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ORIGINAL ARTICLE

Is External Pelvic Radiotherapy Really Needed in Grade 3 Deeply Invasive Endometrial Cancer?

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OBJECTIVE

The aim of this study was to compare vaginal cuff brachytherapy (VBT) and external pelvic radiotherapy (EPRT) regarding oncologic outcomes and toxicity in surgically staged stage IB (International Federation of Gynecology and Obstetrics 2009) grade 3 endometrioid endometrial cancer (EC) patients.

METHODS

Records of 85 patients treated between 1994 and 2018 at two tertiary cancer centers were retrospectively reviewed. Pelvic lymph node dissection (LND) was performed in 14% of patients, pelvic+para-aortic LND in 85%, and sentinel LND in one patient. Patients receiving EPRT±VBT were classified as group 1 and those receiving VBT alone as group 2. The primary endpoint was locoregional recurrence (LRR).

RESULTS

Median dissected lymph node count was 37 (range, 12–110). Lymphovascular space invasion (LVSI) was present in 49% of patients. VBT alone, EPRT alone, and EPRT+VBT were delivered in 65%, 7%, and 28% of patients, respectively. After a median follow-up of 92 months, LRR and distant metastasis (DM) occurred in 3 and 7 patients. LVSI was associated with numerically higher LRR (8% vs. 0%) and DM (15% vs. 0%), although neither reached statistical significance. Among patients with LVSI, EPRT±VBT did not reduce LRR compared with VBT alone, and outcomes were not associated with age. Five-year overall, disease-free, LRR-free, and DM-free survival rates were 84%, 82%, 83%, and 82%, respectively, with no significant difference between treatment groups, including LVSI-positive patients. Acute genitourinary toxicity was significantly higher in the EPRT±VBT group.

CONCLUSION

VBT alone provides adequate disease control with lower toxicity in surgically staged stage IB grade 3 EC, particularly in patients with absent or focal LVSI.

Keywords: Brachytherapy; deep myometrial invasion; endometrial cancer; external radiotherapy; grade 3.
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INTRODUCTION

With an estimated 420,242 new cases and 97,704 associated deaths in 2022, endometrial cancer (EC) is the second most common gynecologic cancer worldwide.[1] The standard treatment of EC consists of surgical staging with hysterectomy and bilateral salpingo-oophorectomy (BSO), followed by adjuvant chemotherapy and/or radiotherapy (RT) based on clinicopathological risk factors. Patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IB, grade 3 EC are considered as the high-intermediate risk (HIR) group regardless of lymphovascular space invasion (LVSI) according to the European Society for Gynecologic Oncology (ESGO)/European Society for Radiotherapy and Oncology (ESTRO)/European Society for Pathology (ESP) 2025 guideline and this group of patients is being upstaged as stage IIC in the latest FIGO 2023 staging system.[2,3] The ESGO-ESTRO-ESP guideline recommends adjuvant external pelvic RT (EPRT) for patients in the HIR group, particularly for ones with a substantial LVSI.[3] However, the role of EPRT after complete surgical staging with lymph node dissection (LND) is still controversial.[3] On the other hand, the recent American Society for Radiation Oncology (ASTRO) guideline strongly recommends EPRT for patients with >50% myometrial invasion and grade 3 disease, regardless of LVSI and type of LN assessment.[4]

Studies have revealed that adjuvant RT increased the locoregional control in patients with early-stage HIR disease, but studies comparing vaginal brachytherapy (VBT) alone and EPRT for patients with grade 3 deeply invasive endometrioid type EC are limited.[5] Trials comparing VBT alone and EPRT in patients with an HIR disease showed no difference in terms of survival but the rate of pelvic recurrence was more common in the VBT alone group than the EPRT group.[6,7] However, early-stage HIR EC is a heterogeneous population and trials comparing VBT alone and EPRT in the HIR group also included patients with stage II disease, in which EPRT is strongly recommended according to the ESGO/ESTRO/ESP 2021 guideline.[6–8] To the best of our knowledge, there is no evidence for the superiority of EPRT to VBT in patients with grade 3 deeply invasive endometrioid type EC after complete surgical staging. Thus, we aimed to compare the impact of VBT alone and EPRT on locoregional control, distant metastasis (DM), and survival in these patients that underwent comprehensive surgical staging.

MATERIALS AND METHODS

Patient Population and Treatment

Medical records of 121 patients who received adjuvant RT after comprehensive surgical staging between 1994 and 2018 for FIGO 2009 stage IB grade 3 disease in two tertiary cancer centers were retrospectively evaluated. Thirty-six patients were excluded from the study due to inadequate nodal evaluation, histopathology other than endometrioid type, and inadequate follow-up; thus, 85 patients were analyzed in this study (Fig. 1). A magnetic resonance imaging and/or transvaginal ultrasonography with clinical examination was performed to evaluate myometrial invasion before surgery for all patients. Eighty-four (99%) patients were treated with total abdominal hysterectomy (TAH) and BSO, and 1 (1%) patient had undergone a type 2 hysterectomy and BSO. Pelvic LND was performed in 14% of patients, pelvic+para-aortic LND in 85%, and sentinel LND in one patient. The decision of adjuvant treatment after surgery was given in multidisciplinary tumor board consisting of gynecologic oncologists, medical oncologists, radiation oncologists, pathologists, and radiologists who were experienced in gynecologic oncology for every patient. Patients were treated with VBT alone, EPRT with or without VBT based on the clinicopathological risk factors after surgery. Since the number of patients that received EPRT alone is low, EPRT alone and EPRT+VBT groups were combined as EPRT±VBT group while performing statistical analyses.

EPRT was performed through two-dimensional (2D) RT, 3D conformal RT (3D-CRT), intensity-modulated RT (IMRT), or volumetric-modulated arc therapy (VMAT). The EPRT dose was prescribed to the pelvic area encompassing the surgical bed and pelvic lymphatics. The VBT dose was prescribed to the vaginal mucosa or to a 5-mm depth from the vaginal surface both in the VBT alone and EPRT+VBT groups.

This retrospective study was conducted in compliance with version of the 1975 Declaration of Helsinki, as revised in 2000, and an informed consent was obtained from each patient before treatment. The ethical approval was obtained from Hacettepe University Institutional Review Board (Date: 21.11.2023, Decision no: 2023/07/12).

Follow-up

Gynecologic examinations were performed in all patients every 3 months for the first 2 years, every 6 months for years 3-5, and annually thereafter. Imaging was performed when there was a suspicion of local/regional or distant recurrence. The acute toxicity includ-

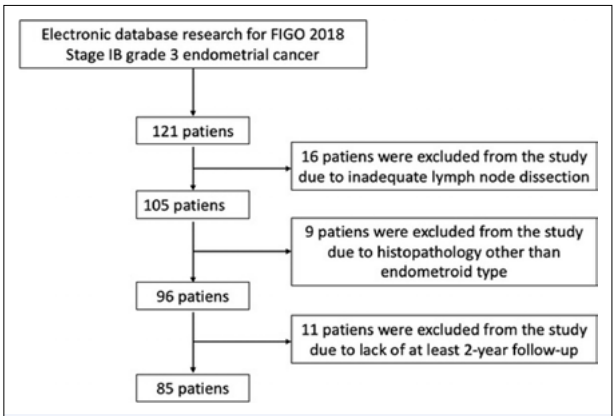


Fig. 1. Flowchart for inclusion and exclusion of patients.

ed any events occurred during RT and the following 90 days after RT while the late toxicity included complaints of more than 3 months after RT. All toxicities were assessed according to the Radiation Therapy Oncology Group/European Organization for the Treatment of Cancer toxicity criteria.[9]

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0. The primary endpoint of this study was locoregional recurrence (LRR) which includes a vaginal cuff and/or pelvic LN recurrence. The secondary endpoints were DM, overall survival (OS), disease-free survival (DFS), LRR-free survival (LRRFS), and DM-free survival (DMFS). All time-related events were calculated from the last day of RT to the last follow-up, death, or recurrence, whichever came first. Survival estimates were calculated using the Kaplan–Meier test and survival was compared between the groups with the log-rank test. The univariate analysis was performed using the log-rank test to evaluate the impact of clinical parameters on survival outcomes. The multivariate analysis was not performed due to the small number of significant predictors in the univariate analysis for survival. The comparison of the clinical parameters between the groups was made by a Chi-square test. P<0.05 was considered statistically significant.

RESULTS

Patient and Tumor Characteristics

The median age of all patients was 62 years (range: 37–81 years). The median number of dissected LNs was 37 (range: 12–110). The median tumor size was 4 cm (range: 1.3–13 cm). All patients had an endometrioid type EC. Forty-two (49%) patients had LVSI. Substantial and focal LVSI was present in 7 (17%) and 6 (14%) of these 42 patients, respectively, but the extent of LVSI was unknown in 29 (69%) patients. Six of seven patients with substantial LVSI received EPRT ±VBT, while one received VBT alone. Median number of dissected LNs were 21 (range, 15–35) and 35 (range, 12–95) in patients with substantial LVSI and no/focal LVSI, respectively.

Table 1 Patient, tumor, and treatment characteristics

Parameters	VBT alone (n=55) (%)	EPRT±VBT (n=30) (%)	p
Age (years)			
≥60	35 (64)	18 (60)	0.741
<60	20 (36)	12 (40)	
Type of surgery			
TAH+BSO	54 (98)	30 (100)	1.000
Type 2 Hysterectomy	1 (2)	0	
Type of LND			
Pelvic	4 (7)	9 (30)	**0.010**
Pelvic and para-aortic	51 (93)	21 (70)	
Tumor size (cm)			
≥4	24 (44)	20 (67)	0.083
<4	23 (42)	8 (27)	
Unknown	8 (14)	2 (6)	
LVSI			
Present	26 (47)	15 (50)	0.600
Absent	16 (29)	12 (40)	
Unknown	13 (24)	3 (10)	
Chemotherapy administration			
Yes	2 (4)	11 (37)	<0.001
No	53 (96)	19 (63)	

VBT: Vaginal brachytherapy; EPRT: External pelvic radiotherapy; LND: Lymph node dissection; LVSI: Lymphovascular space invasion, TAH: Total abdominal hysterectomy; BSO: Bilateral salpingo-oophorectomy.

VBT alone, EPRT alone, and EPRT+VBT were performed in 55 (65%), 6 (7%), and 24 (28%) patients, respectively. EPRT was utilized through 2D-RT, 3D-CRT, IMRT, and VMAT in 2 (7%), 5 (17%), 8 (27%), and 15 (50%) patients, respectively. The median dose of EPRT and VBT was 45.5 Gy (range: 45–50.4 Gy) in median 25 fractions (range: 23–28 fractions) and 27.5 Gy (range: 12–35 Gy) in 5 fractions (range: 2–5 fractions), respectively.

Thirteen (15%) patients received systemic chemotherapy in addition to RT either given before or after RT or with sandwich approach. Age, type of surgery, tumor size, and presence of LVSI were similar between the groups, but pelvic and para-aortic LND and chemotherapy administration were significantly more frequent in the VBT alone group (Table 1).

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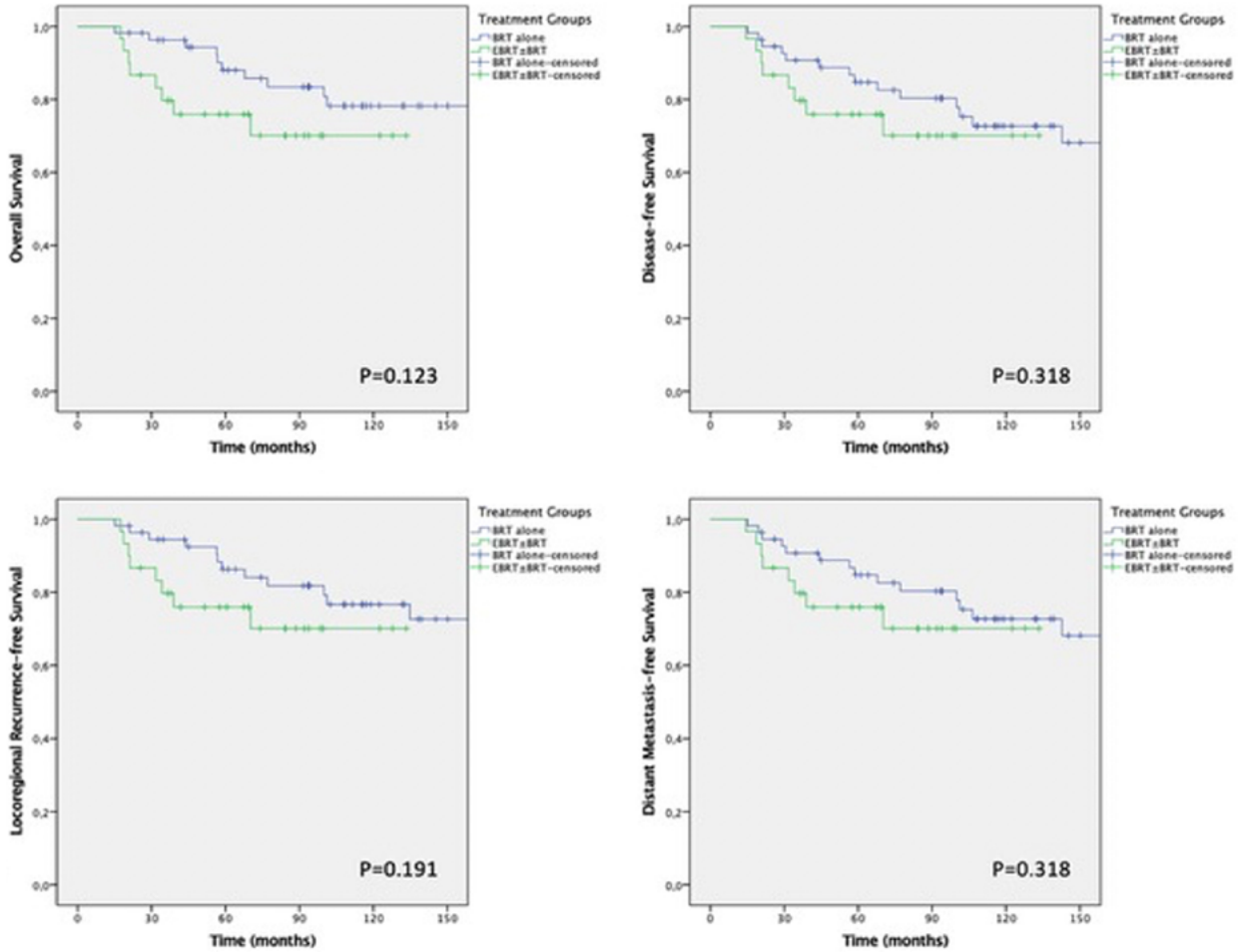


Fig. 2. Comparison of OS, DFS, LRRFS, and DMFS between treatment groups in whole cohort.

OS: Overall survival; DFS: Disease-free survival; LRRFS: Locoregional recurrence-free survival; and DMFS: Distant metastasis-free survival.

Treatment Outcomes

The median follow-up was 92 months (range: 15–336 months). At the last follow-up, three (4%) patients died due to disease progression and 17 (20%) patients due to other causes, respectively. LRR and DM were observed in 3 (4%) and 7(9%) patients, respectively. LRR developed in the vaginal cuff in 2, and pelvic LNs in 1 patient, respectively, all who received VBT alone. The most common site of DM was the intraperitoneal metastases above pelvic periton (43%), followed by lung (29%), inguinal lymph nodes (14%), and bone (14%).

The LRR rate was 5% in patients with VBT and 0% in patients treated with EPRT either with VBT or alone, but the difference was not significant (p=0.286). The median time to LRR was 92 months (range: 15–336 months). LRR rates were higher in patients with LVSI than in those without LVSI; however, the difference was not statistically significant (8% vs. 0%, p=0.275). When the 42 patients with LVSI were analyzed separately, LRR rates remained similar between the treatment groups (EPRT±VBT vs. VBT alone) (0% vs. 13%, p=0.283). LRR occurred in 6% of patients aged ≥60 years, whereas no LRR was observed among patients aged <60 years (p=0.297). DM rates were also higher in patients with LVSI than in those without LVSI, although the difference did not reach statistical significance (15% vs. 0%, p=0.074). DM rates were comparable between patients aged ≥60 and <60 years (10% vs. 7%, p=1.000).

The 5- and 10-year OS, DFS, LRRFS, and DMFS rates were 84% and 74%, 82% and 70%, 83% and 70%, and 82% and 70%, respectively. All survival rates were similar between the treatment groups in the whole cohort and also among patients with positive LVSI (Figs. 2, 3). The seven patients with known substantial LVSI

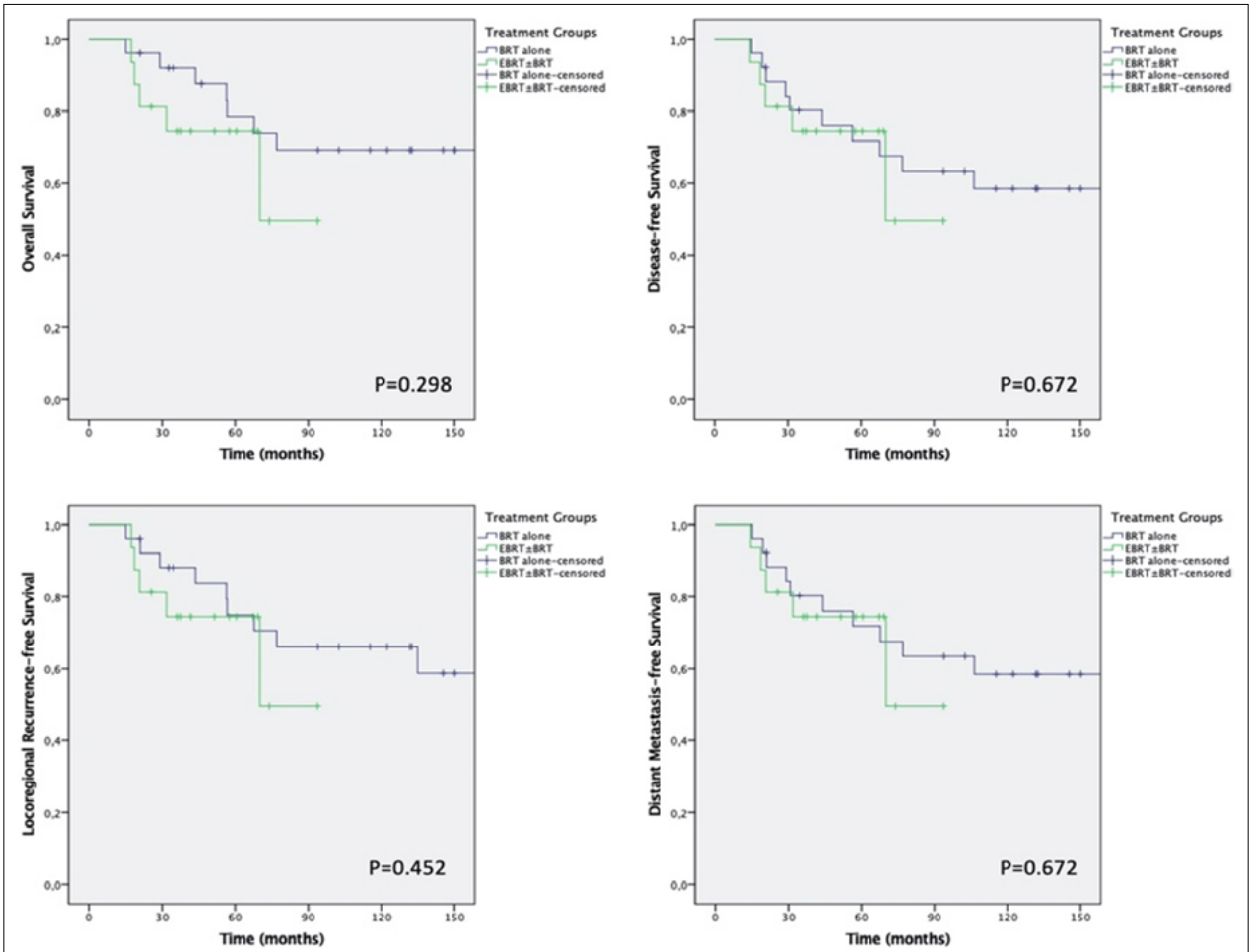


Fig. 3. Comparison of OS, DFS, LRRFS, and DMFS between treatment groups in patients with LVSI.

OS: Overall survival; DFS: Disease-free survival; LRRFS: Locoregional recurrence-free survival; DMFS: Distant metastasis-free survival; and LVSI: Lymphovascular space invasion.

when compared to the patients with known no LVSI or focal LVSI showed statistically significantly worse OS, DFS, LRRFS, and DMFS rates (Fig. 4).

The univariate analysis revealed that age (≥60 vs. <60) and LVSI were significant prognostic factors for both DFS and DMFS. In addition, LVSI was a significant and marginally significant predictor for LRRFS and OS, respectively. Age was also a marginally significant predictor for OS (Table 2).

Toxicity

No grade ≥3 acute toxicity was observed while acute grade 1–2 genitourinary (GU) and gastrointestinal (GI) toxicity was observed in 9 (11%) and 2 (2%) patients, respectively. The rate of acute GU toxicity was higher in the EPRT±VBT group than the VBT alone group (27% vs. 2%, p=0.001). Two (2%) patients developed acute grade 2 dermatitis. Although acute vaginal toxicity was not observed, late vaginal toxicity developed in 5 (6%) patients. The rate of late vaginal toxicity and acute GI toxicity rate was moderately higher in patients treated with EPRT±VBT than those treated with VBT alone (10% vs. 4%, p=0.340 and 7% vs. 0%, p=0.122), though it did not reach a statistical significance. Chronic cystitis and ileus were observed together as late GU and GI toxicities in one patient who received EPRT+VBT. Acute and late GI and GU toxicities were similar in patient's w/wo chemotherapy.

DISCUSSION

In this retrospective study, we observed that the LRR, DM, and survival rates were similar in patients with grade 3 deeply invasive endometrioid type EC treated

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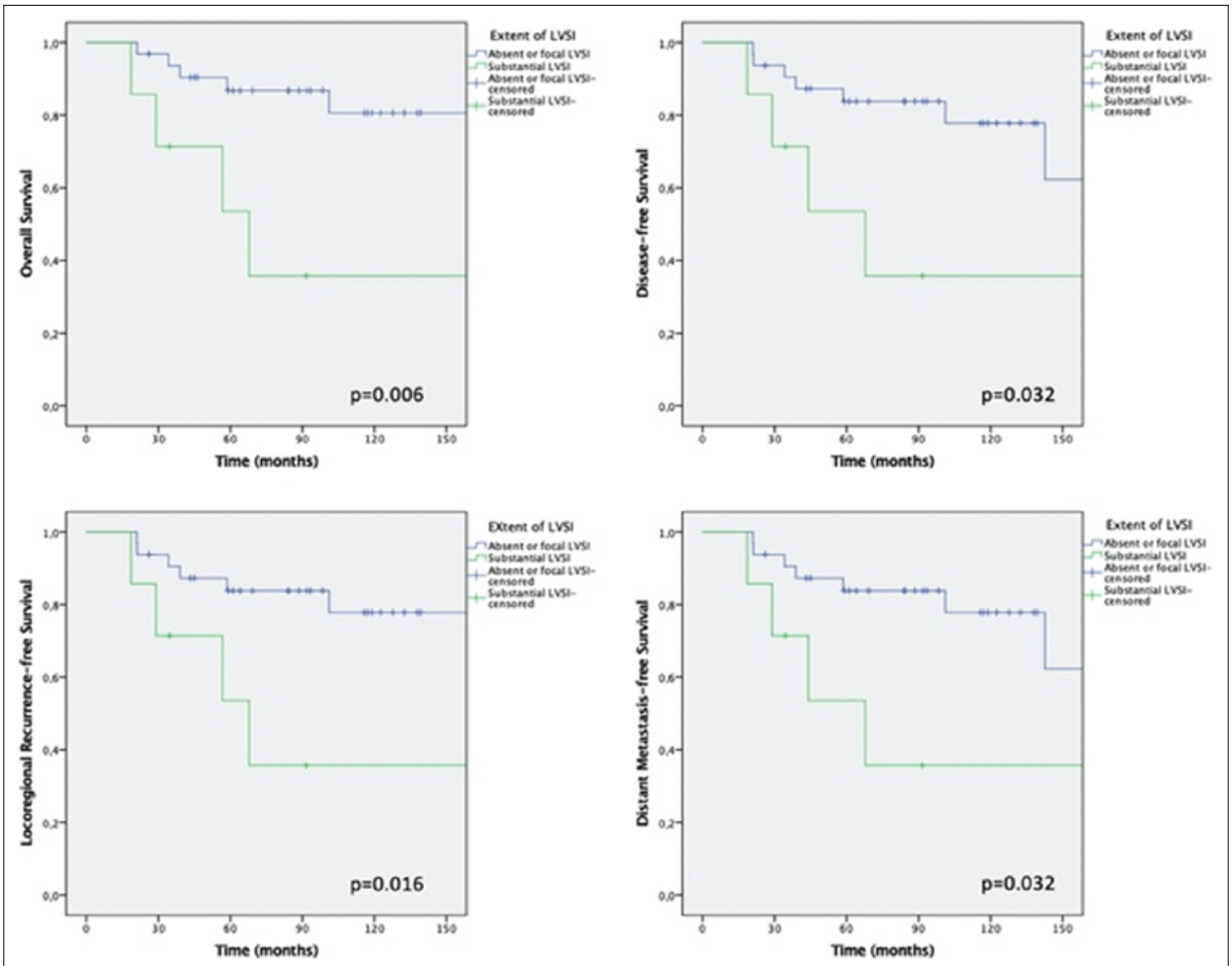


Fig. 4. Comparison of OS, DFS, LRRFS, and DMFS between patients with no/focal LVSI and those with substantial LVSI.

OS: Overall survival; DFS: Disease-free survival; LRRFS: Locoregional recurrence-free survival; DMFS: Distant metastasis-free survival; and LVSI: Lymphovascular space invasion.

with either VBT or EPRT with or without VBT after comprehensive surgical staging with a median follow-up of 92 months. In addition, patients aged ≥60 years had significantly worse DFS and DMFS than younger patients, suggesting that advanced age may represent an adverse prognostic factor in this population. Sixty-five percent of patients in our retrospective study were treated with VBT alone and the remaining with EPRT either alone or combined with VBT. Three (5%) patients who received VBT alone developed an LRR, in whom two experienced vaginal and one experienced pelvic LN recurrence. There was no intrapelvic recurrence among patients treated with EPRT. All treatments were well-tolerated, with acute GU, GI, and late vaginal toxicities moderately higher in the EPRT±VBT group than the VBT alone group. Since the rate of pelvic LN recurrence was very low in our patients with VBT alone, we think that VBT alone seems to be effective and safe in patients with grade 3 deeply invasive endometrioid type EC after comprehensive surgical staging.

According to the ESGO/ESTRO/ESP 2021 guideline, HIR EC is a heterogeneous group, including stage I endometrioid-type disease with a substantial LVSI and stage II disease, as well as stage IB grade 3 endometrioid-type EC regardless of the LVSI status in patients with an unknown molecular classification.[8] Within the HIR group, grade 3 EC is associated with a poorer prognosis which led to the most recent FIGO staging system having them put in the same stage together with aggressive histological subtypes.[2,10] According to the new FIGO 2023 staging, grade 3 disease with any myometrial involvement is considered as stage IIC and non-

Table 2 Univariate analyses for predictors of 5-y OS, DFS, LRRFS, and DMFS

Variables	OS	p	DFS	p	LRRFS	p	DMFS	p
Age (years)								
≥60	78	0.082	75	**0.021**	79	0.209	75	**0.021**
<60	93		93		86		93	
Type of surgery								
TAH+BSO	83	0.584	81	0.269	82	0.282	81	0.269
Type 2 Hysterectomy	100		0		0		0	
Type of LND								
Pelvic	83	0.549	83	0.804	83	0.660	83	0.804
Pelvic and para-aortic	84		81		82		81	
Tumor size (cm)								
≥4	79	0.165	79	0.543	79	0.209	79	0.543
<4	88		83		86		83	
LVSI								
Present	76	0.084	72	**0.027**	74	**0.043**	72	**0.027**
Absent	84		84		84		84	
Chemotherapy administration								
Yes	85	0.525	85	0.738	85	0.626	85	0.738
No	84		81		82		81	
Type of RT								
VBT alone	88	0.123	85	0.318	86	0.191	85	0.318
EBRT±VBT	76		76		76		76	

OS: Overall survival; DFS: Disease-free survival; LRRFS: Locoregional recurrence-free survival; DMFS: Distant metastasis-free survival; RT: Radiotherapy; VBT: Vaginal brachytherapy; EPRT: External pelvic radiotherapy; LND: Lymph node dissection; LVSI: Lymphovascular space invasion; TAH: Total abdominal hysterectomy; BSO: Bilateral salpingo-oophorectomy.

aggressive histology with a substantial LVSI as stage IIB, respectively.[2] However, it is not clear in what stage a patient with aggressive histology and substantial LVSI would be. According to the newest staging system, all patients with HIR and HR criteria should be treated with surgical LN staging either with systematic LND or sentinel LND. However, the cornerstone studies related to adjuvant treatment recommendations of EC patients with risk factors after surgery were based on the former staging system and the majority of these studies were either with TAH/BSO only or with selective lymph node sampling. It is still unclear to treat patients with HIR with always EPRT after comprehensive surgical staging.

Randomized studies have shown that EPRT improved locoregional control in patients with early-stage EC compared with no adjuvant treatment.[11,12] The PORTEC-1 and Gynecologic Oncology Group (GOG)-99 trials revealed that the greatest risk reduction in LRR with adjuvant EPRT was present in the HIR subset.[11,12] The pooled analysis of MRC-ASTEC and NCIC-CT-EN5 trials comparing EPRT with no adjuvant therapy in patients with intermediate- to high-risk early-stage EC showed that the isolated local recurrence rate was low (6.1%) in the observation arm, in which VBT was used in approximately 50% of these patients.[13] Although EPRT reduced the LRR rate, the authors concluded that EPRT cannot be recommended as a standard treatment in these patients considering the lack of OS benefit and increased toxicity.[13]

Besides tumor control, toxicity is of utmost importance in early-stage EC when deciding for adjuvant on treatment. The major disadvantage of EPRT is that it may increase the rates of GI and GU toxicity. The PORTEC-2 trial comparing VBT with EPRT after TAH-BSO in HIR patients showed that there was no significant difference in LRR, DM, or survival rates between patients treated with VBT or EPRT but the quality of life was improved with VBT.[7,14] Another randomized study comparing VBT alone with EPRT+VBT in stage I EC patients of all grades showed the superiority of EPRT+VBT to VBT alone for LRR, but no survival benefit was demonstrated.[15] In that study, late GI toxicity and vaginal tissue reactions were more frequent in EPRT+VBT group than VBT alone group.[15] Considering the lack of survival benefit and a higher toxicity profile, the conclusion of that partic-

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ular study was that combined EPRT+VBT should be reserved for those with high-risk disease only.[15] The other study by GOG, the GOG-249 trial, compared VBT+chemotherapy to EPRT alone in patients with HIR and high-risk stage I-II disease after TAH/BSO and bilateral pelvic and para-aortic LND and within a follow-up time of 53 months VBT+chemotherapy was not shown to be superior EPRT alone in terms of recurrence-free survival and OS with a higher rates of acute toxicity and slightly higher pelvic and para-aortic recurrence.[6] Acute adverse events were more frequent and severe in the VBT and chemotherapy arm in that trial while there was little difference between the arms when evaluating distribution of late toxicity. In our study, we found that the acute toxicity was higher in patients treated with EPRT consistent with the literature. Again, the rate of late vaginal toxicity was higher when EPRT with or without VBT was applied. Only a minority of our patients received systemic treatment, contribution of chemotherapy to the toxicity in our patients was very limited.

Several retrospective studies have demonstrated that both EPRT and VBT alone improved locoregional control, but a number of studies also reported that EPRT prolonged survival, particularly in patients with high-risk features.[16–18] On the contrary, a study based on the Surveillance, Epidemiology, and End Results (SEER) database revealed that VBT alone had a local control and survival benefit in patients with stage IB grade 3 disease.[18] In total, 1,095 patients in whom the majority were treated with LND were included in that particular SEER database analysis and 52% received VBT, 56% received EPRT, 16% received chemotherapy, and 29% received no adjuvant treatment. Survival outcomes were reported to be significantly worse for stage IB grade 3 and stage II grade 3 relative to stage II grades 1–2 in that study and VBT had a local control benefit across all patients that translated into a survival benefit in stage IB grade 3. Atahan et al.,[19] on the other hand, demonstrated that VBT alone after complete surgical staging was effective with minimal toxicity in patients with intermediate- to high-risk stage I disease, but only 13% of all patients had stage IB grade 3 disease in that study. Similarly, a recent Turkish retrospective study also agreed with the supported effectiveness and low toxicity profile of VBT alone in the early-stage HIR or high-risk patients after complete surgical staging.[20] The only retrospective study dedicated to patients with grade 3 deeply invasive endometrioid type EC concluded that adjuvant RT delayed the time to relapse and improved survival, but without any difference between VBT and EPRT in terms of oncologic outcomes.[21] In consistent with the SEER database analysis and similar studies in literature, there was no statistically significant difference in terms of LRR, DM, and survival rates in our patients with FIGO 2009 stage IB grade 3 disease when compared VBT with EPRT. VBT alone in our study was effective with minimal toxicity. However, the number of patients in our study was quite low that may mask the difference between the groups and to keep in mind that the rate of LRR in our patients with VBT alone was 5% compared to 0% in patients with EPRT.

Our study also revealed that LVSI was a significant prognostic factor for survival. The pooled analyses of PORTEC-1 and 2 trials reporting substantial LVSI as the most important prognostic factor for oncologic outcomes suggested the use of 3-tiered LVSI scoring and recommended EPRT±chemotherapy for patients with stage I EC with substantial LVSI.[22] However, it should be noted that routine LND was not required in these studies, and the majority of patients did not undergo pathologic LN evaluation.[7,12] The significance of substantial LVSI in patients with surgical staging of LNs remains still controversial. A few studies reported no significant difference in outcomes among patients with no, focal, or substantial LVSI that underwent a complete LN staging.[23,24] The practice patterns for LN staging and adjuvant treatment recommendations differ between Europe and the USA. While only bulky or suspicious LNs are dissected in the European practice, surgical evaluation of the LNs (i.e., LND or SLNB) is preferred in the USA.[25] In addition, while the ASTRO guideline strongly recommends EPRT for patients with grade 3 deeply invasive endometrioid type EC regardless of LVSI or type of LN assessment, the ESGO/ESTRO/ESP 2021 guideline recommends EPRT for patients in the HIR group, particularly with a substantial LVSI, but VBT alone for patients without LVSI that underwent LND.[4,8] Similar to the practice pattern in the USA, our gynecologic oncology surgeons prefer complete surgical staging in patients with HIR criteria. The majority of our patients were treated with both pelvic and para-aortic LND and the median number of dissected LNs in our study was 37 with a range of 12–110. In the case of inadequate LND as having dissected LNs less than at least 10, all our patients are being treated with EPRT when HIR criteria are present. We could not find a difference in terms of LRR between the treatment groups in patients with positive LVSI which might be responsible for pelvic recurrence. LVSI was present in 47% of our patients treated with VBT alone,

while it was present in 50% of patients treated with EPRT. The information about LVSI was absent for 24% patients with VBT and 10% with EPRT in our cohort and we do not know the extent of LVSI in the majority of our patients. We retrospectively analyzed pathology specimens for the extent of LVSI and of the 42 patients with LVSI, 7 (17%) had substantial LVSI and 6 (14%) patients were with focal LVSI. For the remaining 29 patients, we could not get information about the extent of LVSI. Since we have the adequate data of either having LVSI present or absent, we stratified our patients having LVSI or not and found no difference in terms of oncological outcomes between the treatment groups. However, when compared to seven patients with substantial LVSI with the other ones known with focal or no LVSI, there was statistically significant difference favoring the patients with focal or no LVSI in terms of OS, DFS, LRRFS and DMFS. However, due to the low number small of our patients with substantial LVSI, we cannot make a definitive conclusion in terms of the efficacy of VBT alone or the need for EPRT after comprehensive surgical staging in these patients. In the ongoing PORTEC-4a study, HIR patients are being stratified into risk groups according to molecular subtypes and presence of substantial LVSI and are being randomized to receive either EPRT or VBT.[26] The results of this study might give us a clearer response and change of adjuvant treatment decisions for HIR patients especially when they have substantial LVSI. Furthermore, our findings are consistent with the PORTEC studies and subsequent prognostic analyses, which have consistently shown that increasing age is associated with worse survival outcomes in EC.[10,27] Likewise, patients aged ≥60 years in our cohort had inferior DFS and DMFS despite comparable locoregional control.

The current study has several limitations. First, the frequency of two parameters which may affect the survival rates, that is, the rate of LND and chemotherapy administration are different between the two groups due to the retrospective nature of the study. In addition, the type of LVSI (substantial vs. focal) which is of utmost importance for the decision-making according to the current guidelines was unknown in the majority of patients, since the study included patients treated between 1994 and 2018. Yet, we still found that the prognosis of patients with substantial LVSI was poorer despite comprehensive surgical staging. Another limitation of our study is that molecular classification could not be performed as this study included patients treated before the introduction of the molecular classification for EC. On the other hand, our findings are important since this is the largest study with a very long follow-up period in the literature comparing VBT alone and EPRT±VBT in FIGO 2009 stage IB grade 3 endometrioid-type EC patients. Another strength of our study is that all our patients were treated with complete surgical staging and the median number of dissected LNs was 37 with a minimum number of 12. Even with this comprehensive surgical staging patients with substantial LVSI showed deterioration in terms of locoregional control and survival rates.

CONCLUSION

In conclusion, there is no difference between VBT alone and EPRT±VBT regarding LRR, DM, and survival rates in patients with grade 3 deeply invasive endometrioid type EC that underwent a comprehensive surgical staging. VBT alone seems an effective and safe treatment with minimal toxicity in this group of patients. However, although the LRR and DM rates are similar in patients with no/focal and substantial LVSI, all survival outcomes are inferior in the latter group. Consequently, with limited and perplexing data in hand, a large prospective randomized study is needed to determine the optimal treatment modality in patients with grade 3 deeply invasive endometrioid type EC , and particularly in patients with substantial LVSI in this subset.

Ethics Committee Approval: The study was approved by the Hacettepe University Ethics Committee (no: 2023/07/12, date: 21/11/2023).

Informed Consent: All patients consented to their anonymized data being used for research and educational purposes.

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