

Original Article

Isolated Vaginal Metastases in Endometrial Cancer
and the Role of Adjuvant BrachytherapyEndometriyal Kanserde İzole Vajinal Metastazlar
ve Adjuvan Brakiterapinin Rolü

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ABSTRACT

Aim: The aim of the study was to investigate the effect of adjuvant vaginal brachytherapy (VBT) after initial surgery on local recurrence, disease-free (DFS) and overall survival (OS) in endometrial cancer (EC).

Methods: The data of patients diagnosed with EC in Gynecological Oncology Clinic between 1998 and 2021 were analyzed retrospectively. Patients who underwent total hysterectomy with negative surgical margins were included in the study.

Results: Fifty-six patients who were treated for EC and subsequently developed isolated vaginal metastases (IVM) were evaluated. In the treatment of vaginal recurrence, 20 patients were treated with resection + VBT ± external beam radiotherapy (EBRT) ± chemotherapy and 36 patients were treated with VBT + EBRT ± chemotherapy. The 5-year OS rate for patients who received resection + VBT treatment was 78.8%, and 35.8% for patients who received EBRT + VBT treatment (P= 0.023). Recurrence time did not differ significantly depending on whether or not adjuvant VBT was given (P= 0.463). The mean five-year OS rate was 49.4% and 62.5% in patients who did and did not receive VBT, respectively (P= 0.521). As a result of the evaluation of risk factors that may affect OS in patients with IVM according to Cox regression analysis, none of the prognostic factors were found to have a significant effect.

Conclusion: It was found that adjuvant vaginal brachytherapy did not affect the local recurrence time and overall survival rate in patients operated for endometrial cancer.

Key words: Vaginal metastases, Endometrial cancer, Brachytherapy, Lymph node

ÖZET

Amaç: Bu çalışmanın amacı, endometriyal kanserde (EK) ilk cerrahi sonrası adjuvan vajinal brakiterapinin (VBT) lokal nüks, hastalıksız (HS) ve toplam sağkalım (TS) üzerindeki etkisini araştırmaktır.

Yöntemler: 1998-2021 yılları arasında Jinekolojik Onkoloji Kliniğinde EK tanısı alan hastaların verileri retrospektif olarak incelendi. Çalışmaya cerrahi sınırları negatif olan total histerektomi yapılan hastalar dahil edildi.

Bulgular: EK nedeniyle tedavi edilen ve sonrasında izole vajinal metastaz (IVM) gelişen 56 hasta değerlendirildi. Vajinal nüks tedavisinde 20 hasta rezeksiyon + VBT ± external beam radyoterapi (EBRT) ± kemoterapi ve 36 hasta VBT + EBRT ± kemoterapi ile tedavi edildi. Rezeksiyon + VBT

tedavisi alan hastalarda 5 yıllık TS oranı %78,8, EBRT + VBT tedavisi alan hastalarda ise %35,8 idi (P= 0,023). Nüks süresi, adjuvan VBT verilip verilmemesine bağlı olarak anlamlı farklılık göstermedi (P= 0.463). Ortalama beş yıllık TS oranı VBT alan ve almayan hastalarda sırasıyla %49.4 ve %62.5 idi (P= 0.521). IVM'li hastalarda TS'yi etkileyebilecek risk faktörlerinin Cox regresyon analizine göre değerlendirilmesi sonucunda prognostik faktörlerin hiçbirinin anlamlı etkisi bulunmadı.

Sonuç: Adjuvan vajinal brakiterapinin endometrial kanser nedeniyle opere edilen hastalarda lokal nüks süresi ve genel sağkalım oranını etkilemediği bulundu.

Anahtar kelimeler: Vajinal metastazlar, Endometrium kanseri, Brakiterapi, Lenf nodu

Introduction

Endometrial cancer (EC) is the most common malignancy of the female genital tract and is the fourth most common cancer in women [1]. There has been an increase in the incidence of EC in both premenopausal and postmenopausal women due to changing environmental and nutritional factors (obesity, nulliparity, estrogen replacement therapy) [2]. Although the prognosis is generally very good, approximately 15% recurrence occurs [3]. Relapses usually occur within 3 years of initial treatment. Unfortunately, the 5-year survival rates of recurrent patients are significantly reduced, with salvage therapy success rates of around 16-40% [4,5]. For treatment management purposes, EC patients are subdivided according to their risk of recurrence, taking into account patient age, tumor size, the International Federation of Gynecology and Obstetrics (FIGO) staging, histological type and grade, and lymphovascular space involvement (LVSI) [4]. The overall five-year survival rate is 55% for pelvic recurrences and 17% for extrapelvic recurrences [2]. Half of the recurrences that occur in early-stage patients are confined to the pelvis, with the remainder being isolated extrapelvic metastases (25%) or both pelvic and extrapelvic (25%) recurrences [2]. Early detection of recurrent disease is critical and may affect survival as it is more suitable for localized disease treatment.

Recurrent disease centrally in the vaginal wall or vaginal cuff refers to local recurrence. The treatment approach depends on the specific

site of recurrence, the duration of the disease-free period, the patient's general health, and whether or not they have received prior adjuvant radiotherapy [2]. Although adjuvant radiotherapy reduces the risk of local recurrence, if recurrence occurs, it limits treatment options and has poorer survival [6]. Conventional external radiotherapy, intracavitary brachytherapy, and surgical excision are acceptable treatment options for vaginal recurrences [2]. Pelvic exenteration can usually be considered in patients with localized recurrence and who do not improve after radiation [2]. The aim of the study was to investigate the effect of adjuvant vaginal brachytherapy (VBT) after initial surgery on local recurrence, disease-free and overall survival in endometrial cancer.

Material and method

The data of patients diagnosed with EC in Gynecological Oncology Clinic between 1998 and 2021 were analyzed. Fifty-six cases with local recurrence were evaluated retrospectively. Patients who underwent total hysterectomy with negative surgical margins were included in the study. Patients with distant organ metastases or multiple metastases were excluded from the study. The study was approved by our local ethics committee (Date: 09.12.2022, Decision No: 2022/11-44). All procedures performed comply with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its subsequent amendments or comparable ethical standards

Table 1. Clinical and pathological features of endometrial cancer patients with vaginal recurrence

	VBT not performed (n: 36)	VBT performed (n: 20)	P
Age (years), mean \pm StD	59.1 \pm 10.1	65.6 \pm 8.6	0.097
Ca125, mean \pm StD	29.9 \pm 27.2	22.0 \pm 19.4	0.424
Hemoglobin (gr/dL), mean \pm StD	12.1 \pm 1.9	11.9 \pm 1.0	0.761
Histological type			0.284
- Endometrioid	28 (77.8%)	12 (60.0%)	
- Non-endometrioid	8 (22.2%)	8 (40.0%)	
High grade	12 (33.3%)	12 (60.0%)	0.167
Tumor size (cm), mean \pm StD	3.8 \pm 2.1	4.4 \pm 1.3	0.439
Pelvic lymph node dissection	28 (77.8%)	16 (80.0%)	0.205
Paraortic lymph node dissection	20 (55.6%)	12 (60.0%)	0.312
Deep myometrial invasion	8 (22.2%)	14 (70.0%)	0.019
Cervical stromal involvement	8 (22.2%)	4 (20.0%)	0.642
Adnexal involvement	-	2 (10.0%)	0.357
lymphovascular space invasion	10 (27.8%)	14 (70.0%)	0.039
Adjuvant external beam radiotherapy	8 (22.2%)	12 (60.0%)	0.046
Adjuvant chemotherapy	12 (33.3%)	6 (30.0%)	0.600
Short-term disease free interval (\leq 12 month)	12 (33.3%)	4 (20.0%)	0.454
Stage			0.084
- IA2	18 (50.0%)	-	
- IB	2 (5.6%)	4 (20.0%)	
- IIB	4 (11.1%)	8 (40.0%)	
- IIC	4 (11.1%)	4 (20.0%)	
- IIIC1	2 (5.6%)	-	
- IIIC2	6 (16.7%)	4 (20.0%)	
Treatment of recurrence			0.519
- Resection + VBT \pm EBRT \pm CT	12 (33.3%)	8 (40.0%)	
- VBT + EBRT \pm CT	24 (66.7%)	12 (60.0%)	

StD= Standard deviation, VBT= Vaginal brachytherapy, EBRT= External beam radiotherapy, CT= Chemotherapy

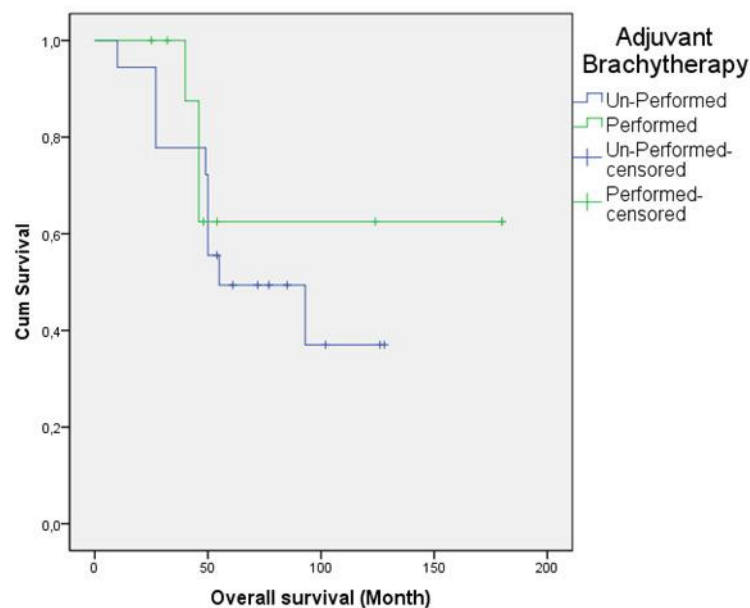


Figure 1. The effect of adjuvant vaginal brachytherapy on overall survival according to Kaplan-Meier curve

FIGO 2023 staging system was used [7]. Surgical procedures, adjuvant treatment methods and survival status of the patients were investigated from the file. LVSI, tumor size, depth of myometrial invasion, cervical involvement, adnexial involvement and lymph node status were analyzed from pathology reports. The diagnosis of vaginal metastasis was made by evaluating the results of speculum examination and biopsy sample. Distant organ metastasis was evaluated with computed tomography or magnetic resonance imaging or positron emission tomography.

All surgical operations were performed by experienced specialists in the field of gynecological oncological surgery. Abdominal exploration was done in detail. After entering the peritoneal cavity, peritoneal washing was performed for cytology. Exploration of the abdominal cavity included systematic examination of the peritoneal surfaces, omentum, colon and small intestine, and paracolic, pelvic, mesenteric, and para-aortic regions, as well as palpation to find suspicious lesions. Procedures included hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, and omentectomy. Systematic complete pelvic paraaortic lymphadenectomy was performed in the presence of deep myometrial invasion, cervical involvement, non-endometrioid histological type, grade 3 tumor. Pelvic lymphadenectomy consisted of removal of lymphatic tissue over the external and common iliac vessels and in the obturator fossa. Para-aortic LN dissection was defined as removal of the aorta starting from the bifurcation, above the inferior vena cava and below the left renal vein.

The adjuvant VBT dose and fractionation regimen is 3 fractions of 7.0 Gy (21 Gy total dose) prescribed to a vaginal depth of 0.5 cm. Vaginal cylinder diameters vary between 2.5 and 3.5 cm. VBT was administered when adequate healing of the vaginal cuff had occurred. Care was taken to ensure that there

was no longer than 8 weeks between surgery and the first brachytherapy fraction. Brachytherapy was applied in an average of 14 days. According to the FIGO 2023 staging system, patients between stages IB-IIC were recommended adjuvant vaginal brachytherapy. Brachytherapy may be considered for stage IIC patients. After the information, the patients made the decision.

All patients were followed up every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. In the control, the vagina was evaluated with a speculum, and the pelvis was examined by ultrasonography. At least once a year, cytology evaluation was performed with a smear from the vagina. Computed tomography or magnetic resonance imaging was performed annually. Disease-free survival (DFS) was defined as the time from the date of primary surgery to detection of recurrence or last observation. Total survival (OS) was defined as the time from the date of primary surgery to death or last observation.

Nominal parameters expressed as mean \pm standard deviation were analyzed using One Way ANOVA. Categorical data, which were evaluated as numbers and percentages, were compared with the help of the Chi-square test. Pearson chi-square test was used if the proportion of groups with less than 5 numbers was $<20\%$. Fisher's precision test was used if the proportion of groups with less than 5 numbers was $>20\%$ and the minimum evoked number was less than 5. Survival analysis was evaluated using the Kaplan-Meier method and results were compared using the log-rank test. Cox regression analysis was used to identify factors affecting survival and results are presented as hazard ratios (HR). Data recording and statistical analyzes were performed using SPSS (statistical package for the social sciences) software (version 17, SPSS, Inc, Chicago, IL). A p value of <0.05 was accepted to indicate statistical significance.

Table 2. Evaluation of risk factors that may affect overall survival in patients with vaginal recurrent endometrial cancer according to Cox regression analysis

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Recurrence therapy (Resection)	0.5	0.1-1.8	0.312	0.3	0.1-7.1	0.930
Lymph node involvement	4.9	1.2-19.8	0.026	5.1	0.1-17.6	0.367
Deep myometrial invasion	2.3	0.7-7.2	0.126	6.2	0.1-9.8	0.184
Cervical stromal invasion	2.3	0.6-9.0	0.212	3.9	0.1-12.4	0.568
Adnexal invasion	0.1	0.1-10.2	0.899	0.4	0.1-11.4	0.893
Lymphovascular space invasion	1.8	0.5-5.5	0.299	2.5	0.2-5.8	0.126
Vaginal brachytherapy	0.6	0.1-2.4	0.535	6.0	0.4-7.9	0.100
High CA125 (>35)	2.4	0.8-7.6	0.112	2.3	0.1-8.7	0.203
Non-endometrioid type	0.8	0.2-3.2	0.835	0.8	0.1-12.6	0.984
High grade (3)	1.0	0.6-1.9	0.781	1.3	0.1-14.2	0.920
Stage II-III	1.6	0.5-5.1	0.393	1.9	0.1-11.3	0.804
Short-term disease free interval	1.4	0.4-4.8	0.408	2.0	0.1-10.6	0.724

OR= Odds ratio, CI= Confidence interval

Results

Fifty-six patients who were treated for EC and subsequently developed isolated vaginal metastases (IVM) were evaluated. The mean age was calculated as 59.1 ± 10.1 and 65.6 ± 8.6 , respectively, in patients who did not receive and received adjuvant VBT at the initial diagnosis ($P= 0.097$). Tumors of 8 (22.2%) patients in the group not given adjuvant VBT and in 8 (40.0%) patients in the group given VBT were non-endometrioid histological type. Deep myometrial invasion was present in 8 (22.2%) patients in the group not given VBT and in 14 (70.0%) patients in the group given VBT ($P= 0.019$). The presence of LVSI was found to be more common in the VBT group ($P= 0.039$). Demographic data and clinical characteristics of endometrial cancer patients with vaginal recurrence, according to the groups that received and did not receive adjuvant VBT, are given in Table 1. In the treatment of vaginal recurrence, 20 patients were treated with resection + VBT \pm external beam radiotherapy \pm chemotherapy and 36 patients were treated with VBT + external beam radiotherapy \pm chemotherapy. The 5-year OS rate for patients who received resection + VBT treatment was 78.8%, and 35.8% for patients who received external beam radiotherapy + VBT treatment ($P= 0.023$).

The median duration of vaginal recurrence in patients who did not receive adjuvant VBT was 20 (3-104) months, and the median time to recurrence of patients who received VBT was 19.5 (6-72) months. Recurrence time did not differ significantly depending on whether or not adjuvant VBT was given ($P= 0.463$). The mean five-year OS rate was 49.4% and 62.5% in patients who did and did not receive VBT, respectively ($P= 0.521$) (Figure 1).

As a result of the evaluation of risk factors that may affect OS in patients with IVM according to Cox regression analysis, none of the prognostic factors were found to have a significant effect (Table 2). In Univariate regression analysis, lymph node involvement was found to be a negative risk factor for OS (OR= 4.9, 95% CI= 1.2-19.8).

Discussion

In our study, EC patients with isolated local recurrence were examined. When the relapse development time was examined, it was determined that adjuvant VBT did not make a difference. In addition, it was determined that adjuvant VBT had no effect on OS. Although VBT was given for local control, it was disappointing that it did not affect our main expectation of survival. In the treatment of isolated vaginal recurrence, the survival of patients who underwent resection in addition

to radiotherapy and chemotherapy was found to be significantly higher.

Endometrial cancer is usually diagnosed at an early stage and has a good prognosis, but the 5-year OS rate for patients who relapse is between 20-50% [8]. The most common site of recurrence is local recurrence in the vagina (30%) [9]. Relapses usually occur within the first three years [10]. For patients with local recurrence, the 3-year probability of survival was 34-64% [9]. IVM can be successfully treated with radiotherapy and/or surgery [11]. Patients who received radiotherapy for local recurrence had a 5-year OS of 75% [12]. More extensive surgery, such as pelvic exenteration, is usually reserved for patients with localized recurrences who do not improve after radiotherapy [2]. The incidence of complications related to the exenteration procedure is around 30-48% and the 5-year OS is around 40-73% [13,14]. In our cohort, the 5-year OS rate for patients who received resection + VBT treatment was 78.8% and 35.8% for patients who received external radiotherapy + VBT treatment ($P= 0.023$). Due to the small number of patients, we could not compare the recurrence treatment options of patients who received adjuvant VBT therapy and the recurrence treatment of patients who did not receive adjuvant VBT therapy. More valuable information can be provided by performing more homogeneous subgroup analyzes with a large number of patients and prospective studies.

Although adjuvant RT significantly reduces the risk of vaginal and intrapelvic recurrence, it has failed to improve overall survival [11,15,16]. Patients with local recurrence who did not receive adjuvant radiation had a better 5-year OS than those who received adjuvant radiotherapy (65% vs. 43%) [6]. In our study, we analyzed that there was no difference in mean five-year OS in patients who received and did not receive VBT ($P= 0.521$), and the

rate was 49.4% and 62.5%, respectively. It has been shown in the literature and in our study that adjuvant VBT treatment does not have a positive effect on OS. Therefore, we think that it is correct to give it to selected patients with more consideration when adjuvant VBT treatment is given. In the literature, patients with a long disease free interval have been shown to have better OS [11]. In our study, Cox-regression analysis showed that short disease-free interval did not have a significant effect on OS. When VBT doses and fractions were evaluated, according to multivariate regression analysis, it was reported that there was no difference in the risk of vaginal recurrence between 7.0 Gy 3 fractions prescribed to 0.5 cm depth, 6.5 Gy 3 fractions prescribed to 0.5 cm depth, or 6.0 Gy 5 fractions [17].

There are some shortcomings of our study. First of all, it can be said to be of a retrospective nature. Depending on this, there may be difficulty in remembering and missing information in the files. Secondly, it can be stated that the number of patients is small. Despite these, we think that our study with a homogeneous case group such as isolated vaginal recurrence in endometrial cancer, which is not very common, contains important results.

In conclusion, it was found that adjuvant vaginal brachytherapy did not affect the local recurrence time and overall survival rate in patients operated for endometrial cancer. Considering that the side effects that may occur due to brachytherapy and its deterioration in quality of life are considered, it is recommended not to be given to every patient, but to selected patients with a high risk of recurrence, considering its limited effect on overall survival. In addition, patients who do not receive adjuvant radiotherapy have an additional weapon for treatment when recurrence occurs

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