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Improving locoregional outcome in high-intermediate-risk and high-risk stage I endometrial cancer with surgical staging followed by brachytherapy

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Purpose: This study aims to assess the locoregional efficacy of postoperative vaginal brachytherapy (VBT) alone in patients undergoing surgical staging for early-stage high-intermediate-risk (HIR) and high-risk (HR) endometrial cancer.

Materials and Methods: One hundred and four patients with early-stage HIR and HR endometrial cancer who underwent surgical staging were treated with adjuvant VBT alone. The patients with stage Ib, grade I–III, stage Ia, grade III, lower uterine segment involvement, and lymphovascular invasion (LVI) were included to study.

Results: The 5- and 10-year overall survival (OS) rates were 87% and 76%, respectively. The 5- and 10-year DFS rates were 86% and 86%, respectively. Among the patients, 92% had endometrioid adenocarcinoma, 2% had undifferentiated carcinoma, 2% had serous papillary carcinoma, and 4% had clear-cell carcinoma. Of the patients, 63% had stage Ib disease, while 37% had stage Ia disease. None of the patients had vaginal or pelvic lymph node recurrence, whereas two had para-aortic lymph node metastasis, one had surgical scar recurrence, one had para-aortic lymph node and brain metastasis, and one had lung metastasis. The presence of lymphatic invasion was found to be a statistically significant prognostic factor for increased distant metastasis rates ($p = 0.020$). Lymphatic invasion was also regarded as an independent prognostic factor for metastasis-free survival ($p = 0.044$).

Conclusion: Our study results suggest that postoperative VBT alone is an effective and safe treatment modality with low complication in patients undergoing surgical staging for HIR and HR endometrial cancer.

Keywords: Brachytherapy, Endometrial cancer

Introduction

Endometrial adenocarcinoma is the most common gynecologic malignancy with the lowest mortality rates [1,2]. About 75% of cases with endometrial cancer are diagnosed with early-stage disease which is confined to the uterus [3]. The treatment of stage I disease is based on total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), and lymph node dissection and/or postoperative external radiation therapy (PORT). Five-year survival for stage I patients is between 80%–90% with a locoregional recurrence rate of 4% to 8% [4-6]. The prognosis is extremely good in stage I disease [7-10], whereas the recurrence rate may vary between 5% and 16% depending on tumor localization, depth of invasion, and pelvic lymph node metastasis and grade [11-14]. Several retrospective and prospective studies have shown that PORT reduces locoregional recurrence but has no impact on overall survival

(OS) [15]. However, adjuvant PORT utilization in the treatment of early-stage disease is controversial due to treatment related side effects including diarrhea, intestinal obstruction, and lymphedema [8,10].

Radical hysterectomy bilateral oophorectomy with pelvic lymphadenectomy was considered to be the standard treatment of endometrial cancer [14,16-18]. In case of poor prognostic factors adjuvant treatment options are considered. Prospective, randomized PORTEC-1 (Postoperative Radiation Therapy in Endometrial Carcinoma trial) study was conducted to compare the efficacy of adjuvant pelvic radiotherapy versus no treatment. At 15 years, locoregional recurrence rate was reported as 5.8% in external beam radiotherapy (EBRT) arm and 15.5% in follow-up arm ($p < 0.001$). In this trial, since the authors reported that vagina was the most frequent site of recurrence in 75% patients undergoing surgery alone [19], they concluded that vaginal brachytherapy (VBT) alone is effective treatment to obtain vaginal control avoiding PORT-related complications [20-25].

In this study, we have assessed the results of postoperative VBT in surgically staged stage I endometrial cancer patients and analysed recurrence patterns and prognostic parameters in high-intermediate-risk and high-risk group patients.

Materials and Methods

A total of 104 patients who underwent postoperative adjuvant VBT for stage I endometrial cancer were retrospectively analyzed between the years 2000 and 2015. A written informed consent was obtained from each patient. The study was conducted according to the principles of the Helsinki Declaration and approval was granted by the institutional Ethics Committee. All patients provided signed informed consent for treatment, and this study was approved by our Institutional Review Board of Uludag University Faculty of Medicine (No. 2008-21/34).

At baseline, all patients were evaluated based on medical history, physical examination findings, laboratory test results, chest X-ray and abdominopelvic tomography scans. Acute and chronic side effects were classified according to the Radiation Therapy Oncology Group (RTOG) criteria. According to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system, all the patients had been re-staged and the patients with stage Ib, grade I–III, stage Ia, grade III, lower uterine segment involvement, and lymphovascular invasion (LVI) were included.

All patients who underwent total abdominal hysterectomy plus bilateral salpingo-oophorectomy within bilateral pelvic node dissection with or without para-aortic dissection were included. Para-aortic lymph node dissection was performed in all except six patients. The patients with high grade histology were treated with adjuvant chemotherapy in addition to VBT.

1. Brachytherapy

High-dose-rate (HDR) afterloading ^{192}Ir (iridium-192) VBT system (GammaMed 12i; Varian Medical Systems, Palo Alto, CA, USA) was delivered to 0.5 cm depth of the vaginal wall. While two-dimensional (2D) technique was used until 2011, image-guided 3D brachytherapy was used after the year of 2011. The median diameter of the cylinder was 3 cm (range, 2.3 to 3.5 cm). The mean length for target volume was 3.8 cm. One patient received VBT at a dose of 8 Gy in 3 fractions (total 24 Gy), one patient at a dose of 6 Gy in 4 fractions (total 24 Gy), whereas the remaining patients received VBT at a dose of 7 Gy in 3 fractions (21 Gy). The median rectal dose was 16.1 Gy (range, 10.3 to 23.8 Gy), while the mean bladder dose was 13 Gy (range, 5.42 to 19.4 Gy).

2. Statistical analysis

OS was defined as the time from the diagnosis to the last follow-up visit. Disease-free survival (DFS) was defined as the time from surgery to the development of distant organ or para-aortic lymph node metastasis or local recurrence. Metastasis-free survival was defined as the time from surgery to the occurrence of first metastases.

Survival was estimated using the Kaplan-Meier survival curves. The log-rank test was used to compare survival rates. Descriptive data were expressed in mean ± standard deviation. A p-value of 0.05 was considered statistically significant. Independent prognostic factors were determined by multivariate Cox regression analysis using a forward stepwise selection.

Results

The mean follow-up was 48.5 months (range, 2 to 130 months). At the time of analysis, two patients died from second primary tumors, four patients from a distant metastasis, and six from an unknown cause. The 5- and 10-year OS rates were 87% and 76%, respectively. The 5- and 10-year DFS rates were 86% and 86%, respectively.

The mean age was 62.5 years (range, 46 to 81 years). The cut-off value of age was 65 years. Thirty-two patients (61%) were under 65 at the time of diagnosis. The mean tumor size was 3.7 cm. The time between surgery and VBT was 41 days (range, 9 to 120 days). Tumor characteristics are shown in Table 1. Serous papillary, undifferentiated and clear-cell carcinomas were classified as high-grade tumors and all the patients with type 2 histology (8%) also received adjuvant chemotherapy.

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Table 1. Tumor characteristics

Characteristic	n (%)
Depth of invasion	
Ia	38 (37)
Ib	66 (63)
Grade	
I	38 (37)
II	40 (38)
III	24 (25)
Squamous variant	
Yes	34 (61)
No	64 (33)
Unknown	6 (6)
LUSI	
Yes	24 (23)
No	80 (77)
Lymphatic invasion	
Yes	30 (29)
No	74 (71)
Vascular invasion	
Yes	4 (96)
No	100 (4)
Tumor size (cm)	
< 3	46 (44)
≥ 3	38 (56)
Tumor volume (cm^3)	
< 13	82 (79)
≥ 13	22 (21)
Number of pelvic nodes	
< 20	56 (54)
≥ 20	48(46)
Number of para-aortic nodes	
< 5	42 (40)
≥ 5	48 (60)
Tumor histology	
Adenocarcinoma	96 (92)
Undifferentiated	2 (2)
Clear cell	4 (4)
Serous papillary	2 (2)

LUSI, lower uterine segment involvement.

Table 2. Prognostic factors associated with DFS, univariate analysis

	DFS (%)	p-value
Lymphatic invasion		0.020
Yes	74	
No	95	
Number of pelvic nodes		0.714
< 20	90	
≥ 20	88	
Number of para-aortic nodes		0.610
< 5	85	
≥ 5	90	
Time surgery-RT (day)		0.966
< 45	92	
≥ 45	84	

DFS, disease-free survival; RT, radiotherapy.

During the follow-up, distant recurrences occurred more frequently than locoregional recurrences. Four patients had paraaortic lymph node metastasis (one patient, stage Ia grade 1; two, stage Ia grade 3; and one, stage Ib grade 3), one had drain site recurrence (stage Ib grade 1), two had para-aortic lymph node and brain metastasis (one patient, stage Ib grade 1; one, stage Ib grade 3) at the same time, and two had lung metastasis (one patient, stage Ib grade 3; one, stage Ia grade 3). There were two patients observed with solid organ metastasis in type 2 histology. LVI was the only predominant prognostic parameter of all. Two out of four patients with para-aortic lymph node metastasis underwent para-aortic radiation therapy and chemotherapy, two of them treated with surgery followed by radiotherapy. All the patients with distant metastasis received chemotherapy except one due to patient's rejection. Although the number of stage Ib grade 3 patients is low, none of them had vaginal or pelvic lymph node recurrence during the follow-up.

In the analysis, OS rate was significantly higher in patients in whom more than 20 lymph nodes were dissected (p = 0.033). OS rate tended to be lower in patients with LVI (p = 0.088) but it was not found to be significant. In univariate log-rank analysis, presence of LVI was found to be a statistically significant prognostic factor for increased distant metastasis rates (p = 0.020) in Table 2.

Ten-year DFS rates were 69% and 92% in patients with and without LVI, respectively. In multivariate analysis consisting the variables; LVI, the depth of myometrial invasion, disease grade, tumor histology, and age, only LVI found to be an independent prognostic factor for DFS (p = 0.044) (Table 3). The number of pelvic lymph nodes (< 20 and ≥ 20) and para-aortic lymph nodes (< 5 and ≥ 5), and time from surgery to VBT (< 45 days and ≥ 45 days) were not associated with DFS (p = 0.714, p = 0.610, and p = 0.966, respectively).

Neither univariate nor multivariate analysis age, tumor histology, stage and grade, depth of invasion, the ratio of invasion, estrogen and progesterone receptors, lower uterine segment involvement, the presence of squamous differentiation, the number of para-aortic lymph nodes dissected, duration between surgery and VBT, and a second primary tumor presence were not found associated with improved OS rates.

Multivariate Cox regression analysis confirmed that there was no

Table 3. Cox regression analysis for disease-free survival

	HR	p-value	95% CI
Tumor histology	0.694	0.636	2.4 (1.3–4.3)
Grade			
I	0.011	0.532	0.7 (0.3–1.4)
II			
III			
Myometrium invasion			
< 1/2	0.965	0.901	1.5 (0.9–2.5)
> 1/2			
LVI			
Yes	1.604	0.044	4.1 (2.2–7.6)
No			
Age (yr)			
< 65	1.810	0.403	1.0 (0.9–1.0)
≥ 65			

LVI, lymphovascular invasion; HR, hazard ratio; CI, confidence interval.

Table 4. Cox regression analysis for overall survival

	HR	p-value	95% CI
Metastases			
Yes	1.15	0.017	1.5 (1.01–1.29)
No			
Grade			
I	2.15	0.714	1.2 (0.11–2.78)
II			
III			
Myometrium invasion			
< 1/2	1.03	0.610	1.01 (1.4–1.43)
> 1/2			
LVI			
Yes	2.68	0.966	1 (0.82–1.05)
No			
Age (yr)			
< 65	2.16	0.491	2.0 (0.69–2.65)
≥ 65			

LVI, lymphovascular invasion; HR, hazard ratio; CI, confidence interval.

relationship between OS and prognostic factors such as LVI, myometrial invasion, the number of dissected lymph nodes and grade. Metastasis was only found as a poor prognostic factor for OS ($p = 0.017$) (Table 4).

As the long-term side effects, we encountered that 16 patients (15%) had grade I vaginal mucositis, while 50 patients (48%) had cystitis and grade I dysuria. None of the patients had grade II-III vaginal mucositis and cystitis.

Discussion and Conclusion

Most patients diagnosed with early-stage endometrial cancer are treated with surgery alone and have low risk of recurrence. This risk is significantly higher for some women with high-risk factors which is required adjuvan radiation therapy and/or chemotherapy. EBRT improves both local and regional control, but does not reduce the risk of death and also associated with increasing side effects [26-29]. Even in advances in radiotherapy techniques and image guided treatment, PORT following surgery has been reported to increase the incidence of genitourinary, and gastrointestinal side effects compared with brachytherapy alone [30,31].

In the Gynecological Oncology Group 99 (GOG-99) study, adjuvant therapy indication following definite surgical staging was identified based on the definitions of intermediate and high-risk patient groups. The patients at ≥ 70 years of age with any risk factor (grade II–III, the presence of LVI, outer third myometrial invasion), those at ≥ 50 years of age with at least two risk factors, and those at any age with three risk factors were randomized to either adjuvant pelvic PORT or observation. The study results demonstrated adjuvant PORT decreased the risk of pelvic or vaginal recurrence compared to the observation arm; however, there was no statistically significant difference in survival between the groups [10,32]. Similarly, in the PORTEC-I study, a total of 714 patients were divided into two groups: (1) TAH + BSO followed by adjuvant PRT; (2) observation arm. PORT substantially decreased locoregional reccurence (5% vs. 14%; $p < 0.001$); however, 10- and 15-year survival rates were similar between the groups [33,34]. In addition, 5-year survival after any relapse significantly lower in PORT patients compared to the control group. The crucial point of this study, the vaginal cuff was the most common site of recurrence in the observation arm [33].

Furthermore, toxicity is one of the main determinant factors in choosing the best treatment approach, as PORT and VBT produce similar survival rates in the early-stage tumors [7,35]. According to the updated staging system the risk of locoregional recurrence is reported 14.3% with comprehensive surgery in even stage Ib grade III disease [36]. On this basis, follow-up alone after comprehensive surgical staging may yield high survival rates [17,37,38]. Although data with VBT alone is limited due to small number of randomized clinical studies, recent studies have suggested to apply VBT in high-risk node (-) disease in patients undergoing lymph node dissection [17,23,39]. Additionally, VBT has been shown to reduce the morbidity with providing high local control rates in the clinical trials [21-25]. Neverthless adjuvant PORT is still widely adopted approach due to controversial studies [40,41].

One of the initial studies in which VBT was assigned as a sepa-

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rate arm was carried out by Aalders et al. [7] which included 540 patients. All patients with stage Ib grade III and stage Ic based on definite surgical staging results were randomized to no further treatment or classified as postoperative VBT + PORT. Combined therapy decreased locoregional recurrence without any impact on survival, compared to VBT alone. On the other hand, the high rate of locoregional recurrence in VBT alone was associated with not performing lymph node dissection and the study results were found controversial in terms of efficacy of VBT. Moreover, in a recent pivotal PORTEC-II study with a large sample size, VBT and PORT were compared among the patients with early-stage disease at an intermediate-high-risk group [35]. There was no statistically significant difference in the 5-year local recurrence, locoregional control, distant metastasis, and survival rates; however, a higher number of patients receiving pelvic radiation therapy had side effects.

The rate of vaginal recurrence has been reported to be 5% in patients undergoing surgical staging without adjuvant therapy [42], while it has been estimated to be 10% in patients undergoing incomprehensive or no surgical staging [8]. However, in a study including patients with stage Ic grade III disease, vaginal recurrence was found to be 4.6% among the patients undergoing radical hysterectomy, followed by brachytherapy during a 48-month follow-up [43]. Similarly, Rahatli et al. [38] included 62 patients with stage Ib grade I–III disease and performed postoperative VBT on 21%. Five-year DFS rate was 94.4% and OS rate was 93.1%. The authors concluded that, although the majority of the patients did not receive postoperative adjuvant therapy, stage Ib disease with low recurrence rates could be managed with surgery alone.

Several studies have shown that vaginal recurrence is associated with deep myometrial invasion, high-grade disease, LVI, and cervical involvement in patients receiving no adjuvant therapy [11,33]. Recent data have suggested that LVI may be a prognostic factor for vaginal recurrence in poorly differentiated tumors with minimal deep invasion [44]. On the other hand, although myometrial invasion is a predictive factor for survival [32,45], some authors have suggested that it has no impact on DFS and recurrence [17,44]. In consistent with the current literature datas, the depth of myometrial invasion was not associated with locoregional recurrence and survival in our study. Even though LVI was a significant factor for DFS, the predominant failure was distant metastasis. Regarding there was no regional failure with VBT only and LVI was the most important factor DFS, additional adjuvant chemotherapy might be considered for these patients with LVI [46].

Furthermore, grade is a major prognostic factor for vaginal and pelvic recurrence [23,24]. Several studies have shown that progression-free survival (PFS) [5] and DFS rates are lower in grade III disease [47]. In addition, one-third of stage Ic grade III tumors may distantly metastasize [8]. In such cases, more aggressive treatment options including chemotherapy can be administered due to high risk of pelvic and distant metastases. In a subgroup analysis conducted by the Nordic Society of Gynecological Oncology/European Organization for the Research and Treatment of Cancer (NSOG/EORTC) task force, chemotherapy contributed to improved PFS rates in this patient population [48]. In the current study, however, a higher number of patients with stage Ib grade III had distant metastases, indicating no statistically significant difference. We also found no contributor factor for DFS and OS.

Moreover, VBT alone and chemotherapy have been increasingly widely adopted as effective treatment modalities in early-stage high-risk tumor histology and high-grade tumors. In Mayo Clinic study, 103 patients with stage I serous papillary and clear-cell carcinoma received postoperative VBT or VBT + chemotherapy (34%) and 5-year OS rate was found to be 84% with a vaginal recurrence rate of 3% and locoregional recurrence rate of 7% [49]. The authors concluded that VBT was effective in preventing vaginal recurrences in patients with comprehensive surgical staging and stage I serous papillary and clear-cell carcinoma. Larger sites for VBT were not considered appropriate, as the rate of pelvic and extra-pelvic recurrences was low. In a review stage I–II serous papillary received adjuvant VBT + chemotherapy and local control rate was found to be 97.5% (range, 91% to 100%), and OS to be 93% (range, 82% to 94%) during a mean of 24.8-month follow-up period [50]. In our study, despite the limited number of high-grade tumor histology, none of the patients treated with VBT + chemotherapy had locoregional recurrence.

Additionally, LVI is known to increase the risk of vaginal recurrence [8,10,18,51]. The presence of LVI is also significantly associated with lymph node metastasis, tumor recurrence, and survival [52]. In our study, we obtained decreased DFS in the patients with LVI without any impact on local control and OS.

Currently, surgical approaches have attempted to add pelvic paraaortic lymphadenectomy to definite diagnosis and radical hysterectomy [11,53]. As a result, Lutman et al. [54] showed an association between the number of lymph nodes dissected and survival. The survival rate increased in high-risk patients with stage I–II endometrial cancer, if more than 12 lymph nodes were dissected. In consistent with these findings, we also observed that OS rate was significantly higher in patients in whom more than 20 lymph nodes were dissected. No pelvic lymph node recurrence despite VBT can be a determinant factor for identifying the need for lymphadenectomy as an adjuvant therapy.

Vaginal bracytherapy is an effective and adequate treatment modality in early-stage endometrial cancer even in stage Ib grade III disease with low cost and toxicity rate [21]. The most common

side effects include mucosal telangiectasia, atrophy, stricture or adhesion. Dose distribution is often localized with VBT; therefore, radiation dose absorbed by the small intestines can be neglected and rectal dose can be adjusted below the threshold. In our study, none of the patients had serious complications and the quality of life was preserved.

In conclusion, given the fact that the vaginal cuff is the most common site of recurrence in early-stage endometrium cancer, VBT alone is safe and efficient treatment in surgically staged disease. In exceptional, it has been suggested to add chemotherapy to brachytherapy in the patients with stage Ib grade III and unfavorabl histopathological reports according to guidelines.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contribution

Conceptualization: CDA, SA; Investigation and methodology: CDA; Project administration: CDA; Resources: SKC; Supervision: CDA; Writing of the original draft: CDA; Writing of the review and editing: MK; Software: CDA; Validation: SA; Formal analysis: CDA; Data curation: CDA; Visualization: CDA. All the authors have proofread the final version.

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