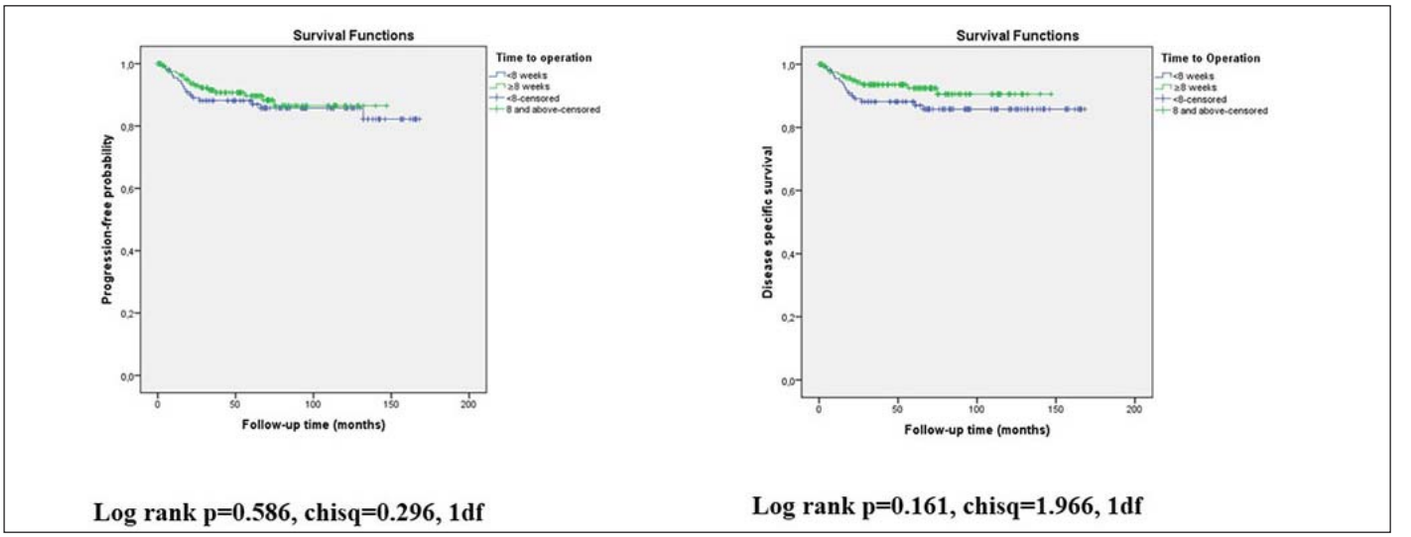

Figure 1: *Progression-free and disease-specific survival curves of the patients with endometrial cancer in relation to time to operation*

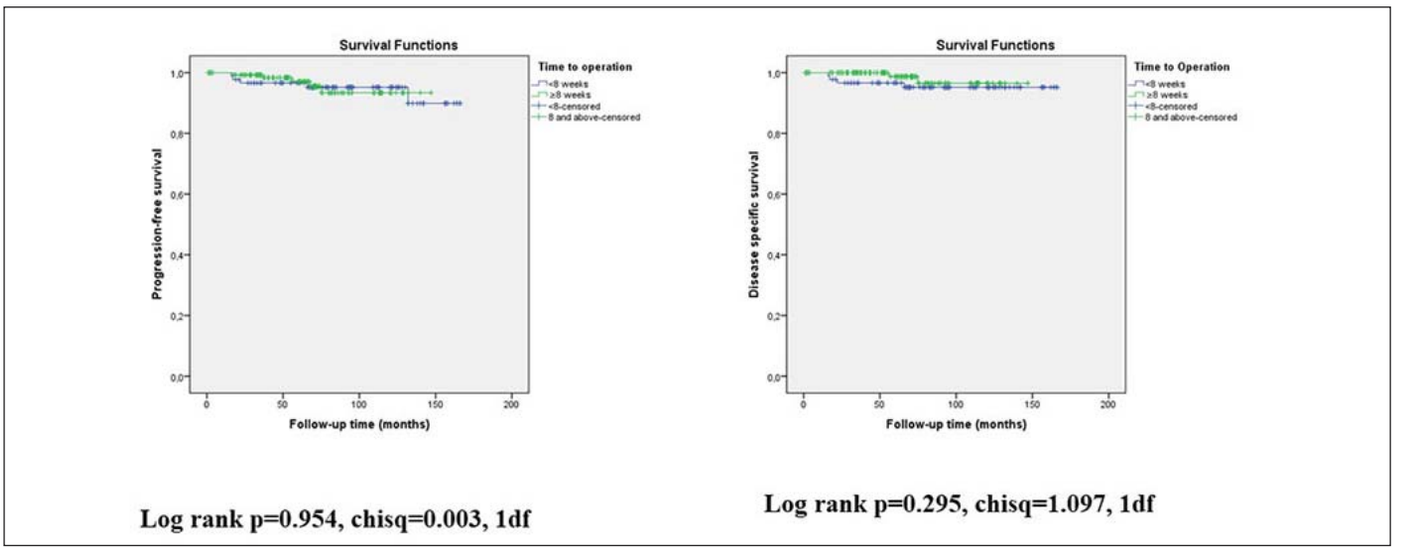

Figure 2: *Progression-free and disease-specific survival curves of the patients with endometrioid grade 1 and 2 endometrial cancer in relation to time to operation*

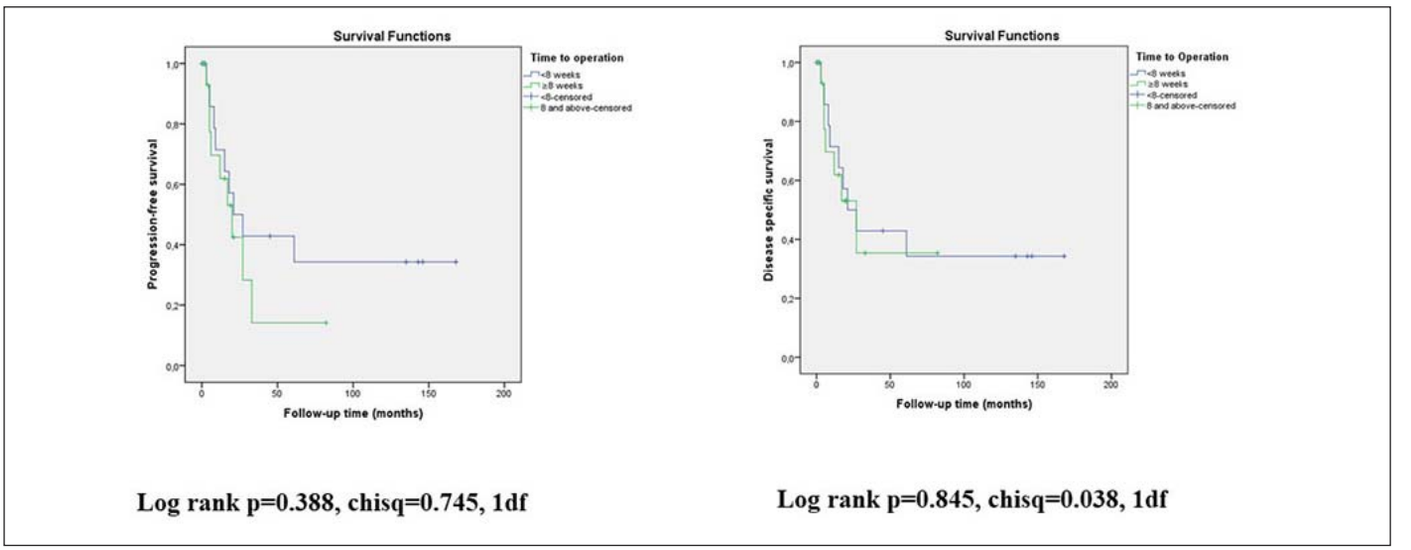

Figure 3: *Progression-free and disease-specific survival curves of the patients with endometrioid grade 3 and non-endometrioid endometrial cancer in relation to time to operation*

evaluating time until surgery was conducted by Menczer et al in 1995. Similar to our results, these authors showed that the time until surgery does not affect the prognosis of patients with endometrial cancer (7).

Pirog et al have evaluated the effect of elapsed time between the beginnings of complaints to surgery on the stage of disease in 182 endometrioid endometrial cancer patients. A significant difference was not found between stage 1 and stage 2-4, who were operated on before and after one month (71% vs 29%, respectively; p=0.87) (8).

In contrast to our results, the study conducted in Scotland included 703 endometrial cancer patients to assess time elapsed between diagnosis of endometrial cancer to surgery. Patients who were operated on before 40 days had a worse survival than those operated between 40-61 days (HR: 0.50 95% CI 0.30-0.82) (9).

A total of 9 417 endometrial cancer patients was assessed in Ontario's health care system. Patients were divided into four groups according to time of diagnosis to surgery (before 2 weeks, 2-6 weeks, 6-12 weeks, and 12 weeks). When the patients operated before 2 weeks were taken as a reference, patients operated between 2-6 weeks had HR 0.64 (95% CI 0.55-0.75), patients operated between 6-12 weeks had HR 0.65 (95% CI 0, 55-0.77), and patients operated over 12 weeks had HR 0.80 (95% CI 0.67-0.97) for recurrence and death. They speculated that patients who operated on before 2 weeks had the worst prognosis because of not being managed by a gynecologist oncologist and inadequate preoperative investigation. However, in our study, all patients were operated on by a gynecologist oncologist. Additionally, they included uterine sarcomas in the study, which had very different behavior. This study proved that patients with comorbidities were operated on later than without comorbidities (10).

Similarly, Matsuo et al included 435 endometrioid endometrial cancer patients in their study to assess the effect of time to surgery on survival. Patients were divided into 4 groups according to time between diagnosis to surgery (2 weeks, 2-6 weeks, 6-12 weeks, and 12 weeks). Five-year survival showed a significant difference between the groups (62%.5 vs 93.6% vs 95.2 % vs 100% p<0.05) (11).

In another study, 112 041 patients with endometrial cancer were evaluated using the American National Cancer Database (NCDB). It was determined that patients who were operated on for more than 6 weeks after diagnosis had shorter survival than those who were operated on before 6 weeks (HR 1.14 95% CI 1.09-1.20) (12).

Dolly et al retrospectively analyzed 889 patients with endometrial cancer. The mean time from diagnosis to surgery was found to be 43.35 days in living patients while it was 64.84 days in patients who were died. Thus the patients having poor prognosis had a longer period between diagnosis and operation (13).

Shalowitz et al investigated endometrial cancer patients using the NCDB database. Similar to our study analysis, they divided the study population into low-risk (endometrioid type grade 1-2) and high-risk (endometrioid type grade 3 and non-endometrioid tumors) groups. The study showed that patients in the low-risk group who were operated on in the first 2 weeks and after 8 weeks had worse survival (HR: 1.4 95% CI 1.3-1.5). Factors that affected time to surgery were being uninsured (1.3 weeks 95% CI 1.1-1.5) and comorbidity (1.0 week 95% CI 0.8-1.2). When the high-risk group was evaluated, surgery in the first 2 weeks resulted in poor outcomes (HR: 1.5 95% CI 1.3-1.6), and surgery after 2 weeks did not have a significant effect on survival (14).

National Cancer Database retrospectively examined 284 499 patients with endometrial cancer. Patients were divided into endometrioid and non-endometrioid histology groups. In the endometrioid group, being operated after 6 weeks had worse survival in stage 1 (HR: 1.22 99% CI (1.16-1.29); p<0.0001) and stage 2 (HR: 1.18 99% CI (1.06-1.33); p=0.0001) patients. In the non-endometrioid group, time to surgery longer than 6 weeks did not change the overall survival (15).

Limitations of our study are retrospective design and small sample size in the high-risk group. Despite this limitation, we contributed much to the literature in which there is limited evidence about this topic. Analysis of all potential confounding factors including clinical and demographical characteristics of the patients, examination of histopathology slides by the experienced gynecological pathologists, evaluation of all included factors that may affect the survival outcomes of EC by multivariate analysis are other strengths of our study.

In conclusion, the time delay between diagnosis and surgery of the patients with endometrial cancer has no prognostic importance for recurrence and survival outcomes. Further research with prospective nature is needed for ideal treatment intervals in endometrial cancer patients.

Acknowledgment: The authors would like to thank the participants of this study.
Funding: There is no funding.
All participants signed informed written consent before being enrolled in the study.
Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.
Competing interests: The authors declare that they have no competing interests.
Authors' contributions: EC raised the presented idea. EC and HGC designed the study. HGC conducted the analyses. EC and HGC developed the first draft of the manuscript. All authors contributed to the writing of the paper, and have read and approved the final manuscript.

References

1. Concin N, Creutzberg CL, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP Guidelines for the management of patients with endometrial carcinoma. Virchows Arch. 2021;478(2):153-90. Doi: 10.1007/s00428-020-03007-z.
2. Chan JK, Sherman AE, Kapp DS, Zhang R, Osann KE, Maxwell L, et al. Influence of gynecologic oncologists on the survival of patients with endometrial cancer. J Clin Oncol. 2011;29(7):832-8. Doi: 10.1200/JCO.2010.31.2124.
3. Ramirez PT, Chiva L, Eriksson AGZ, Frumovitz M, Fagotti A, Gonzalez Martin A, et al. COVID-19 Global Pandemic: Options for Management of Gynecologic Cancers. Int J Gynecol Cancer. 2020;30(5):561-3. Doi: 10.1136/ijgc-2020-001419.
4. Menczer J. Diagnosis and treatment delay in gynecological malignancies. Does it affect outcome? Int J Gynecol Cancer. 2000;10(2):89-94. Doi: 10.1046/j.1525-1438.2000.00020.x.
5. Pergialiotis V, Haidopoulos D, Tzortzis AS, Antonopoulos I, Thomakos N, Rodolakis A. The impact of waiting intervals on survival outcomes of patients with endometrial cancer: A systematic review of the literature. Eur J Obstet Gynecol Reprod Biol. 2020;246:1-6. Doi: 10.1016/j.ejogrb.2020.01.004.
6. Colombo I, Zaccarelli E, Del Grande M, Tomao F, Multinu F, Betella I, et al. ESMO management and treatment adapted recommendations in the COVID-19 era: gynaecological malignancies. ESMO Open. 2020;5(Suppl 3): e000827. Doi: 10.1136/esmoopen-2020-000827.
7. Menczer J, Krissi H, Chetrit A, Gaynor J, Lerner L, Ben-Baruch G, et al. The effect of diagnosis and treatment delay on prognostic factors and survival in endometrial carcinoma. Am J Obstet Gynecol. 1995;173(3 Pt 1):774-8. Doi: 10.1016/0002-9378(95)90340-2.
8. Pirog EC, Heller DS, Westhoff C. Endometrial adenocarcinoma-lack of correlation between treatment delay and tumor stage. Gynecol Oncol. 1997;67(3):303-8. Doi: 10.1006/gyno.1997.4874.
9. Crawford SC, Davis JA, Siddiqui NA, de Caestecker L, Gillis CR, Hole D, et al. The waiting time paradox: population based retrospective study of treatment delay and survival of women with endometrial cancer in Scotland. BMJ. 2002;325(7357):196. Doi: 10.1136/bmj.325.7357.196.
10. Elit LM, O'Leary EM, Pond GR, Seow HY. Impact of wait times on survival for women with uterine cancer. J Clin Oncol. 2014;32(1):27-33. Doi: 10.1200/JCO.2013.51.3671.
11. Matsuo K, Opper NR, Ciccone MA, Garcia J, Tierney KE, Baba T, et al. Time interval between endometrial biopsy and surgical staging for type I endometrial cancer: association between tumor characteristics and survival outcome. Obstet Gynecol. 2015;125(2):424-33. Doi: 10.1097/AOG.0000000000000636.
12. Strohl AE, Feinglass JM, Shahabi S, Simon MA. Surgical wait time: A new health indicator in women with endometrial cancer. Gynecol Oncol. 2016;141(3):511-5. Doi: 10.1016/j.ygyno.2016.04.014.
13. Dolly D, Mihai A, Rimel BJ, Fogg L, Rotmensch J, Guirguis A, et al. A delay from diagnosis to treatment is associated with a decreased overall survival for patients with endometrial cancer. Front Oncol. 2016;6:31. Doi: 10.3389/fonc.2016.00031. eCollection 2016.
14. Shalowitz DI, Epstein AJ, Buckingham L, Ko EM, Giuntoli RL 2nd. Survival implications of time to surgical treatment of endometrial cancers. Am J Obstet Gynecol. 2017;216(3):268.e1-268.e18. Doi: 10.1016/j.ajog.2016.11.1050.
15. AlHilli MM, Elson P, Rybicki L, Khorana AA, Rose PG. Time to surgery and its impact on survival in patients with endometrial cancer: A National cancer database study. Gynecol Oncol. 2019;153(3):511-6. Doi: 10.1016/j.ygyno.2019.03.244.