Oncological Outcomes of Stage II Endometrial Cancer

A Retrospective Analysis of 250 Cases

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Objective: The aim of this study was to investigate the effect of different surgical approaches, adjuvant therapy, and pathological characteristics on oncological outcomes in patients with 2009 International Federation of Gynecology and Obstetrics (FIGO) stage II endometrial cancer (EC).

Methods: A multicenter, retrospective department database review was performed to identify patients with FIGO 2009 stage II EC who underwent surgical staging between 2002 and 2015 at 5 gynecologic oncology centers in Turkey.

Results: Original pathology reports of 4867 patients who underwent surgical treatment for EC were analyzed. The study group consisted of 250 FIGO stage II patients. Of these patients, 203 (81.2%) had endometrioid and 47 (18.8%) had nonendometrioid histologic subtype of EC. Whereas 199 patients (79.6%) underwent type I hysterectomy, the remaining 51 patients (20.4%) underwent radical hysterectomy. Of the 250 patients, 208 patients (83.2%) had adjuvant therapy including radiotherapy (pelvic external beam radiotherapy and/or vaginal brachytherapy [VBT]) and/or platinum-based chemotherapy. Disease recurred in 29 patients (11.6%). The 5-year disease-free survival (DFS) and overall survival (OS) for the entire cohort were 82% and 85%, respectively. Multivariate analysis showed that only adjuvant treatment (P = 0.001; hazard ratio, 4.02; 95% confidence interval, 1.72–9.36) was significantly associated with DFS. According to multivariate analysis, only age older than 60 years (P = 0.01; hazard ratio, 3.03; 95% confidence interval, 1.3–7.04) was identified as an independent risk factor for OS. However, there were no differences in OS when evaluated by grade, histology, tumor size, type of hysterectomy, or adjuvant treatment.

Conclusions: In stage II EC, adjuvant external beam radiotherapy ± VBT were associated with increased DFS but not OS. However, the benefit of VBT alone on DFS could not be demonstrated. Only age was an independent risk factor for OS. Type of hysterectomy and histologic subtype of the tumor for patients with uterus-confined disease improved neither DFS nor OS in our study group.

Key Words: Adjuvant treatment, Endometrial cancer, Radical hysterectomy, Stage II

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Endometrial cancer (EC) is the most common gynecologic malignancy, with an estimated 319,600 new cases that occurred in 2012 worldwide. In Turkey, there are approximately 3800 new cases and 520 cancer-related deaths each year from EC. The lifetime risk is 2.5% for EC, and it accounts for 6% of all cancers in women.[1,2]

Endometrial carcinoma is surgically staged according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) system.[3] The revised FIGO 2009 staging system had a revision for stage II disease such that only patients with cervical stromal invasion were classified as stage II EC, and cervical glandular involvement was eliminated from stage II disease and considered as stage I disease.[4] While most cases are diagnosed at an early stage (stage I), stage II disease represents approximately 6% of all ECs.[5] Stage II EC is usually treated with either extrafascial or radical hysterectomy. Radical hysterectomy has been recommended for patients with stage II EC because up to 13% of patients with EC have parametrial involvement.[6] Adjuvant radiotherapy (RT) is often used after primary surgical treatment. Because most studies on stage II EC have been limited by retrospective design and low incidence rate, management of patients with stage II EC remains controversial. As a result, treatment strategies rely on observational studies, and still there is a lack of consensus on the optimal surgical management and role and type of adjuvant treatment for stage II disease. Furthermore, the most publications in the literature related with stage II EC include patients with cervical glandular involvement, and the data dealing with FIGO 2009 stage II EC are limited. Therefore, this multicenter retrospective study was designed to investigate the effect of different surgical approaches (simple or radical hysterectomy), adjuvant therapy (brachytherapy, external beam radiation, or chemotherapy), and pathological characteristics on oncological outcomes in patients with 2009 FIGO stage II EC.

MATERIALS AND METHODS

This observational retrospective multicenter study included 5 participating gynecologic oncology centers from Turkey: Hacettepe University Faculty of Medicine (Ankara), Etlik Zubeyde Hanim Women's Health and Training Hospital (Ankara), Zekai Tahir Burak Women's Health Education and Research Hospital (Ankara), Tepecik Education and Research Hospital (Izmir), and Akdeniz University Faculty of Medicine (Antalya). From January 2002 to December 2015, patients who had been diagnosed as having FIGO stage II EC in the gynecology-oncology division of each hospital were recruited. The institutional ethical committee approval was not sought because this study represented a retrospective database review. However, all patients signed an informed consent that allows the participating institutions to use their clinical data.

Original pathology reports of 4867 patients who underwent surgical treatment for EC were analyzed. All operations were performed by gynecologic oncologists. All surgical specimens were evaluated by specialized gynecologic pathologists at each institution. Inclusion criteria were as follows: (1) all types of histology, (2) no intraoperative evidence of extrauterine spread, (3) performance of pelvic ± para-aortic lymphadenectomy, and (4) histopathologically proven cervical stromal involvement. A total of 259 patients with cervical stromal involvement were identified. Five patients who did not undergo lymphadenectomy were excluded. Four patients were also excluded from the analysis who had missing information regarding postoperative adjuvant treatment and vital status while the study was being conducted. The remaining 250 FIGO stage II patients who were subject to comprehensive surgical staging consisting of total hysterectomy (simple, radical, or modified radical hysterectomy) with bilateral salpingo-oophorectomy, peritoneal washing, and pelvic ± para-aortic lymphadenectomy constituted our study group.

All patients were staged according to the 2009 FIGO staging system. Pathology reports of patients who were operated on between 2002 and 2009 were retrieved from the files and restaged according to the FIGO 2009 staging system. Pathology slides have not been reviewed, and restaging was performed on the basis of the original pathology reports. Patients with cervical stromal involvement were considered as stage II. The clinical and pathological characteristics of the patients were evaluated, including patient age, depth of myometrial invasion, tumor size, presence of lymphovascular space invasion (LVSI), number of removed lymph nodes, peritoneal cytology, adjuvant therapy, recurrence, and survival. The adjuvant treatment consisted of RT (pelvic external beam RT [EBRT] and/or vaginal brachytherapy [VBT]), chemotherapy, and RT plus chemotherapy (CRT). Patients with surgical stage II EC entered a routine surveillance program, and visits were scheduled for every 3 months for the first 2 years, every 6 months until 5 years, and annually thereafter. Surveillance consisted mainly of questioning patients about symptoms, physical examination, and vaginal vault smear. The survival status of patients was determined as dead or alive at the time of last follow-up. End points included tumor recurrence, disease-free survival (DFS), and overall survival (OS).

Data record and statistical analyses were performed using Statistical Package for Social Sciences for Windows 20 (IBM SPSS Inc, Chicago, IL). The categorical variables were expressed as number and percentage and were analyzed using Pearson χ^2 test or Fisher exact test, as appropriate. The Mann-Whitney U test was used to analyze the difference between samples that were from nonnormal distributions. Overall survival was calculated from time of diagnosis until death or time of last follow-up. Disease-free survival was calculated from time of diagnosis until the diagnosis of disease recurrence.

The life-table analysis was used to estimate OS and DFS of patients with surgical stage II EC, and survival differences were analyzed using the Wilcoxon rank sum test. $P < 0.05$ was considered to indicate statistical significance. Multivariate analysis was performed using Cox regression analysis.

RESULTS

A total of 250 consecutive patients with a mean age of 59.4 years (range, 35–86 years) were analyzed. Whereas 203 cases (81.2%) had endometrioid type of tumor, women with nonendometrioid histologic subtypes had serous papillary in 15 (6%), carcinosarcoma in 12 (4.8%), clear cell in 8 (3.2%), mucinous in 1 (0.4%), and mixed-type histology in 11 cases (4.4%). Pathological examination revealed low-grade (FIGO grades I–II) and high-grade (FIGO grade III) tumor in 167 patients (66.8%) and 83 patients (33.2%), respectively. Most patients (59.2%) had deep myometrial invasion. The LVSI and cervical glandular involvement was detected in 98 patients (39.2%) and 174 patients (69.6%), respectively. Two hundred eight patients (83.2%) had a tumor measuring more than 2 cm in diameter based on the final pathology report. Most patients (79.6%) underwent type I hysterectomy. The median number of removed lymph nodes was 39 (range, 8–133). Demographic, clinical, and pathological characteristics of the study patients are presented in Table 1.

Adjuvant treatment decisions for all patients were made by multidisciplinary tumor board in each center. Of the 250 patients, 42 patients (16.8%) did not receive adjuvant therapy. The remaining 208 patients (83.2%) had adjuvant therapy that included RT (EBRT and/or VBT) and/or platinum-based chemotherapy. Adjuvant treatment characteristics of patients with stage II EC are summarized in Table 2.

Disease recurred in 29 patients (11.6%). Characteristics of patients with recurrent disease are summarized in Table 3. The 5-year DFS for the entire cohort was 82%. Recurrent disease was located in the vaginal cuff in 12 patients and other pelvic structures in 5 patients. Three patients had peritoneal carcinomatosis, and 4 patients had liver metastasis. The remaining 5 patients had lung metastasis. The median number of removed lymph node was 36 (range, 10–102) among the patients with recurrent disease, whereas it was 40 (range, 8–133) among the patients who did not have recurrent disease. However, the difference was not statistically significant ($P = 0.47$). In addition, cervical glandular involvement was detected in 19 patients (65.5%) who had recurrent disease, whereas it was found in 155 patients (70.1%) who did not have recurrent disease ($P = 0.43$). Of the 29 patients with recurrent disease, 22 patients (75.9%) had endometrioid, and 7 patients (24.1%) had nonendometrioid histology. No statistically significant relationship was found between the histologic type of the tumor and recurrent disease ($P = 0.19$). Of the factors analyzed for correlation with DFS in patients with stage II EC, the presence of deep myometrial invasion, LVSI, and adjuvant treatment significantly correlated with DFS in the life-table analysis ($P = 0.01$, $P = 0.02$, and $P = 0.003$, respectively) (Table 4). Possible risk factors for DFS were added into the multivariate analysis. The examined factors included age, myometrial invasion, LVSI, and adjuvant treatment. Multivariate analysis showed

TABLE 1. Demographic and surgicopathological characteristics of 250 patients with stage II EC

Characteristic	All Population (n = 250)
Age,* y	59.4 ± 10.0
Histology†	
Endometrioid	203 (81.2)
Nonendometrioid	47 (18.8)
Serous	15 (6.0)
Carcinosarcoma	12 (4.8)
Clear cell	8 (3.2)
Mucinous	1 (0.4)
Mixed type	11 (4.4)
FIGO grade†	
I	86 (34.4)
II	81 (32.2)
III	83 (33.2)
Myometrial invasion†	
None	4 (1.6)
≤50%	98 (39.2)
>50%	148 (59.2)
Cervical glandular involvement†	
Yes	174 (69.6)
No	76 (30.4)
LVSI†	
Yes	98 (39.2)
No	119 (47.6)
Unknown	33 (13.2)
Primary tumor size,† cm	
≤2 cm	42 (16.8)
>2 cm	208 (83.2)
Lymphadenectomy procedure†	
Only pelvic	10 (4.0)
Pelvic and para-aortic	240 (96.0)
Hysterectomy procedure†	
Type 1	199 (79.6)
Type 2	24 (9.6)
Type 3	27 (10.8)
No. lymph nodes removed‡	39 (3–133)
Pelvic lymph nodes	28 (3–82)
Para-aortic lymph nodes	12 (6–55)
Peritoneal cytology†	
Positive	5 (2.0)
Negative	231 (92.4)
Unknown	14 (5.6)
Recurrences†	
None	221 (88.4)
Locoregional	17 (6.8)
Distant	12 (4.8)

*Numerical variables are expressed as mean ± SD.
†Categorical variables are expressed as number (%).
‡Numerical variables are expressed as median (min–max).

TABLE 2. Adjuvant treatment characteristics of patients with stage II EC

Type of Surgery	VBT	EBRT	VBT + EBRT	CRT	None
Type 1 hysterectomy + BSO + staging*	12 (92.3)	31 (96.9)	80 (80.8)	50 (78.1)	26 (61.9)
Type 2 hysterectomy + BSO + staging	1 (7.7)	—	6 (6.1)	7 (10.9)	10 (23.8)
Type 3 hysterectomy + BSO + staging	—	1 (3.1)	13 (13.1)	7 (10.9)	6 (14.3)

*Pelvic and/or para-aortic lymph node dissection ± peritoneal cytology.
BSO, bilateral salpingo-oophorectomy.

that only adjuvant treatment ($P = 0.001$; hazard ratio, 4.02; 95% confidence interval, 1.72–9.36) was significantly associated with the DFS (Fig. 1). In addition, the type of adjuvant radiation was statistically associated with DFS. Whereas adjuvant VBT alone was not associated with an improved DFS, a significant improvement of 5-year DFS was achieved in the EBRT ± VBT arm (Table 4).

The 5-year OS for all patients was 85%. Potential risk factors associated with OS are shown in Table 2 Of the factors analyzed for correlation with 5-year OS in patients with stage II EC, the presence of deep myometrial invasion, age, and LVSI were found to be significant predictors of 5-year OS in the life-table analysis ($P = 0.008$, $P = 0.01$, and $P = 0.002$, respectively). Possible significant risk factors for survival in the univariate analysis including age, myometrial invasion, and LVSI were added into the multivariate Cox regression analysis. According to multivariate analysis, only age older than 60 years (hazard ratio, 3.03; 95% confidence interval, 1.3–7.04; $P = 0.01$) was identified as an independent risk factor for OS (Fig. 2). However, there were no differences in OS when evaluated by grade, histology, tumor size, type of hysterectomy, or adjuvant treatment.

DISCUSSION

This retrospective multicenter study is one of the largest to report on oncological outcomes in stage II EC using the 2009 FIGO staging system. Because most of the previous studies regarding stage II EC were performed using the 1988 FIGO staging system, patients with cervical glandular involvement were also included in the analysis. Therefore, the current study was designed to analyze data from patients with 2009 FIGO stage II EC. Previous studies have shown that stage II EC constitutes approximately 7% to 10% of all ECs.[7,8] However, stage II disease was found to constitute 5.1% of all cases of EC in the current study. This difference was probably due to the absence of cervical glandular involvement in the new staging system.

Reported recurrence rates for stage II EC vary from 10% to 28%.[9,10] In the present study, recurrence rate was 11.6%. Despite these high recurrence rates, the current recommendations for adjuvant treatment in stage II EC remain controversial. After surgery, adjuvant treatment with EBRT ± VBT and/or chemotherapy may be considered. Previous studies have shown that adjuvant RT was associated with an improvement in local control but without an OS benefit.[11,12] On the other hand, Frandsen et al[9] reported that adjuvant RT improved neither DFS nor OS. In contrast, Wright et al[13] evaluated 1577 patients with stage II EC and found that adjuvant RT was associated with an improvement in survival in patients with high-risk pathologic features who underwent radical hysterectomy. Conversely, Mariani et al[14] did not observe any recurrence among patients who had radical hysterectomy, regardless of the administration of adjuvant RT. However, they found that adjuvant RT improved local control in patients who had simple hysterectomy.[14] The study published by Ayhan et al[15] evaluated 48 stage II EC patients and compared patients treated with simple hysterectomy plus RT with patients who had radical hysterectomy without adjuvant therapy. They reported that OS and DFS rates were not significantly different between the 2 groups.[15] Another important study related with stage II EC was published by Cornelison et al,[16] who reported that there was no significant survival difference in radiation versus no radiation in simple or radical hysterectomy groups. Our study results indicate that patients with stage II EC who underwent adjuvant EBRT ± VBT after surgery had better DFS regardless of the type of hysterectomy when compared with patients treated with surgery alone. On the other hand, VBT alone was not associated with an improved DFS. However, we also observed that adjuvant treatment did not improve OS. In addition, we could not detect a similar effect by adjuvant CRT. However, Hogberg et al[17] reported that the use of adjuvant chemotherapy with RT was related with an improved DFS, and there was no effect on OS in patients with stages I to III EC with no residual tumor and high-risk histopathologic features. Another important study related with the use of adjuvant chemotherapy published by Susumu et al,[18] and they compared pelvic RT and chemotherapy in patients with stages IC to IIIC EC and suggested a survival advantage of chemotherapy for EC patients with high to intermediate risk including those with stage II disease. Recently, the randomized PORTEC-3 trial has been presented, which investigated the benefit of adjuvant chemotherapy plus RT versus pelvic RT alone for patients with high-risk EC (FIGO stage I grade 3 with deep myometrial invasion and/or LVSI; stage II or III; or serous/clear cell histology). Six hundred sixty patients were enrolled in this study (330 patients received CRT and 330 patients received RT alone). The authors have concluded that adjuvant chemotherapy plus pelvic RT for the treatment of high-risk EC did not significantly improve 5-year DFS and OS, compared with RT alone.[19] Our finding may be associated with histologic subtype's distribution of patients who had adjuvant CRT. Among 64 patients who had adjuvant CRT in our study, 34 had endometrioid, 10 had serous, 10 had mixed (serous and endometrioid) histology, 6 had clear cell histology, and 4 had carcinosarcoma. In other words, patients with generally more adverse features might have been offered adjuvant CRT in the current study.

Radical hysterectomy has been frequently recommended for clinical stage II EC patients with suspected gross cervical involvement. Some studies have found that radical hysterectomy

TABLE 3. Demographic and surgicopathological characteristics of 29 patients with recurrent stage II EC

Characteristic	Recurrent Population (n = 29)
Age,* y	62 (36–81)
Histology†	
Endometrioid	22 (75.9%)
Nonendometrioid	7 (24.1%)
Serous	2
Carcinosarcoma	4
Clear cell	1
FIGO grade†	
I	8 (27.5%)
II	10 (34.5%)
III	11 (38%)
Myometrial invasion†	
≤50%	6 (20.6%)
>50%	23 (79.4%)
LVSI†	
Yes	14 (48.3%)
No	11 (38%)
Unknown	4 (13.7%)
Primary tumor size,† cm	
≤2 cm	5 (17.2%)
>2 cm	24 (82.8%)
Lymphadenectomy procedure†	
Only pelvic	4 (13.8%)
Pelvic and para-aortic	25 (86.2%)
Hysterectomy procedure†	
Type 1	21 (72.4%)
Type 2	4 (13.8%)
Type 3	4 (13.8%)
Adjuvant treatment†	
None	9 (31%)
VBT	3 (10.4%)
EBRT ± VBT	9 (31%)
CRT	8 (27.6%)
Recurrences†	
Vaginal cuff	12 (41.4%)
Other pelvic structures	5 (17.2%)
Upper abdomen	3 (10.3%)
Liver	4 (13.8%)
Lung	5 (17.2%)

*Numerical variables are expressed as median (min–max).
†Categorical variables are expressed as number (%).

was associated with an increased DFS or OS. Cohn et al[20] reported a significantly better 5-year DFS rate in patients who had radical hysterectomy compared with patients treated with simple hysterectomy (94% vs 76%). Similarly, Sartori et al[21] evaluated 203 patients with stage II EC and compared patients who underwent simple hysterectomy and radical hysterectomy.

TABLE 4. Five-year OS and DFS rates by prognostic factors

Variables	5-y DFS		5-y OS	
	%	*P*	%	*P*
Age, y				
≤60	89%	0.05	92%	0.01*
>60	71%		74%	
FIGO grade				
I–II	85%	0.07	87%	0.18
III	82%		81%	
Histology				
Endometrioid	84%	0.12	86%	0.45
Nonendometrioid	82%		76%	
Myometrial invasion				
≤50%	91%	0.01*	95%	0.008*
>50%	75%		78%	
LVSI				
No	84%	0.02*	92%	0.002*
Yes	78%		73%	
Primary tumor size, cm				
≤2	86%	0.9	85%	0.1
>2 cm	81%		82%	
Type of hysterectomy				
Simple	83%	0.89	83%	0.21
Radical	79%		89%	
Adjuvant treatment				
No	66%	0.003*	71%	0.17
Yes	84%		86%	
VBT	67%	0.4	67%	0.46
EBRT ± VBT	90%	0.001	89%	0.20
CRT	77%	0.12	84%	0.22

CRT, chemoradiotherapy; EBRT, external beam radiotherapy; LVSI, lymph-vascular space invasion; VBT, vaginal brachytherapy.

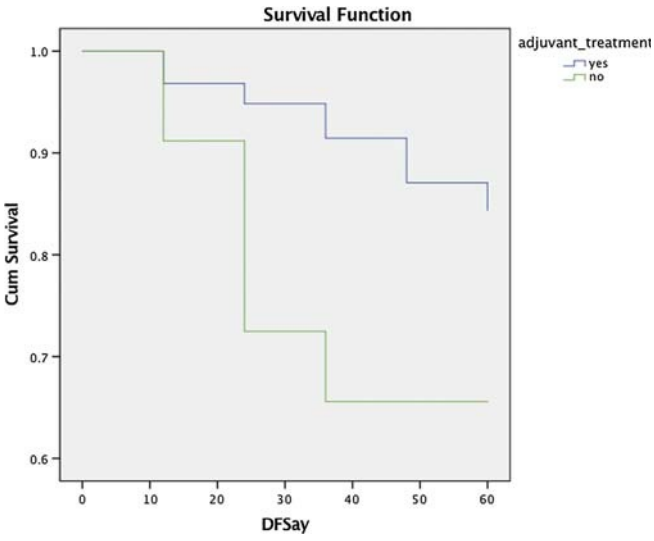

FIGURE 1. Disease-free survival and adjuvant treatment.

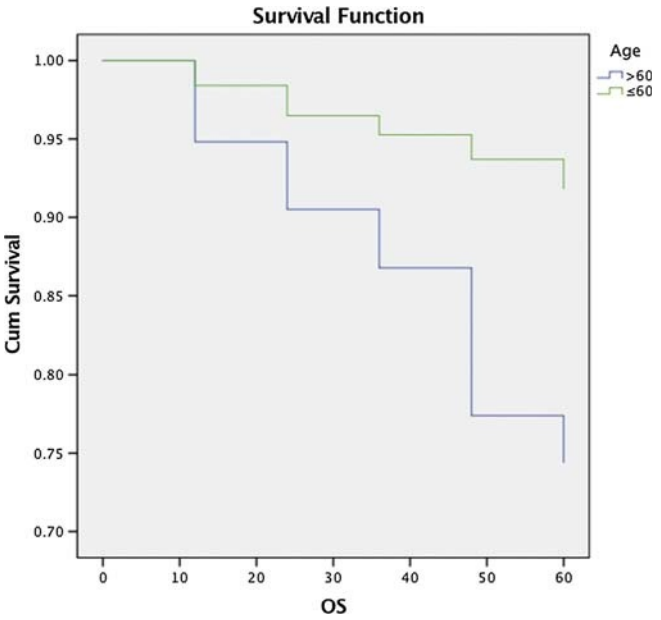

FIGURE 2. Overall survival and age.

They found a significant improvement in 5-year OS that was 94% in the radical hysterectomy group versus 79% in the simple hysterectomy group. Likewise, the study published by Cornelison et al[16] revealed that radical hysterectomy was associated with better survival when compared with simple hysterectomy for stage II EC. On the other hand, similar results could not be obtained by other investigators.[13,22] A recent study published by Takano et al[23] evaluated 300 patients with stage II EC. They compared 186 patients treated with radical hysterectomy, and 114 had simple hysterectomy; they found that the type of hysterectomy was not an independent prognostic factor for DFS and OS. In addition, they also reported that perioperative and late adverse events were more common in patients treated with radical hysterectomy.[23] In the present study, we compared 51 patients who had radical hysterectomy, with 199 patients with simple hysterectomy. In our multivariate analysis, radical hysterectomy improved neither DFS nor OS.

This study included nonendometrioid histologies in order to evaluate the effect of tumor histology on oncological outcomes in patients with stage II EC. Another important result of this study was that the histologic type of the tumor had no impact on DFS or OS in multivariate analysis when surgical staging confirmed that the disease was confined to the uterus. Similar results were found by Frandsen et al,[9] who reported that tumor histology was not associated with OS. In contrast, Lanciano et al[24] found that the histologic type of the tumor was an independent predictor of DFS in stage II EC. Because very few studies have addressed this issue, the effect of histologic subtypes of the tumor in surgically staged II EC still needs further investigation.

Our study has a number of limitations. Because of the retrospective nature of the study, the presence of other possible confounding variables such as selection bias that might have affected our results could not be ruled out. Different treatment regimens used over a period of 15 years are the other limiting factors that might potentially negatively affect the comparisons. Another limitation of the present study is that data were collected from 5 different institutions with potential differences in surgical and clinical management. Despite these limitations, our study contributes to the limited body of knowledge on this topic because of the large number of patients with 2009 FIGO stage II EC.

It seems reasonable to conclude that in stage II EC adjuvant EBRT ± VBT were associated with increased DFS but not OS. However, the benefit of VBT alone on DFS could not be demonstrated. Only age was an independent risk factor for OS. The type of hysterectomy and histologic subtype of the tumor for women with uterus-confined disease improved neither DFS nor OS in our study group.

REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87–108.
2. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin*. 2011;61:69-90.
3. Creasman W. Revised FIGO staging for carcinoma of the endometrium. *Int J Gynaecol Obstet*. 2009;105:109.
4. Lewin SN. Revised FIGO staging system for endometrial cancer. *Clin Obstet Gynecol*. 2011;54:215–218.
5. Yamagami W, Nagase S, Takahashi F, et al. Clinical statistics of gynecologic cancers in Japan. *J Gynecol Oncol*. 2017;28:e32.
6. Yura Y, Tauchi K, Koshiyama M, et al. Parametrial involvement in endometrial carcinomas: its incidence and correlation with other histological parameters. *Gynecol Oncol*. 1996;63:114–119.
7. Ahmad K, Kim YH, Deppe G, et al. Radiation therapy in stage II carcinoma of the endometrium. *Cancer*. 1989;63:854–858.
8. Eltabbakh GH, Moore AD. Survival of women with surgical stage II endometrial cancer. *Gynecol Oncol*. 1999;74:80–85.
9. Frandsen JE, William TS, Dodson MK, et al. Survival analysis of endometrial cancer patients with cervical stromal involvement. *J Gynecol Oncol*. 2014;25:105–110.
10. Larson DM, Copeland LJ, Gallager HS, et al. Prognostic factors in stage II endometrial carcinoma. *Cancer*. 1987;60:1358–1361.
11. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2004;92:744–751.
12. ASTEC/EN.5 Study Group; Blake P, Swart AM, Orton J, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. *Lancet*. 2009;373:137–146.
13. Wright JD, Fiorelli J, Kansler AL, et al. Optimizing the management of stage II endometrial cancer: the role of radical hysterectomy and radiation. *Am J Obstet Gynecol*. 2009;200:419 e1-419 e7.
14. Mariani A, Webb MJ, Keeney GL, et al. Role of wide/radical hysterectomy and pelvic lymph node dissection in endometrial cancer with cervical involvement. *Gynecol Oncol*. 2001;83:72–80.
15. Ayhan A, Taskiran C, Celik C, et al. The long-term survival of women with surgical stage II endometrioid type endometrial cancer. *Gynecol Oncol*. 2004;93:9–13.
16. Cornelison TL, Trimble EL, Kosary CL. SEER data, corpus uteri cancer: treatment trends versus survival for FIGO stage II, 1988–1994. *Gynecol Oncol*. 1999;74:350–355.

17. Hogberg T, Signorelli M, Carlos FO, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer—results from two randomised studies. *Eur J Cancer*. 2010;46:2422–2431.
18. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. *Gynecol Oncol*. 2008;108:226–233.
19. de Boer SM, Powell ME, Mileshkin LR, et al. Final results of the international randomized PORTEC-3 trial of adjuvant chemotherapy and radiation therapy (RT) versus RT alone for women with high-risk endometrial cancer. *J Clin Oncol*. 2017;35, (suppl; abstr 5502)
20. Cohn DE, Woeste EM, Cacchio S, et al. Clinical and pathologic correlates in surgical stage II endometrial carcinoma. *Obstet Gynecol*. 2007;109:1062–1067.
21. Sartori E, Gadducci A, Landoni F, et al. Clinical behavior of 203 stage II endometrial cancer cases: the impact of primary surgical approach and of adjuvant radiation therapy. *Int J Gynecol Cancer*. 2001;11:430–437.
22. Leminen A, Forss M, Lehtovirta P. Endometrial adenocarcinoma with clinical evidence of cervical involvement: accuracy of diagnostic procedures, clinical course, and prognostic factors. *Acta Obstet Gynecol Scand*. 1995;74:61–66.
23. Takano M, Ochi H, Takei Y, et al. Surgery for endometrial cancers with suspected cervical involvement: is radical hysterectomy needed (a GOTIC study)? *Br J Cancer*. 2013;109:1760–1765.
24. Lanciano RM, Curran WJ Jr, Greven KM, et al. Influence of grade, histologic subtype, and timing of radiotherapy on outcome among patients with stage II carcinoma of the endometrium. *Gynecol Oncol*. 1990;39:368–373.

