

Original Article

Isolated Vaginal Metastases of Endometrial Cancer and Their Role in Adjuvant Brachytherapy

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ABSTRACT

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

Methods: The data of patients diagnosed with EC at the gynecological oncology clinic between 1998 and 2021 were retrospectively analyzed. 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 rates for patients who received resection+VBT treatment were 78.8% and 35.8% for patients who received EBRT+VBT treatment ($p=0.023$). The recurrence time did not significantly differ depending on whether or not adjuvant VBT was given ($p=0.463$). The mean 5-year OS rates were 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: This study found that adjuvant VBT did not affect local recurrence time and OS rate in patients with EC.

Keywords: Vaginal metastasis, endometrial cancer, brachytherapy, lymph node

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 because of changes in environmental and nutritional factors (obesity, nulliparity, estrogen replacement therapy) [2]. Although the prognosis is generally excellent, recurrence occurs in approximately 15% of cases [3]. Relapses usually occur within 3 years of initial treatment. Unfortunately, the 5-year survival rate of patients with recurrence is 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, International Federation of Gynecology and Obstetrics (FIGO) staging, histological type and grade, and lymphovascular space involvement (LVSI) [4]. The overall 5-year survival rate is 55% for pelvic and 17% for extrapelvic recurrences [2]. Half of the recurrences 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

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disease is critical and may affect survival because it is more suitable for localized disease treatment.

The term recurrent disease central to the vaginal wall or vaginal cuff refers to local recurrence. The treatment approach depends on the specific site of recurrence, duration of 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, recurrence can limit treatment options and prolong survival [6]. Conventional external radiotherapy, intracavitary brachytherapy, and surgical excision are acceptable treatment options for vaginal recurrence [2]. Pelvic exenteration is usually considered in patients with localized recurrence who do not improve after radiation [2]. The aim of this study was to investigate the effect of adjuvant vaginal brachytherapy (VBT) after initial surgery on local recurrence, disease-free survival (DFS), and overall survival (OS) in patients with EC.

Methods

The data of patients diagnosed with EC at the gynecological oncology clinic between 1998 and 2021 were analyzed. Fifty-six cases of local recurrence were retrospectively evaluated. Patients who underwent total hysterectomy with negative surgical margins were included in the study. Patients with distant or multiple organ metastases were excluded from the study. The study was approved by University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Local Ethics Committee (date: 09.12.2022, decision no: 2022/11-44). All procedures were performed in compliance 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.

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

All surgical procedures were performed by experienced specialists in the field of gynecological oncology 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, small intestine, and paracolic, pelvic, mesenteric, and para-aortic regions, as well as palpation to identify suspicious lesions. The procedures included hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, and omentectomy. Systematic complete pelvic para-aortic lymphadenectomy was performed in the presence of deep myometrial invasion, cervical involvement, non-endometrioid histological type, and 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 can vary between 2.5 and 3.5 cm. VBT was administered when adequate vaginal cuff healing occurred. Care was taken to ensure no longer than 8 weeks between surgery and the first brachytherapy fraction. Brachytherapy was performed on an average of 14 days. According to the FIGO 2023 staging system, patients between stages 1B-2C were recommended adjuvant VBT. Brachytherapy may be considered for stage 3C patients. After obtaining the information, patients made a 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 group, the vagina was evaluated using a speculum, and the pelvis was examined using ultrasonography. At least once a year, cytology was evaluated using a smear of the vagina. Computed tomography or magnetic resonance imaging was performed annually. DFS was defined as the time from the date of primary surgery until the detection of recurrence or last observation. Total survival (OS) was defined as the duration from the date of primary surgery until death or last observation.

Statistical Analysis

Nominal parameters were expressed as mean±standard deviation and analyzed using one-way ANOVA. Categorical data, which were evaluated as numbers and percentages, were compared using the chi-square test. Pearson's 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 number of evoked signals was less than 5. Survival analysis was performed 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 the results are presented as hazard ratios. Data recording and statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 17, SPSS, Inc, Chicago, IL). A p value of <0.05 was set to indicate statistical significance.

Results

Fifty-six patients who were treated for EC and subsequently developed isolated vaginal metastases (IVM) were evaluated. Mean ages were calculated as 59.1±10.1 and 65.6±8.6, respectively, in patients who did not receive adjuvant VBT at the initial diagnosis (p=0.097). Tumors of 8 (22.2%) patients in the group who were not administered adjuvant VBT and in 8 (40.0%) patients in the group who were administered VBT were of the non-endometrioid histological type. Deep myometrial invasion was present in 8 (22.2%) patients in the group who

were not administered VBT and in 14 (70.0%) patients in the group who were administered VBT ($p=0.019$). The presence of LVSI was more common in the VBT group ($p=0.039$). Demographic data and clinical characteristics of patients with EC and vaginal recurrence according to the groups that received and did not receive adjuvant VBT are presented in Table 1. For 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 rates for patients who received resection+VBT treatment were 78.8% and 35.8% for patients who received EBRT+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 in patients who received VBT was 19.5 (6-72) months. The recurrence time did not significantly differ depending on whether or not adjuvant VBT was given ($p=0.463$). The mean 5-year OS rates were 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). Univariate regression analysis identified lymph node involvement as a negative risk factor for OS (odds ratio=4.9, 95% confidence interval=1.2-19.8).

Discussion

In this study, patients with EC with isolated local recurrence were examined. When the relapse development time was examined, adjuvant VBT was found to not have a significant effect. In addition, 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 significantly higher.

EC is usually diagnosed at an early stage and has a good prognosis; however, the 5-year OS rate for patients who relapse is between 20% and 50% [8]. The most common site of recurrence is 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

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

	VBT not performed (n=36)	VBT performed (n=20)	p
Age (years), mean±SD	59.1±10.1	65.6±8.6	0.097
CA125, mean±SD	29.9±27.2	22.0±19.4	0.424
Hemoglobin (gr/dL), mean±SD	12.1±1.9	11.9±1.0	0.761
Histological type			
- Endometrioid	28 (77.8%)	12 (60.0%)	0.284
- Non-endometrioid	8 (22.2%)	8 (40.0%)	
High grade	12 (33.3%)	12 (60.0%)	0.167
Tumor size (cm), mean±SD	3.8±2.1	4.4±1.3	0.439
Pelvic lymph node dissection	28 (77.8%)	16 (80.0%)	0.205
Para-aortic 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 (≤12 month)	12 (33.3%)	4 (20.0%)	0.454
Stage			
- 1A2	18 (50.0%)	-	0.084
- 1B	2 (5.6%)	4 (20.0%)	
- 2B	4 (11.1%)	8 (40.0%)	
- 3C	4 (11.1%)	4 (20.0%)	
- 3C1	2 (5.6%)	-	
- 3C2	6 (16.7%)	4 (20.0%)	
Recurrence treatment			
- Resection+VBT±EBRT±CT	12 (33.3%)	8 (40.0%)	0.519
- VBT+EBRT±CT	24 (66.7%)	12 (60.0%)	

SD: Standard deviation, VBT: Vaginal brachytherapy, EBRT: External beam radiotherapy, CT: Chemotherapy

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 rates for patients who received resection+VBT treatment were 78.8% and 35.8%, respectively, 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 between patients who did and did not receive adjuvant VBT therapy. More valuable information can be obtained by performing more homogeneous subgroup analyses with a larger number of patients and prospective studies.

Although adjuvant RT significantly reduces the risk of vaginal and intrapelvic recurrence, it does not improve OS [11,15,16].

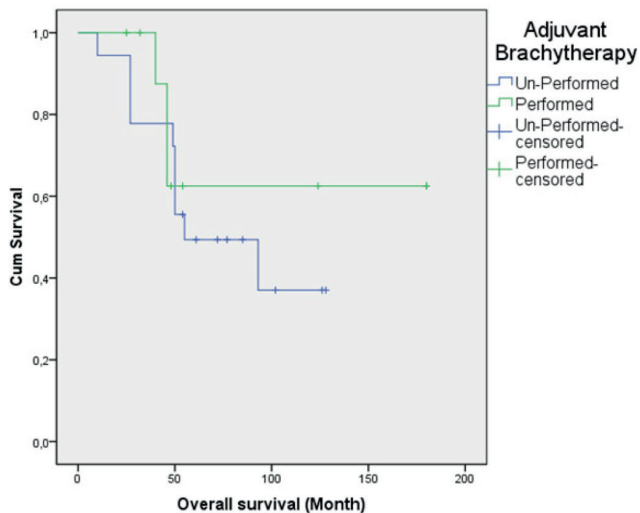


Figure 1. Effect of adjuvant vaginal brachytherapy on overall survival according to Kaplan-Meier curve

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 whether there was no difference in the mean 5-year OS between patients who received and did not receive VBT ($p=0.521$), and the rates were 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 appropriate 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 the present study, Cox regression analysis showed that a short disease-free interval did not have a significant effect on OS. When VBT doses and fractions were evaluated, according to multivariate regression analysis, there was no difference in the risk of vaginal recurrence between the 7.0 Gy 3 fractions prescribed at a 0.5 cm depth, the 6.5 Gy 3 fractions prescribed at a 0.5 cm depth, or the 6.0 Gy 5 fractions [17].

Study Limitations

There are some shortcomings in our study. First, it can be said to be of a retrospective nature. Depending on this, there may be difficulty in remembering and/or missing information in files. Second, it can be concluded that the number of patients was small. Despite these, we believe that our study with a homogeneous case group, such as isolated vaginal recurrence in EC, which is not common, provides important results.

Conclusion

In conclusion, adjuvant VBT did not affect the local recurrence time or OS rate of patients with EC. 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

Table 2. Evaluation of risk factors that may affect overall survival among patients with vaginal recurrent endometrial cancer using 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 2-3	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

a high risk of recurrence, considering its limited effect on OS. In addition, patients who do not receive adjuvant radiotherapy have an additional tool for treatment when recurrence occurs.

Ethics

Ethics Committee Approval: The study was approved by University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Local Ethics Committee (date: 09.12.2022, decision no: 2022/11-44).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.Özd., Concept: G.A., P.T.Ö., Design: İ.Ç., Data Collection or Processing: Z.E.Ç., Analysis or Interpretation: K.G., Literature Search: A.Ö., M.S., Writing: V.G.

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