Received: 16 Mar 2023 | **Accepted:** 11 Apr 2023 **Genel Tıp Derg. Volume** 33/**Issue** 2 (April), 232-238
DOI: 10.54005/geneltip.1265954

ORIGINAL ARTICLE

Long-term Survival Outcomes of Early-stage Grade 1 and 2 Endometrioid-Type Endometrial Cancer Patients

Erken Evre Grade 1 ve 2 Endometrioid Tip Endometrium Kanseri Tanılı Olgularda Uzun Dönem Sonuçları

[1]Fazıl Avcı, [2]Onder Eren, [1]Ahmet Bilgi, [3]Hamit Basaran, [4]Murat Celik, [2]Melek Caglayan, [1]Cetin Celik

[1]Selcuk University, Medical Faculty, Department of Obstetric and Gynecology, Konya
[2]Selcuk University, Medical Faculty, Department of Medical Oncology, Konya
[3]Selcuk University, Medical Faculty, Department of Radiation Oncology, Konya
[4]Selcuk University, Medical Faculty, Department of Pathology, Konya

Correspondence

Fazıl Avcı, Selcuk University, Medical Faculty, Department of Obstetric and Gynecology, Konya

E-Mail: fazilavci01@hotmail.com

How to cite ?

Avcı F. , Eren O. Ö. , Bilgi A. , Başaran H. , Celik M. , Caglayan M. , Celik C. Long-term survival outcomes of early-stage grade 1 and 2 endometrioid-type endometrial cancer patients. Genel Tıp Dergisi. 2023; 33(2): 232-238

ABSTRACT

Aim: Early-stage endometrioid-type endometrial cancer (EC) has a favorable prognosis. The recurrence is still the biggest issue. There are differences in the literature in terms of treatment modalities in the early-stage. The aim of the study is to retrospectively investigate the long-term survival outcomes of early-stage grade 1 and 2 endometrioid-type endometrial cancer patients.
Methods: Out of 327 cases, 294 cases in stage 1 and 33 cases in stage 2 were evaluated. Age, stage, tumor size, histologic grade, degree of myometrial invasion, presence of lymphovascular invasion (LVSI), peritoneal cytology positive, presence of recurrence, overall survival (OS), and disease-free survival (DFS) between two groups were evaluated statistically.
Results: The mean age of 327 patients was 64.0±10.0 years. Out of 327, 65.7% were ≥60 years, and 90% were stage 1, 74.6% were grade 1, 1.8% had positive peritoneal cytology, 8.3% had LVSI and 86% had ≤50% myometrial invasion. Recurrence was detected in 6.4% of patients. 40.7% of patients received adjuvant radiotherapy. Only the adjuvant radiotherapy found a significant association between two groups. Only presence of recurrence in terms of OS and DFS durations was a significant parameter in the regression analysis.
Conclusion: Development of recurrence in the early-stage endometrioid-type EC is the main prognostic predictor for survival. The early diagnosis and treatment of recurrence have a positive impact on the prognosis.

Key words: Endometrial cancer, endometrioid, recurrence, survival

ÖZ

Amaç: Erken evre endometrioid tipi endometrium kanser (EK) iyi bir prognoza sahiptir. Rekürrens hala en büyük sorundur. Literatürde erken evrede tedavi yöntemleri açısından farklılıklar vardır. Çalışmanın amacı erken evre grade 1 ve 2 endometrioid tip endometrium kanseri tanılı olgularda uzun dönem sonuçlarını retrospektif olarak araştırmaktır.
Yöntemler: Toplam 327 olgudan evre 1'de 294 olgu ve evre 2'de 33 olgu değerlendirildi. İki grup arasında yaş, evre, tümör çapı, grade, myometrial invazyon derecesi, lenfovasküler invazyon (LVSI) varlığı, periton sitolojisi pozitifliği, rekürrens varlığı, genel sağkalım (OS) ve hastalıksız sağkalım (DFS) süreleri istatistiki olarak değerlendirildi.
Bulgular: Toplam 327 olgunun yaş ortalaması 64,0±10,0 yıl olarak hesaplandı. 327 olgudan 60 yaş ve üstü olgular %65,7, olguların %90'ı evre 1 ve %74,6'sı grade 1, periton sitolojisi %1,8 oranında pozitif, ve LVSI varlığı %8,3'ünde pozitif, ve %50'den az myometrial invazyon olguların %86,5'inde saptandı. Rekürrens, olguların %6,4'ünde saptandı. Olgulara adjuvan radyoterapi %40,7 oranında uygulandı. Olgular evre 1 ve evre 2 olarak karşılaştırıldığında sadece adjuvan radyoterapi tedavisi açısından anlamlı fark saptandı. OS ve DFS süreleri açısından regresyon analizinde sadece rekürrens varlığı anlamlı faktör olarak saptandı.
Sonuç: Endometrioid tip endometrium kanserinde rekürrens gelişmesi sürvi açısından en önemli prognostik faktördür. Rekürrensin erken tanı ve tedavisi ile prognoz olumlu yönde etkilenmektedir.

Anahtar kelimeler: endometrioid, endometrium kanser, rekürrens, survi

Introduction

Endometrial cancer (EC) is one of the most prevelant gynecological tumor (1). According to the current data, 417.367 new EC cases and 97.370 deaths due to EC have been reported (2, 3). According to the histological type of EC, it is divided into two groups as endometrioid-type type 1 and non-endometrioid type type 2 (4). Type 1 EC patients have a total 5-year survival rate as high as 95% and are typically treated with surgery alone (5, 6). Although approximately 75% of early-stage EC cases have an good prognosis, development of recurrence is still observed in cases accepted with adjuvant and surgery therapy (7). However, in routine practice as a subgroup analysis, early-stage type 1 EC cases are at high risk of develeopment of recurrence and death (8-10). Recurrent cancers significantly reduce survival. 5-year survival has been reported as 55% for pelvic and 17% for extrapelvic recurrence (7). The overall recurrence rate of patients diagnosed with early-stage EC is about 15% (11, 12). In addition, it has been reported that the factors affecting the tumor aggressiveness, different pathological types, and response to treatment of recurrent ECs, especially in the early-stage EC groups, are heterogeneous (13). Adjuvant therapy and follow-up protocols for patients diagnosed with EC after adjuvant therapy are not clear in the guidelines (14, 15). Numerous clinicopathological variables, including FIGO stage, degree of myometrial invasion, histological

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - iThenticate
Complaints: geneltip@selcuk.edu.tr

grade, presence of LVSI, and histologic type, have been demonstrated to have had an impact on recurrence (13, 16-18). In addition, different recurrence behaviors were observed in patients who received different radiotherapy modalities (14, 15). We planned to investigate the long-term survival outcomes of early-stage grade 1 and 2 endometrioid-type EC patients performed in this clinic.

Material and methods

This clinical study was conducted by the Selçuk University, Faculty of Medicine, Ethics Committee on 18.10.2022 with the decision numbered 2022/417. The study cases consisted of cases with early-stage (stage 1 and 2) grade 1 and 2 endometrioid-type EC diagnosed in …. University Gynecology and Obstetrics Clinic between December 2010 and November 2021.

All cases underwent preoperative endometrial biopsy and imaging methods such as Computed Tomography (CT) or Magnetic Resonance (MRI) were used. The cases were staged according to the classification of the International Federation of Gynecology and Obstetrics (FIGO-2009) (19). Standard treatment for early-stage EC included total hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection, and depending on risk parameters (20). The inclusion criteria were FIGO histological grade 1-2, endometrioid-type, patients who underwent hysterectomy + bilateral salpingoophorectomy + pelvic paraaortic lymph node dissection. Exclusion criteria included FIGO stage 3-4, grade 3 endometrioid-type EC and non-endometrioid type EC, lymph node positive, pelvic radiotherapy or chemotherapy history. A statistical analysis was performed on age, stage, tumor size, histologic grade, degree of myometrial invasion, and presence of LVSI, peritoneal cytology positive, presence of recurrence, OS, and DFS. OS was termed the time from the end of treatment to the date of death or last follow-up and DFS was termed as the time from the end of treatment to the development of recurrence or metastasis.

A multidisciplinary committee made the decision to begin adjuvant therapy based on worldwide recommendations; these treatment may have included vaginal brachytherapy (VBT), external beam radiation (EBRT), or chemotherapy (21). EBRT therapy was given to the pelvic region using the intensity modulated radiotherapy (IMRT) method or three-dimensional conformal radiotherapy (3D-CRT) tecnique, using a total dose of 45 Gy in 25 fractions. High-dose brachytherapy was delivered to the upper part of the vagina with a vaginal roller. The modaliy of treatment included 5.5 Gy per fraction for five fractions received 5 mm below the vaginal surface in postoperative VBT only. When VBT was received in combination with EBRT, doses of 5.5-6 Gy per fraction were given for three fractions. Postoperative follow-up was made every 3-4 months for the first 2 years, every 6 months for the next 5 years, and then annually. Follow-up protocols consisted of physical exams such as gynecological exams and imaging (22).

Statistical analysis

SPSS version 21 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Descriptive features (mean, standard deviation) in the study were evaluated with the help of Descriptive Statistical Tests. The normal distribution of the variables were analyzed according to the Kolmogorove Smirnov test. Comparisons between groups for parameters with a normal distribution approach were analyzed with the Independent T-Test, and for parameters without a normal distribution approach, comparisons between groups were tested with Mann Whitney U Test. Pearson Chi-Square and Fisher's Exact Test were used for categorical parameters. Logistic regression analysis was used to determine risk factors (HR) among group variables. 95% confidence interval and significance $p<0.05$ were accepted. Survival times for the variables were defined by the Kaplan-Meier method and survival curves were analyzed using the log-rank test. Cox regression analysis was used to evaluate risk parameters.

Results

The mean age of 327 patients was 64.0±10.0 years (Table 1). Out of 327 patients, 65.7% were aged ≥60 years, 90% were stage 1, 74.6% were grade 1, 1.8% were peritoneal cytology positivity, 8.3 % were presence of LVSI and 86.5% were ≤50% myometrial invasion. The mean tumor size was in 4.0±2.3 cm and presence of recurrence was not detected in 93.6% of the cases. Adjuvant radiotherapy was applied at a rate of 40.7% of the patients. The 5-year OS of the cases was 99.1% and the OS during all the study was 96.3%. OS and DFS durations were calculated as 155.0±3.8 and 154.6±4.0 months, respectively. A significant difference was only found when the cases were compared as stage 1 (n=294 cases) and stage 2 (n=33 cases) in terms of adjuvant radiation treatment. According to the OS and DFS durations of early-stage cases, there was no significant association in the Kaplan-Mayer analysis (p=0.587 and p=0.559, respectively, Table 2, Figure 1-2). Only the existence of recurrence was found as a significant factor in the regression analysis of the patients in OS and DFS (p=0.009 HR=6,150 (95% CI 1.574-24.023), and p=0.007, HR 6.613 (95% CI 1.696-25.781), Table 3, Figure 3, and 4). However, Kaplan-Meier analysis showed a significant association between OS and DFS durations in terms of recurrence (p=0.004 and p=0.003, respectively, Table 4, Figures 5 and 6).

Table 1: Comparison of characteristic factors in 327 cases with endometrial cancer

Variables		Value	%
Age, year		64,0±10,0	
	<60 age	112	34,3
	≥60 age	215	65,7
Stage			
	I	294	90,0
	II	33	10,0
Grade			
	1	244	74,6
	2	83	25,4
Peritoneal fluid			
	Benign	321	98,2
	Malign	6	1,8
Presence of LVSI			
	Yes	27	8,3
	No	300	91,7
Myometrial İnvasion			
	<%50	283	86,5
	>%50	44	13,5
Tumor size, cm		4,0±2,3	
Recurrence			
	Yes	21	6,4
	No	306	93,6
Adjuvant radiotherapy			
	Yes	133	40,7
	No	194	59,3
Ex status			
	Yes	12	3,7
	No	315	92,3
DFS, months		154,6±4,0	
OS, months		155,0±3,8	

Table 3: Cox regression analysis of risk factors on OS and DFS in early stage endometrial cancer

Parame-ters	DFS				OS			
			%95 CI				%95 CI	
	P value	HR	Lower	High	P value	HR	Lower	High
Tumor size	0,215	1,202	0,898	1,609	0,198	1,210	0,905	1,616
Grade	0,407	0,481	0,085	2,711	0,440	0,511	0,093	2,808
Presence of LVSI	0,635	1,749	0,174	17,593	0,667	1,652	0,168	16,270
Myo-metrial invasion	0,698	0,728	0,14	3,622	0,757	0,777	0,157	3,850
Stage	0,196	3,420	0,529	22,104	0,206	3,342	0,515	21,687
Adjuvant radiother-apy	0,821	0,850	0,209	3,460	0,802	0,835	0,205	3,408
Presence of Recur-rence	0,007	6,613	1,696	25,781	0,009	6,150	1,574	24,023

LVIS: lymphovascular space invasion

Table 2: Comparison of characteristic factors of cases with early stage endometrioid type endometrial cancer according to groups

Parameters		Stage 1 (n=294)	%	Stage 2 (n=33)	%	P value
Age, year		63,7±10,0		66,0±8,7		0,205
Age interval						0,614
	<60	102	34,7	10	30,3	
	≥60	192	65,3	23	69,7	
Menopause status						0,490
	Pre	23	7,8	1	3,0	
	Post	271	92,2	32	97,0	
Grade						0,562
	1	218	74,1	26	78,8	
	2	76	25,9	7	21,2	
Peritoneal fluid						0,475
	Benign	289	98,3	32	97,0	
	Malign	5	1,7	1	3,0	
Presence of LVSI						0,629
	Yes	25	8,5	2	6,01	
	No	269	91,5	31	26,9	
Myometrial invasion						0,594
	≤%50	253	86,1	30	23,9	
	>%50	41	13,9	3	9,1	
Tumor size, cm		4,0±2,3		3,5±2,0		0,396
Recurrence						0,112
	Yes	21	7,1	0	0	
	No	273	92,9	33	100	
Adjuvant radiotehrapy						0,001
	Yes	100	34	33	100	
	No	194	66	00	0	
Ex status						0,346
	Yes	10	3,4	2	6,01	
	No	284	96,6	31	26,9	
DFS, months		155,1±4,3		139,5±10,2		0,559
OS, months		155,2±4,2		141,0±9,3		0,587

LVIS: lymphovascular space invasion, DFS: disease free survival and OS: overall survival

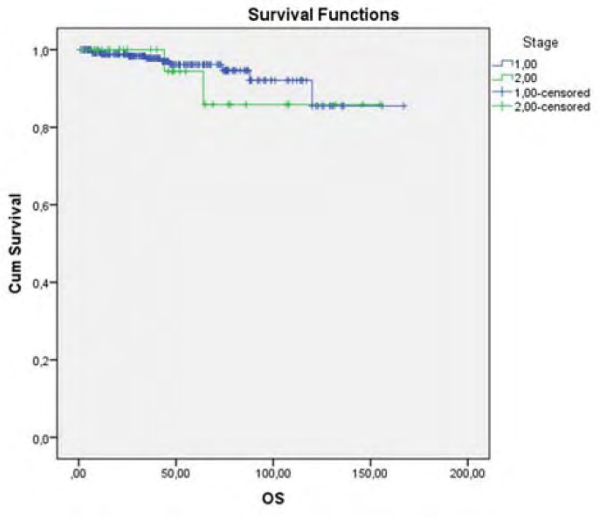

Figure 1: Kaplan-Meier analysis on OS in early stage endometrial cancer

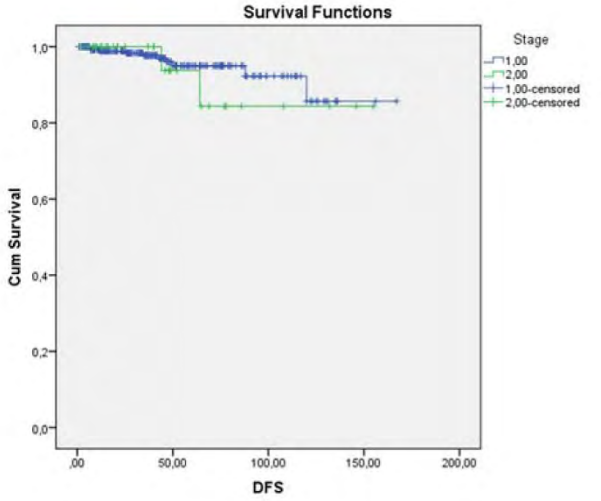

Figure 2: Kaplan-Meier analysis on DFS in early stage endometrial cancer

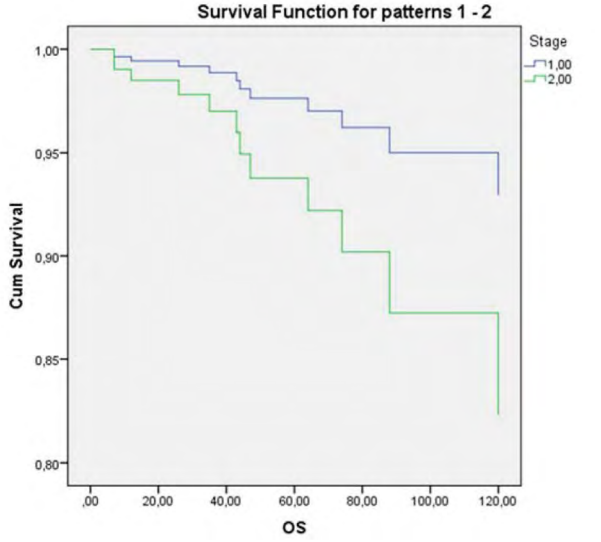

Figure 3: Cox regression analysis on OS in early stage endometrial cancer

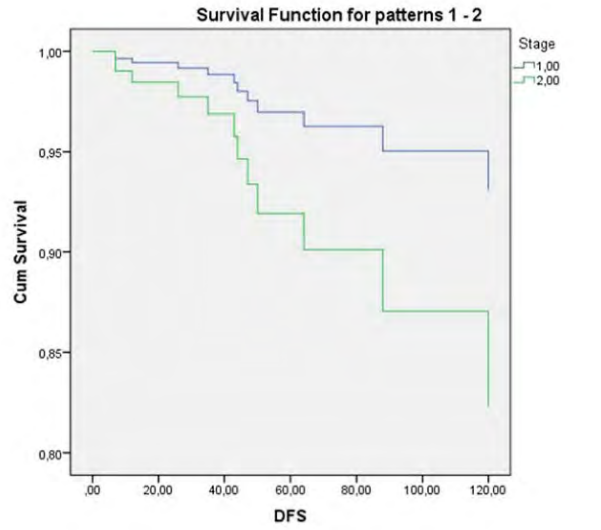

Figure 4: Cox regression analysis on DFS in early stage endometrial cancer

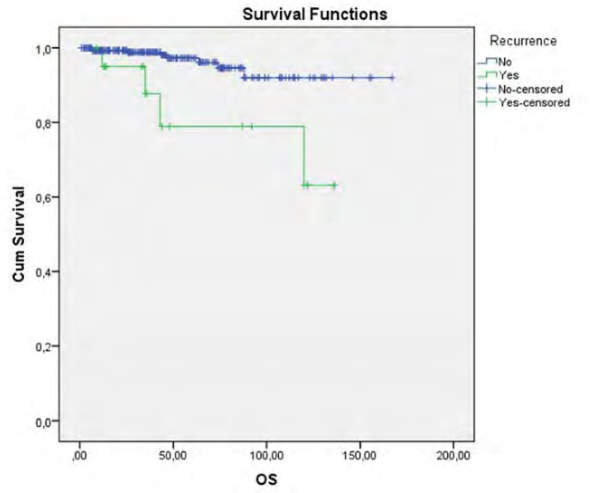

Figure 5: Kaplan-Meier analysis on OS of recurrence in early-stage endometrial cancer

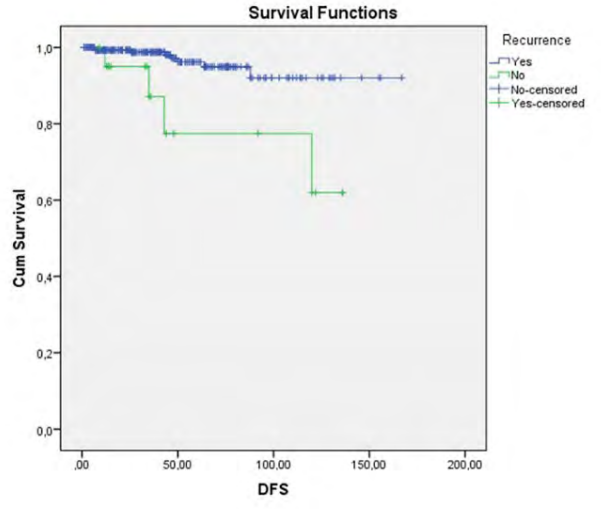

Figure 6: Kaplan-Meier analysis of recurrence on DFS in early-stage endometrial cancer

Table 4: Analysis of DFS and OS log rank values according to the presence of recurrence according to Kaplan-Mayer analysis

Parameters	DFS					OS			
			%95 CI				%95 CI	
	P value	Mean ±SD	Lower	High	P value	Mean ±SD	Lower	High
Recurrence								
Yes	0,003	110,3±12,0	87,0	133,7	0,004	111,7±11,2	89,7	133,7
No		158,4±3,3	152,0	164,8		158,7±3,1	152,5	164,8

Discussion

In this present study, 5-year overall survival was 99.1% in early-stage EC patients and overall survival during thoroughout the study was 96.3%. Only the adjuvant radiation treatment was significantly different when the cases were evaluated as stage 1 and stage 2. Stage 1 recognized all recurrences, whereas stage 2 detected no recurrence. The OS and DFS durations of the patients did not differ significantly. The development of recurrence is the only significant factor among the patients in terms of survival time.

The distribution of the groups and the factors included in early-stage EC researches vary across the literature. Among these studies, Nout et al. (23) involved 427 patients with stage 1 or 2 randomized high-intermediate risk EC diagnoses who received treatment for 18 to 78 months using pelvic external beam irradiation (n=214 cases) and vaginal brachytherapy (n=213 cases). In the follow-up, it was found that the groups were similar in terms of stage. In the research of prognostic variables in endometrioid-type EC stage IA (n=430) and IB (n=91) recurrence, Han et al. (24) analyzed 521 cases between 1993 and 2013. According to the combination of vaginal brachytherapy, external beam radiotherapy, and vaginal brachytherapy, stage 1 (n=324) and stage 2 (n=37) cases were evaluated by Jin et al. (25) in the adjuvant radiotherapy study consisting of 361 cases with early stage, medium risk, and high risk EC between 2003 and 2015. According to Francis et al.'s (11) analysis of early-stage EC recurrence patterns and salvage treatment outcomes, 2669 cases were classified as being in stage IA (61%), IB (32%), or II (6%). In the study involving 40 cases with early stage endometrioid-type EC, Imoboden et al., (26) showed that no significant association between the groups according to stage was found, including recurrence group (n=20) and control group (n=20). In a retrospective investigation of 284 recurrences (recurrence group, n=22, and non-recurrence group, n=262) by Ocak et al., (27) early-stage IA (n=221) and IB (n=63) were examined. On the other hand, Ren et al.(28) divided the 858 cases diagnosed with early-stage EC into 4 groups (low risk n = 301, medium risk n = 250, high medium risk n=164, and high risk n=143) in their recurrence research following postoperative irradiation. The distribution of stages differed significantly between the groups. In a multicenter investigation on recurrence, prognosis, and risk factors in early-stage EC, Dou et al.(29) reported that a total of 2974 patients (non-recurrent, n=2785 and recurrent, n=189) cases were assessed. In this study, 327 cases of early-stage endometrial cancer were diagnosed; they were separated into two groups as stage 1 (n=294) and stage 2 (n=33), and it was found that they were comparable to each other in line with the literature.

Francis et al. (11) reported that age distribution of patients was recorded as 45% and 55%, respectively. When the cases were reported as <60 years and ≥60 years in the studies. Nout et al. (23) and Ren et al.'s (28) studies were similar. Ocak et al. (27) assessed the mean age as 60 years. Imoboden et al. (11) and Han et al. (24) reported that there was no significant association according to age. The age ranges of the patients in this study were 34.3% and 65.7%, respectively, whereas the age ranges between the groups were similar and consistent with the studies.

When the studies were evaluated based on histologic grade, it was reported that Nout et al.'s (23) distribution of grades 1,2, and 3 was similar. On the other hand, while Ocak et al. (27) similarly recorded grades 1% (48.9%), 2 (43.7%), and 3 (7.4%), Francis et al. (11) reported grades 1 (57%), 2 (28%), and 3 (14%). In their study, grades 1,2, and 3 showed a significant difference according to Han et al., (24). Also, there were similarities between the grades 1,2, and 3 according to Jin et al. (25). There were similarities between grade 1 and 2 according to Imoboden et al. (11). Similar to this study, 25.4% of the cases were classified as grade 2 and 74.6% as grade 1, respectively. Additionly, a significant association among the groups in terms of histologic grade was not found. In addition, cases in grade 3 were not included in the study groups.

One of the risk factors of EC is presence of LVSI in EC, and studies have reported variable outcomes for LVSI in early-stage endometrial cancer. According to Ren et al.(28) and Imoboden et al. (11), a significant association was reported regarding the presence of LVSI. In their studies, Nout et al.(23), Han et al. (24), and Ocak et al.(27) reported that there were similarities between the groups. In this present study, no significant association in the presence of LVSI was found. Histological type is one of the prognostic factors in EC. Histological types were described as endometrioid (91%) and other types (9%), and it is significant in terms of type 1 and type 2 in the studies of Ren et al.,(28), and Francis et al. (11). Han et al.,(24), Ocak et al.,(27) and Imoboden et al.(11) only evaluated endometrioid-type cases. In similar to these studies, cases in this study that exclusively had endometrioid-type histology were assessed.

For staging and invasion, the myometrial invasion degree is crucial. In Ren et al.'s study(28), a significant association between the groups in terms of myometrial invasion was reported; however, no significant association between the groups in this study was found.

In the study of Matsua et al., (30) stage 1 endometrioid-type EC between 2010 and 2016 on early stage EC prognosis, 1081 (4.4%) peritoneal cytology positivity was detected in 24.800 cases, despite the fact that it was excluded from the staging. The study found that positive peritoneal cytology was associated with decreased survival for stage I endometrioid-type EC. On the other hand, similar to the study of Dai et al. (31) and Todove et al. (32), this study showed that there was no significant association in survival between the groups.

EBRT modality can reduce the development of locoregional recurrence, but more effective local treatment has no impact an survival time (23, 33). Therefore, VBT modality alone is currently recommended for the intermediate-risk or high-intermediate risk group. But, the optimal adjuvant therapy for the high-risk patient group is still controversial (22, 34) In terms of adjuvant radiotherapy in the early stage of EC, Nout et al., (23), Jin et al. (25), and Ren et al. (28), applied to all cases at a rate of 100% in their study. However, adjuvan radiotherapy were applied to 56% of cases by Ocak et al. (27), 65.9% of cases by Han et al. (24) and 25% of cases by Francis et al.,(11), it was applied at a rate of 40.7% in this study.

Early stage EC recurrence rates have been reported at different rates in the studies. Recurrence rates were reported as 7.9% by Ren et al., (28) 7.2% by Francis et al. (11), 7.7 % by Ocak et al. (27). 6.4% by Dou et al. (29), 5.8% by Jin et al.(25), and 5.6% by Han et al. (24). Besides, Nout et al. (23) showed the total recurrence locoregional as 5.1% in 5 years follow-up and a similar association was found between the groups according to recurrence. In accordance with the literature, the total recurrence rate was 6.4% in this present study, and a similar association between the groups according to recurrence was found. While 5-year survival in Ren et al.'s study (28) was 94.6%, it was reported as 99.1% in this study. Investigating the effect of early-stage EC on prognosis, Nout et al. (23) found that there was a similar association in OS and DFS between the two groups. Jin et al. (25) reported that it was associated with similar local control and long-term survival outcomes between the two groups, and no difference was found in terms of survival and recurrence. Similarly, in this study, no difference was found between the two groups in terms of recurrence and survival duration.

Nowadays, it was thought that late recurrences and micrometastases in areas that did not receive radiotherapy may be after a long latent period and may be evident in non-high-risk cases(28). However, it remains unclear whether isolated tumor cells or micrometastases have had an adverse effect on the prognosis of intermediate-risk endometrial cancer(32). However, it is thought that the development of late recurrences can be detected by the risk classification of endometrial cancer and new molecules (35, 36). Limitations of the present study were that it was a single center, had no analysis of risk groups, unknown recurrence site, unknown adjuvant radiotherapy pattern, and it was retrospective. Its strengths were that it was a large case series consisting only of early-stage endometrioid histological type cases and it is important to investigate its effects on survival. As a result, early-stage endometrioid-type endometrial cancer has a favorable prognosis, and development of recurrence is the main prognostic predictor for survival. The early diagnosis and treatment of recurrence have a positive impact on the prognosis.

Acknowledgements

None

Author Contributions

Fazıl Avcı: Materials, Writing article, Design, Critical review. Onder Eren: Writing article, Design, Critical review. Ahmet Bilgi: Analysis and/or interpretation, Critical review. Hamit Basaran: Critical review, Idea / concept. Murat Celik: Critical review, Idea /concept, data collection and/or processing. Melek Caglayan: Literature review, references and design, data collection and/or processing. Cetin Celik: Analysis and/or interpretation, control/supervision. All authors read and approved the final manuscript.

References

1.Siegel RL MK, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020 Jan;70(1):7-30. .

2.Tung HJ, Huang HJ, Lai CH. Adjuvant and post-surgical treatment in endometrial cancer. Best Pract Res Clin Obstet Gynaecol. 2022 Jan;78:52-63.

3.Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.

4.McDonald ME, Bender DP. Endometrial Cancer: Obesity, Genetics, and Targeted Agents. Obstet Gynecol Clin North Am. 2019 Mar;46(1):89-105. .

5.Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006 Nov;95 Suppl 1:S105-43. .

6.Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C et al. ESMO Guidelines Working Group. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct;24 Suppl 6:vi33-8. .

7.Connor EV, Rose PG. Management Strategies for Recurrent Endometrial Cancer. Expert Rev Anticancer Ther. 2018 Sep;18(9):873-885. .

8.Scholten AN, van Putten WL, Beerman H, Smit VT, Koper PC, Lybeert ML et al. PORTEC Study Group. Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys. 2005 Nov 1;63(3):834-8. .

9.Nugent EK, Bishop EA, Mathews CA, Moxley KM, Tenney M, Mannel RS et al. Do uterine risk factors or lymph node metastasis more significantly affect recurrence in patients with endometrioid adenocarcinoma? Gynecol Oncol. 2012 Apr;125(1):94-8. .

10.Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD et al. Gynecologic Oncology Group. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004 Mar;92(3):744-51. .

11.Francis SR, Ager BJ, Do OA, Huang YJ, Soisson AP, Dodson MK et

al. Recurrent early stage endometrial cancer: Patterns of recurrence and results of salvage therapy. Gynecol Oncol. 2019 Jul;154(1):38-44.

12.Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC et al. PORTEC Study Group. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol. 2003 May;89(2):201-9.

13.Wortman BG, Nout RA, Bosse T, Creutzberg CL. Selecting Adjuvant Treatment for Endometrial Carcinoma Using Molecular Risk Factors. Curr Oncol Rep. 2019 Jul 31;21(9):83. .

14.Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Cancer Care Ontario Program in Evidence-based Care Gynecology Cancer Disease Site Group. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006 Jun;101(3):520-9. .

15.Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021 Jan;31(1):12-39.

16.Bendifallah S, Ouldamer L, Lavoue V, Canlorbe G, Raimond E, Coutant C et al.. Groupe de Recherche FRANCOGYN. Patterns of recurrence and outcomes in surgically treated women with endometrial cancer according to ESMO-ESGO-ESTRO Consensus Conference risk groups: Results from the FRANCOGYN study Group. Gynecol Oncol. 2017 Jan;144(1):107-112.

17.Nomura H, Aoki D, Susumu N, Mizuno M, Nakai H, Arai M et al. Analysis of the relapse patterns and risk factors of endometrial cancer following postoperative adjuvant chemotherapy in a phase III randomized clinical trial. Gynecol Oncol. 2019 Dec;155(3):413-419.

18.Dabi Y, Uzan J, Bendifallah S, Ouldamer L, Lavoué V, Canlorbe G et al. Groupe de Recherche FRANCOGYN. Prognostic value of local relapse for patients with endometrial cancer. Eur J Surg Oncol. 2017 Nov;43(11):2143-2149.

19.Pecorelli S. Revised FIGO staging for carcinoma of the vulva c, and endometrium. Int J Gynaecol Obstet. 2009 May;105(2):103-4. doi: 10.1016/j.ijgo.2009.02.012. Erratum in: Int J Gynaecol Obstet. 2010 Feb;108(2):176.

20.Abu-Rustum NR, Yashar CM, Bradley K, Campos SM, Chino J, Chon HS et al. NCCN Guidelines® Insights: Uterine Neoplasms, Version 3.2021. J Natl Compr Canc Netw. 2021 Aug 1;19(8):888-895.

21.Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J et al. ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016 Jan;27(1):16-41. doi: 10.1093/annonc/mdv484. Epub 2015 Dec 2. Erratum in: Ann Oncol. 2017 Jul 1;28(suppl_4):iv167-iv168. PMID: 26634381.

22.Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR et al. Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018 Feb;16(2):170-199.

23.Nout RA, Smit VT, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC et al. PORTEC Study Group. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet. 2010 Mar 6;375(9717):816-23.

24.Han KH, Kim HS, Lee M, Chung HH, Song YS. Prognostic factors for tumor recurrence in endometrioid endometrial cancer stages IA and IB. Medicine (Baltimore). 2017 May;96(21):e6976. .

25.Jin M, Hou X, Sun X, Zhang Y, Hu K, Zhang F. Impact of different adjuvant radiotherapy modalities on women with early-stage intermediate- to high-risk endometrial cancer. Int J Gynecol Cancer. 2019 Oct;29(8):1264-1270.

26.Imboden S, Tapia C, Scheiwiller N, Kocbek V, Altermatt HJ, Janzen J et al. Early-stage endometrial cancer, CTNNB1 mutations, and the relation between lymphovascular space invasion and recurrence. Acta Obstet Gynecol Scand. 2020 Feb;99(2):196-203. .

27.Ocak B, Sahin AB, Oz Atalay F, Ozsen M, Dakiki B, Ture S et al. Why do some patients with stage 1A and 1B endometrial endometrioid carcinoma experience recurrence? A retrospective study in search of prognostic factors. Ginekol Pol. 2021 Jun 9.

28.Ren K, Wang W, Sun S, Hou X, Hu K, Zhang F. Recurrent patterns after postoperative radiotherapy for early stage endometrial cancer: A competing risk analysis model. Cancer Med. 2022 Jan;11(1):257-267. .

29.Dou Y, Song K, Fu Y, Shen Y, Zhang C, Yao S et al. Chinese Endometrial Carcinoma Consortium (CECC). Risk Factors and Prognosis of Early Recurrence in Stage I-II Endometrial Cancer: A Large-Scale, Multi-Center, and Retrospective Study. Front Med (Lausanne). 2022 Apr 14;9:808037. .

30.Matsuo K, Matsuzaki S, Nusbaum DJ, Machida H, Nagase Y, Grubbs BH et al. Malignant peritoneal cytology and decreased survival of women with stage I endometrioid endometrial cancer. Eur J Cancer. 2020 Jul;133:33-46.

31.Dai Y, Dong Y, Cheng Y, Hou H, Wang J, Wang Z et al. Prognostic significance of lymphovascular space invasion in patients with endometrioid endometrial cancer: a retrospective study from a single center. J Gynecol Oncol. 2020 May;31(3):e27. .

32.Todo Y, Kato H, Okamoto K, Minobe S, Yamashiro K, Sakuragi N. Isolated tumor cells and micrometastases in regional lymph nodes in stage I to II endometrial cancer. J Gynecol Oncol. 2016 Jan;27(1):e1. .

33.Chodavadia PA, Jacobs CD, Wang F, Havrilesky LJ, Chino JP, Suneja G. Off-study utilization of experimental therapies: Analysis of GOG249-eligible cohorts using real world data. Gynecol Oncol. 2020 Jan;156(1):154-161.

34.Klopp A, Smith BD, Alektiar K, Cabrera A, Damato AL, Erickson B et al. The role of postoperative radiation therapy for endometrial cancer: Executive summary of an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol. 2014 May-Jun;4(3):137-144. .

35.Stelloo E, Nout RA, Osse EM, Jürgenliemk-Schulz IJ, Jobsen JJ, Lutgens LC et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 2016 Aug 15;22(16):4215-24. .

36.Wortman BG, Nout RA, Bosse T, Creutzberg CL. Selecting Adjuvant Treatment for Endometrial Carcinoma Using Molecular Risk Factors. Curr Oncol Rep. 2019 Jul 31;21(9):83.