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Evaluation of vaginal brachytherapy for treating early-stage endometrial cancer according to the European Society of Medical Oncology 2020 risk stratification

Avrupa Tıbbi Onkoloji Derneği 2020 kılavuzu risk sınıflamasına göre erken evre endometrium kanseri tedavisinde vajinal brakiterapinin etkinliğinin incelenmesi

Duygu Cebecik Özmüş[1], Zeliha Güzelöz[2], Muzaffer Şancı[3]

[1]*Sakarya Training and Research Hospital, Clinic of Gynecology and Obstetrics, Sakarya, Turkey*

[2]*University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Radiation Oncology, İzmir, Turkey*

[3]*University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Gynecological Oncology, İzmir, Turkey*

Abstract

Objective: The aim was to evaluate vaginal brachytherapy (VB) after surgery in early-stage endometrial cancer.

Materials and Methods: The patients with Stage I-II endometrial adeno-cancer operated between 1998 and 2018 and whose adjuvant therapies had been arranged were evaluated retrospectively.

Results: A total of 618 patients were enrolled. In 409 patients in the low-risk group, the vaginal, pelvic recurrence, and distant metastasis rates were found to be higher in the VB group. When the results of 112 patients in the intermediate-risk group were evaluated, there was no statistically significant difference between the vaginal, pelvic recurrence, and distance metastasis rates. In 89 patients in the intermediate-high risk group, vaginal recurrence rates were 0%, 4.8%, 0%, and 25% for VB, external beam radiotherapy, combination radiotherapy, and the follow-up groups, respectively (p=0.010), and pelvic recurrence rates were found to be 18.2%, 0%, 1.9% and 0% (p=0.036). Distant metastasis rates were 0%, 0%, 9.6% and 0% (p=0.229). When the overall survival in all groups was examined, no significant difference was found between the groups.

Conclusion: In conclusion, no adjuvant treatment is a proper approach for low-risk patients. Brachytherapy can be considered a suitable option for the intermediate risk group. Combined treatments instead of VB in the high-intermediate risk group would be preferred in terms of local control.

Keywords: Brachytherapy, adjuvant radiotherapy, vaginal administration, endometrial cancer

Öz

Amaç: Çalışmada amacımız erken evre endometrium kanserinde vajinal brakiterapinin (VB) etkinliğini araştırmaktır.

Gereç ve Yöntemler: 1998-2018 yılları arasında ESMO kliniğimizde opere edilen ve adjuvan tedavileri düzenlenen Evre I-II endometrioid adeno karsinom tanılı hastalar retrospektif olarak değerlendirilmiştir.

Bulgular: Çalışmaya 618 hasta dahil edildi. Düşük riskli hasta grubunda olan 409 hasta incelendiğinde vajinal, pelvik rekürrens ve uzak metastaz oranları VB grubunda daha yüksek bulundu. Orta risk grubunda olan 112 hastanın sonuçları değerlendirildiğinde vajinal, pelvik rekürrens ve uzak metastaz oranlarında istatistiksel olarak anlamlı bir sonuç bulunmadı. Yüksek-orta risk grubunda olan toplam 89 hastanın VB, dış ışın radyoterapi, kombine radyoterapi ve takip grupları için sırası ile vajinal rekürrens oranları %0, %4,8, %0, %25 (p=0,010), pelvik rekürrens oranları %18,2, %0, %1,9, %0

PRECIS: In this study, using our 20-years data we examined the efficacy of vaginal brachytherapy in early-stage endometrial cancer.

Address for Correspondence/Yazışma Adresi: Duygu Cebecik Özmüş MD,
Sakarya Training and Research Hospital, Clinic of Gynecology and Obstetrics, Sakarya, Turkey
Phone: +90 535 863 02 68 **E-mail:** duygucebecik@gmail.com **ORCID ID:** orcid.org/0000-0001-5368-9436

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(p=0,036) olarak bulundu. Uzak metastaz oranları %0, %0, %9,6, %0 idi (p=0,299). Genel sağkalımlar karşılaştırıldığında sırası ile %100, %95,2, %92,3, %75 olarak bulundu (p=0,534).

Sonuç: Beklenenin aksine düşük risk grubunda VB uygulanan hastaların lokal yineleme oranları daha yüksek bulundu. Bu grubun sağkalımları karşılaştırıldığında VB uygulanan hastaların sağkalımlarının istatistiksel anlamlı olmamak ile birlikte daha düşük olduğu görüldü. Orta risk grubundaki hastalarda tedavi grupları arasında rekürrens, uzak metastaz ve genel sağkalım açısından fark saptanmamıştır. Beklenildiği gibi yüksek-orta risk grubunda ise takip ve brakiterapi uygulanan hastalarda istatistiksel anlamlı olarak yüksek lokal yineleme gözlenmiştir. Bu grup hastalarda dış ışın radyoterapi ya da kombine tedavi seçeneği tercih edilmelidir.

Anahtar Kelimeler: Brakiterapi, adjuvan radyoterapi, vajinal uygulama, endometrium kanser

Introduction

The adjuvant therapy approach has changed over time in early-stage endometrial cancer. This approach began with combination therapies like external beam radiotherapy (EBRT)+vaginal brachytherapy (VB), which has left its place to no adjuvant or single modality therapies. The indication for adjuvant therapy is based on the evaluation of clinicopathological prognostic factors, including age, grade, stage of the disease, myometrial invasion, and lymphovascular space invasion (LVSI). These factors guide predicting the likelihood of disease recurrence after surgery. In patients with low-risk endometrial cancer (stage 1 endometrioid, grade 1-2, <50% myometrial invasion, LVSI negative), adjuvant treatment is not recommended[1]. A randomized trial of 645 patients with low-risk endometrial cancer treated with brachytherapy also showed no advantage for the use of adjuvant VB[2]. Large randomized trials with patients are considered intermediate risk, and a meta-analysis by Kong et al.[3] found that EBRT reduced pelvic recurrence but had no benefit on overall survival[4,5]. These trials identified a subgroup of patients who benefited the most from adjuvant EBRT, named as the high-intermediate risk group. Only in this subgroup was the risk of relapse was observed to be high enough to consider adjuvant radiotherapy (RT)[4]. In patients with intermediate risk endometrial cancer (stage1 endometrioid, grade 1-2, >50% myometrial invasion, LVSI negative) adjuvant brachytherapy is recommended[1]. However, not performing routine adjuvant RT is also an alternative approach[6]. A recent pool data analysis from the PORTEC-1 and PORTEC-2 trials showed that both LVSI and grade 3 are risk factors for distant metastasis and/or or regional nodal recurrence[7]. In patients who have high-intermediate risk endometrial cancer, adjuvant VB is recommended to decrease vaginal recurrence and adjuvant EBRT is recommended for LVSI unequivocally positive to reduce pelvic recurrence[1].

Materials and Methods

In our study, patients diagnosed with Stage I and Stage II endometrioid adenocarcinoma underwent surgery in our clinic between 1998 and 2018, and adjuvant therapy was decided in the multi-disciplinary tumor council and was retrospectively evaluated. Ethics committee approval was obtained from the Health Sciences University İzmir Tepecik Training and Research Hospital Ethics Committee (decision no: 2020/12-44, date: 12.10.2020). Our study was conducted following the ethical standards described in the 1975 Declaration of Helsinki, as revised in 2000.

The inclusion criteria were being over 18 years of age, Stage I-II cancer with endometrioid histology, and not having received adjuvant chemotherapy. The exclusion criteria were history of concomitant or past malignancy, non-endometrioid histology, advanced-stage disease, patients who received adjuvant chemotherapy, and those without follow-up data that could not be accessed. Risk classification was based on the 2020 European Society for Medical Oncology (ESMO)/European Society of Gynaecological Oncology/European Society for Radiotherapy & Oncology guideline[6]. Table 1 presents the summary of the risk classification created based on the guideline.

After endometrial biopsy and radiological staging, all patients underwent routine hysterectomy and bilateral salpingo-oophorectomy. Lymph node assessment was made according to pre-operative imaging and intraoperative frozen section results. The surgical stage was performed according to the International Federation of Gynecology and Obstetrics 2009 classification[8].

Table 1. Risk classification according to the 2020 ESMO/ESGO/ESTRO guideline

Low risk	-Patients in Stage 1A endometrioid, low grade and not having lymphovascular invasion (or local lymphovascular invasion)
İntermediate risk	-Patients in Stage 1B endometrioid, low grade and not having lymphovascular invasion (or local lymphovascular invasion) -Patients in Stage 1A endometrioid, high grade and not having lymphovascular invasion (or local lymphovascular invasion) -Stage 1A non-endometrioid tumor, no myometrial invasion
High-intermediate risk	-Patients with Stage 1 endometrioid lymphovascular invasion (irrespective of grade and myometrial invasion) -Patients with Stage 1B endometrioid, high grade (irrespective of lymphovascular invasion) -Patients in Stage 2

ESMO: European Society for Medical Oncology, ESGO: European Society of Gynaecological Oncology, ESTRO: European Society for Radiotherapy & Oncology

Adjuvant treatment was determined at the multi-disciplinary gynecological oncology tumor council. According to the final pathology report, patients have suggested no adjuvant treatment, VBT, EBRT, or combination therapy (EBRT+VB).

Patients who had received radiotherapy before 2004 were treated with 2-dimensional radiotherapy, and those who had received radiotherapy after 2004 were treated with 3-dimensional conformal RT and intensity-adjusted RT technique. Pelvic external RT was administered as a total of 45-50.4 Gy/1.8 Gy daily. Brachytherapy was applied at a dose of 6-7 Gy daily in 1-3 fractions. The patients were followed up once every three months during the first two years, every six months during the following five years, and once yearly for up to 10 years. When required, the patients underwent vaginal examination, ultrasound examination, and recurrences were evaluated with positron emission tomography-computed tomography, magnetic resonance imaging, and biopsy. In our study, the mean postoperative follow-up period of the patients was 130.29±14.41 months.

The study's primary endpoint was to determine vaginal, pelvic recurrence, or distant metastases in patients undergoing brachytherapy compared with other adjuvant therapy options. The secondary endpoint was to evaluate survival according to the risk groups.

Statistical Analysis

Continuous data are given as mean ± standard deviation. Categorical data are given as a percentage (%). Shapiro-Wilk test was used to investigate the suitability of the data for normal distribution. In the comparison of normally distributed groups, independent sample t-test analysis was used for cases with two groups, and One-Way ANOVA for cases with three or more groups. The Mann-Whitney U test was used for cases with two groups and the Kruskal-Wallis H test for cases with three or more groups in the comparison of groups that did not conform to the normal distribution. Pearson chi-square and Pearson Exact chi-square analyzes were used in the analysis of the created cross tables. Survival Analyzes were used to calculate and compare lifespans. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used in the analysis. A value of $p<0.05$ was accepted as a criterion for statistical significance.

Table 2. Demographic information

	n	%
Stage		
IA	439	71.0
IB	145	23.5
II	34	5.5
Lymphovascular invasion		
Negative	559	90.5
Poisitive	59	9.5
Age		
<60	399	64.6
≥60	219	35.4
Grade		
1	339	54.9
2	247	40
3	32	5.1

Results

The data of 618 patients who met the inclusion criteria were analyzed. The median duration of follow-up was 72 months (36-132), and the median age was 56 (50-62). Hysterectomy was performed in all patients. Of the cases, 523 underwent abdominal, 84 underwent laparoscopically, 8 underwent robotically and 2 underwent vaginal hysterectomy. Laparotomy was completed in 6 of the 84 patients who had undergone laparoscopy. Five patients underwent ovarian sparing surgery. Median 4500 cGy (4500-5040) adjuvant external RT and 1800 cGy (1300-2100) brachytherapy was administered.

The distribution of demographic information and the prognostic characteristics according to the adjuvant treatment options is presented in Table 2 and Table 3.

In our study, 618 early-stage patients were compared according to the risk stratification and treatment groups.

A comparison of low-risk patients according to treatment groups is given in Table 4.

When the treatment results were compared in the low-risk group, vaginal recurrence, pelvic recurrence, distant metastasis, and total recurrence rates were significantly higher in the VB group (p=0.007 for vaginal recurrence, p=0.027 for pelvic recurrence, p=0.034 for distant metastasis). The overall survival rates were found to be 94.9%, 97.8%, 100% and 98.3% (p=0.567).

The evaluation of patients in the intermediate-risk group by treatment groups is presented in Table 5.

When the recurrence rates of patients were compared according to the treatment groups between intermediate-risk patients, no pelvic recurrence was observed in this group, and no statistically significant difference was observed. The overall survival rates were 100%, 97.8%, 93.9%, 80%, respectively (p=0.223). The follow-up group had the shortest survival.

The treatment groups' evaluation of the high-intermediate risk patients is been presented in Table 6.

The vaginal recurrence rate was 4.8% and 25% in the EBRT and follow-up groups, respectively (p=0.01), and the pelvic recurrence rate was 18.2% in the VB group, in the high intermediate risk group the difference was statistically significant (p=0.036). When the overall survival rates were compared, they were 100%, 95.2%, 92.3%, and 75% for VB, EBRT,

combination therapy, and the follow-up groups, respectively (p=0.534). In the intermediate-high risk group, significantly higher recurrence rates were observed in the follow-up and VB groups.

When the recurrence rates were evaluated according to age, as a cut of 60 years, there was no statistical significance in terms of vaginal and pelvic recurrence (p=0.702 and p=0.671 for vaginal and pelvic recurrence, respectively). However, the distant metastasis rate was significantly higher in patients greater than or equal to 60 years (1.3% vs. 5%, p=0.01).

As the prognostic factors such as age, grade, stage, presence of LVSI for overall survival and disease-free survival were analyzed, the existence of lymphovascular invasion was the most influential variable on overall survival (hazard ratio: 5.855, 95% confidence interval, p<0.001). When the same data were analyzed for disease-free survival, stage and tumor grade were the most influential variables.

Discussion

According to our results, adjuvant therapy did not provide additional benefits in low-risk patients, similar to the literature. In a prospective study by Sorbe et al.[2] comparing VB and no adjuvant treatment groups in low-risk patients, no significant difference was observed in terms of recurrence and overall survival. In our study, no adjuvant treatment decision was taken in 72% (n=294), and VB was applied to 14.5% (n=59) of low-risk group patients, and vaginal, pelvic recurrence, and distant metastasis rates in the VB group were found to be significantly higher. That is because of unbalanced randomization between the groups due to the retrospective nature of the data. This is a limitation of our study. While 84.7% of the patients in the VB group had grade 2 disease, this rate was 16% in the no adjuvant treatment group. This may be a reason for high recurrence rates in the brachytherapy arm. Additionally, the biological equivalent dose of VB used in the study of Sorbe seems higher than that in our research. This was evaluated as one of the influencing factors even though it was insufficient to explain the difference.

The PORTEC-1 and the GOG-99 studies investigated the effectiveness of adjuvant radiotherapy for intermediate early-stage endometrial cancer[4,5]. These studies were designed to evaluate the effectiveness of pelvic radiotherapy according to recurrence. According to the PORTEC-1 research, while the local recurrence rates were observed to decrease significantly in patients who had received pelvic radiotherapy (14% vs. 4%), no significant difference was found in the overall survival (81% in the radiotherapy group, 85% in the control group). The treatment-related toxic effects were observed at a rate of 25% in the radiotherapy group; this rate was 6% in the control group[4]. The results of the GOG-99 study also supported these data. Twenty-four-month cumulative outcomes were compared while the recurrence rate was 3% in the radiotherapy group, 12% recurrence was observed in the group not receiving radiotherapy, and the difference was statistically significant

Table 3. Prognostic characteristics

	VBT (n=97)	EBRT (n=115)	VBT + EBRT (n=94)	No adjuvant treatment (n=303)	p
Stage					
IA	64 (66%)	62 (54%)	12 (13%)	296 (98%)	<0.001
IB	33 (34%)	51 (44%)	52 (55%)	6 (2%)	
IC	0 (0%)	2 (2%)	30 (32%)	1 (0%)	
Grade					
1	16 (16%)	40 (35%)	28 (30%)	251 (83%)	<0.001
2	78 (80%)	61 (53%)	54 (57%)	51 (17%)	
3	3 (3%)	14 (12%)	12 (13%)	1 (0%)	
LVI					
Positive	11 (11%)	18 (16%)	25 (27%)	3 (1%)	<0.001
Negative	86 (89%)	97 (84%)	69 (73%)	300 (99%)	
Risk classification					
High-intermediate	11 (11%)	21 (18%)	52 (55%)	4 (1%)	<0.001
Intermediate	27 (28%)	47 (41%)	33 (35%)	5 (2%)	
Low risk	59 (61%)	47 (41%)	9 (10%)	294 (97%)	
Age	61.0 (54.0-64.0)	57.0 (52.0-62.5)	57.0 (53.0-63.0)	54.0 (48.0-59.0)	<0.001

EBRT: External beam radiotherapy, VB: Vaginal brachytherapy

Table 4. Distribution of low-risk patients

n=409	VB (n=59)	EBRT (n=47)	VB+EBRT (n=9)	No adjuvant treatment (n=294)	p
Age (median)	52.00 (50-62)	60.00 (54-66)	64.00 (52-64)	57.00 (52-63)	0.149
Grade					
1	9 (15.3%)	9 (19.1%)	2 (22.2%)	247 (84.0%)	<0.001
2	50 (84.7%)	38 (80.9%)	7 (77.8%)	47 (16.0%)	
3	(0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Lymp node dissection					
Without	8 (13.6%)	10 (21.3%)	2 (22.2%)	61 (20.7%)	0.634
With	51 (86.4%)	37 (78.7%)	7 (77.8%)	233 (79.3%)	
Vaginal recurrence	3 (5.1%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0.007
Pelvic recurrence	2 (3.4%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0.027
Distant metastasis	3 (5.1%)	0 (0.0%)	0 (0.0%)	2 (0.7%)	0.034
Overall recurrence	8 (13.6%)	1 (2.1%)	0 (0.0%)	3 (1.0%)	0.001
5-years survival	58 (98%)	47 (100%)	9 (100%)	294 (99%)	0.536
Overall survival	56 (94.9%)	46 (97.8%)	9 (100%)	289 (98.3%)	0.567

EBRT: External beam radiotherapy, VB: Vaginal brachytherapy

Table 5. Distribution of intermediate-risk patients

(n=112)	VBT (n=27)	EBRT (n=47)	VBT+EBRT (n=33)	Noadjuvant treatment (n=5)	p
Age (median)	58.00 (53.00-60.00)	53.00 (50.50-55.50)	56.50 (50.25-61.25)	51.00 (34.00-51.00)	0.107
Grade					
1	6 (22.2%)	29 (61.7%)	11 (33.3%)	2 (40.0%)	<0.001
2	19 (70.4%)	11 (23.4%)	22 (66.7%)	3 (60.0%)	
3	2 (7.4%)	7 (14.9%)	0 (0.0%)	0 (0.0%)	
Lymp node dissection					
Without	6 (22.2%)	8 (17.0%)	4 (12.1%)	2 (40.0%)	0.426
With	21 (77.8%)	39 (83.0%)	29 (87.9%)	3 (60.0%)	
Vaginal recurrence	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.365
Pelvic recurrence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Distant metastasis	0 (0.0%)	1 (2.1%)	3 (9.1%)	0 (0.0%)	0.222
Overall recurrence	1 (3.7%)	1 (2.1%)	3 (9.1%)	0 (0.0%)	0.470
5-years survival	25 (100%)	47 (100%)	32 (97%)	4 (80%)	0.110
Overall survival	27 (100%)	46 (97.8%)	31 (93.9%)	4 (80%)	0.223

EBRT: External beam radiotherapy, VB: Vaginal brachytherapy

(p<0.01). The forty-eight-month overall survival rates were reported to be 92% in the RT group and 86% in the non-RT-receiving group (p=0.55)[5]. The number of patients followed in the intermediate-risk group was small in our study. Although this was a limitation of the study, not finding a difference between the treatment groups was consistent with the literature. After the GOG-99 and PORTEC-1 trials, for the intermediate risk group, radiation therapy was evaluated as an effective treatment. The effectiveness of VB and pelvic radiation therapy in the high- intermediate-risk group was compared in the

Table 6. Distribution of high-intermediate risk group patients

(n=89)	VBT (n=11)	EBRT (n=21)	VBT+EBRT (n=52)	No adjuvant treatment (n=4)	p
Age	61.50 (55.00-61.50)	52.00 (49.00-63.50)	58.00 (51.00-63.00)	50.00±6.16 -	0.559
Grade					
1	1 (9.1%)	2 (9.5%)	15 (28.8%)	2 (50.0%)	0.169
2	9 (81.8%)	12 (57.1%)	25 (48.1%)	1 (25.0%)	
3	1 (9.1%)	7 (33.3%)	12 (23.1%)	1 (25.0%)	
Lymp node dissection					
Without	2 (18.2%)	3 (14.3%)	11 (21.2%)	1 (25.0%)	0.909
With	9 (81.8%)	18 (85.7%)	41 (78.8%)	3 (75.0%)	
Vaginal Recurrence	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (25.0%)	0.010
Pelvic Recurrence	2 (18.2%)	0 (0.0%)	1 (1.9%)	0 (0.0%)	0.036
Distant metastasis	0 (0.0%)	0 (0.0%)	5 (9.6%)	0 (0.0%)	0.299
Overall recurrence	2 (18.2%)	1 (4.8%)	6 (11.5%)	1 (25.0%)	0.541
5-years survival	11 (100%)	20 (95%)	47 (94%)	3 (75%)	0.332
Overall survival	11 (100%)	20 (95%)	46 (92.3%)	3 (75%)	0.534

PORTEC-2 study[9]. In the 5-year results of this study, vaginal and pelvic recurrence rates were not statistically significant between the groups. No difference was observed in the distant metastasis rates and survival. Wortman et al.[10] reported the 10-year outcomes of the study, and no differences were observed between the groups in local recurrence, distant metastasis, and overall survival. When the results of our study were analyzed, no significant difference was observed in the disease-free survival and the overall survival between VB, EBRT, combination therapy, and the follow-up groups in high-intermediate-risk patients.

When we examined the results of high-intermediate-risk patients, the presence of vaginal recurrence in the EBRT group and pelvic recurrence in the VB group brought the question of whether we should choose combination therapy for these patients. No significant difference was observed in distant metastasis or overall survival. However, the highest distant metastasis rate found in the combination therapy group was striking. The high rate of grade 3 disease in this group may have increased the distant metastasis risk.

In a retrospective study by Jin et al.[11], VB and combination therapy were compared in the high-intermediate and the high-risk groups of patients according to the 2016 ESMO guideline, and no significant difference was not observed between the groups in overall survival. The study did not conduct a subgroup analysis between the two risk groups. In our study, the intermediate and high-intermediate risk groups were evaluated individually. This may explain the higher recurrence rates in the high-intermediate risk group. Additionally, the inclusion of Stage II patients according to the new classification system[12] who received combination therapy may be the other reason to explain the high recurrence rate.

The most critical step in deciding on adjuvant therapy is being able to determine the recurrence risk. The multi-variable analysis performed age, grade, LVSI, and stage. While stage and grade were the most important variables for disease-free survival, lymphovascular space involvement was the most influential variable for overall survival. In the PORTEC-1 study, lymphovascular space was not evaluated, and age was the most important risk factor. In the PORTEC-2 study, which included patients above 60 years, lymphovascular invasion was reported to be the most critical factor for local recurrences. In the variation analysis by Jin et al.[11], tumor grade was found to be the most important variable for disease-free and overall survival.

In the study by Cisek et al.[13], the age above 70 years was the most important variable for overall survival; and stage was the most important variable for disease-free survival. Our study determined a statistically significant difference for only distant metastasis in the group above 60.

Study Limitation

This article is a retrospective article based on 20 years of data. In this period, diagnostic methods used and possible method and device differences in radiotherapy may adversely affect the reliability of the data. We revised these data to current clinicopathological parameters but could not use molecular parameters. Additionally, in this period, diagnostic methods

used and possible method and device differences in radiotherapy may adversely affect the reliability of the data.

Conclusion

In conclusion, no adjuvant treatment is an appropriate approach for low-risk patients. VB did not provide an additional benefit for these patients.

In the intermediate-risk group, VB seems to be a preferable option as EBRT and combination radiation therapy exhibited similar results.

In the high-intermediate risk group, VB alone was insufficient compared with treatment modalities. In these patients, selecting combination therapies may be an appropriate approach for local control.

We believe that there will be changes in the decision of adjuvant treatment of endometrial cancer with further studies evaluating age, clinicopathological data, genetic characteristics and immunohistochemical data together.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Health Sciences University İzmir Tepecik Training and Research Hospital Ethics Committee (decision no: 2020/12-44, date: 12.10.2020).

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Authorship Contributions

Surgical and Medical Practices: D.C.Ö., Z.G., M.Ş., Concept: D.C.Ö., Z.G., M.Ş., Design: D.C.Ö., Z.G., M.Ş., Data Collection or Processing: D.C.Ö., Z.G., M.Ş., Analysis or Interpretation: D.C.Ö., Z.G., M.Ş., Literature Search: D.C.Ö., Z.G., M.Ş., Writing: D.C.Ö., Z.G., M.Ş.

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