RESEARCH ARTICLE

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Retrospective Analysis of All Types of Adjuvant Radiotherapy in Endometrial Cancer: Single-Center Experiences in a Middle-Income Country

Nadee Chitapanarux[1], Ekkasit Tharavichitkul[2]*, Kittikun Kittidachanan[2], Pooriwat Muangwong[2], Somvilai Chakrabandhu[2], Pitchayaponne Klunklin[2], Wimrak Onchan[2], Bongkot Jia-Mahasap[2], Piyapasara Toapichattrakul[2], Imjai Chitapanarux[2]

Abstract

Objective: We retrospectively analyzed the efficacy, focusing on overall survival (OS) and the patterns of failure, along with the toxicities of adjuvant radiotherapy (RT) in endometrial cancer patients. **Methods:** Two-hundred and nineteen patients with endometrial cancer patients who received adjuvant radiotherapy ± adjuvant chemotherapy (ACT) from January 2014 to December 2018 were investigated for overall survival (OS), local recurrence-free survival rate (LRFS), regional recurrence-free survival rate (RRFS), and distant metastasis-free survival rate (DMFS). **Result:** Two-hundred and fourteen patients were evaluated. The numbers of VBT alone, EBRT plus VBT, and adjuvant chemotherapy (ACT) plus EBRT plus VBT were 65 (30.4%), 80 (37.4%), and 69 (32.2%) patients, respectively. Stage I (107 patients) was the most common followed by stage III (87 patients). With a median follow-up time of 67 months (IQR 56–78), the 5-year overall survival rates for VBT alone, EBRT plus VBT, and EBRT plus VBT plus ACT were 84.4%, 65%, and 57.4%, respectively. The most common severe (grade 3-4) acute toxicity was neutropenia (4.6%), followed by diarrhea (3.7%). Grade 3–4 late proctitis was found in only 1.9%. On multivariate analysis, advanced age (HR 6.15, p: 0.015), lymph node involvement (HR 6.66, p: 0.039), cervical involvement (HR 10.60, p: 0.029), and substantial LVSI (HR 21.46, p: 0.005) were associated with a higher risk of death. **Conclusion:** Advanced age (>65), substantial LVSI, lymph node involvement, and cervical stromal involvement were associated with poor overall survival. These findings here will help identifying high-risk patients and would make it possible to avoid unnecessary adjuvant treatment among patients with a good prognosis.

Keywords: endometrial cancer- adjuvant radiotherapy- treatment outcomes- toxicities- middle-income country

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Introduction

Endometrial cancer, accounting for approximately 4% of all cancers in women [1], is the world's second-most common gynecological cancer [2]. Furthermore, it is considered one of the leading causes of death due to gynecological cancer, especially in countries with high socioeconomic status [3]. In Thailand, the incidence of endometrial cancer increased from 2.8 per 100,000 persons in 1999 to 4.3 per 100,000 persons in 2011 [3]. The latest study of trends in the incidence of endometrial cancer from southern Thailand also projected an ASR (Aged-standardized incidence rate) of 8 per 100,000 people in 2030 [4]. The population-based data in Northern Thailand also revealed the continuously rising number of new endometrial cancer cases, from 48 in 2007 to 72 in 2012 and 93 in 2017 (https://w2.med.cmu.ac.th/cmcr/data-dashboard/).

Radiotherapy (RT), including vaginal brachytherapy (VBT) or external beam radiotherapy (EBRT), are radiotherapy options for adjuvant treatments for endometrial cancer. It is indicated for intermediate, high-intermediate, and high-risk patients according to the joint European Society of Gynecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) guidelines [5]. For intermediate-risk stage I, VBT is recommended, according to the PORTEC II study [6-8]. A combination of EBRT and VBT is recommended for the other risks [9, 10]. In our practice, adjuvant RT was VBT alone in the patients with stages IAG3, IBG1, and IBG2, and a combination of both modalities in the patients with

*[1]Faculty of Medicine, Chiang Mai University, Thailand. [2]Division of Radiation Oncology, Faculty of Medicine, Chiang Mai University, Thailand. *For Correspondence: ekkasit.t@cmu.ac.th*

at least stage IBG3. In EBRT, the dose of 45–50.4 Gy in conventional fractionation is used. For VBT, the doses of 21 Gy in 3 fractions and 7 Gy in 1 fraction are utilized as monotherapy and boost treatment, respectively.

In this study, we investigated the treatment results, focusing on overall survival, pattern of failure and toxicities of adjuvant RT in all stages of endometrial cancer treated in our center.

Materials and Methods

Patient selection

We retrospectively collected data from the medical records of endometrial cancer patients who received adjuvant RT at Faculty of Medicine, Chiang Mai University from 2014 to 2018. All patients received surgical staging, and complete surgical staging (a removal of the uterus, cervix, adnexa, and pelvic and para-aortic lymph node tissues, and obtaining pelvic washings for comprehensive endometrial cancer staging) was performed on 181 patients (84.6%). The inclusion criteria were patients with all FIGO stages of endometrial cancer who had indications to receive adjuvant RT and were at least 18 years old. Adjuvant chemotherapy (ACT) was indicated with the EBRT plus VBT group in at least stage III or an early stage with high-risk features. Exclusion criteria were patients who did not complete the RT course or having previous radiotherapy. The institutional review board approved this study with the study code RAD-2565-08943. The age, pathological stage, radiotherapy profiles, treatment outcomes, and toxicity (based on RTOG toxicity scoring system) data were collected.

Radiotherapy

The indication for post-operative RT was based on the European Society of Gynecological Oncology (ESGO) guidelines [5]. EBRT was applied with a 6 or 10 MV linear accelerator. The area of EBRT was the whole pelvic area, including the vaginal cuff, paravaginal tissue, and pelvic lymph node (LN) from the common iliac to obturator groups. In the case of the paraaortic lymph node (IIIC2), extended field radiotherapy (EFRT) was needed to cover the pelvic and paraaortic areas. The conventional dose of 45–50.4 Gy in 1.8–2 Gy per fraction is used in our practice. For VBT, an intravaginal cylinder was used with the Ir-192 radioisotope. The size of the applicator in VBT has been designed according to vaginal cuff fitting. In our practice, we used a dose of 21 Gy in three fractions for monotherapy and 7 Gy in one fraction for boost treatment. For ACT, the six cycles of carboplatin (AUC5) and paclitaxel (175 mg/m^2) were assigned thrice a week.

Post-operative follow-up

After treatment was finished, patients were scheduled for follow-up. The program was every 3 months in the first 2 years, every 6 months in the 3rd to 5th years, then annually. Vaginal and general examinations were performed, and special investigations (abdominal CT or others) were required as indicated.

Statistical analysis

The data on age, stage, pathological results, radiotherapy treatment, follow-up period, toxicity, and patient status were collected. In terms of survival status, the data were retrieved from our cancer registry unit. Descriptive statistics were used to evaluate the characteristic data. Overall survival (the status of the patient from treatment until death) outcomes were calculated by the Kaplan-Meier method and the log-rank test. Prognostic factors were analyzed using univariate and multivariate analyses with Cox regression analysis. All variables in the univariate analysis were included in the multivariate analysis. In the two-tailed test, p 0.05 was significant. All analyses were performed using STATA software (Stata Corp., College Station, TX).

Results

From 2014 to 2018, 219 patients with endometrioid carcinoma received adjuvant RT in our division. Five patients were excluded due to missing data (Figure 1). Then, 214 patients could be evaluated. The median age was 58 years. Stage I was the most common (50%), followed by stage III (40.7%). The complete surgical staging was performed on 181 patients (84.6%). Patients who received adjuvant VBT as monotherapy, adjuvant EBRT plus VBT, and ACT + EBRT plus VBT were 65, 80, and 69 patients, respectively. In the ACT plus EBRT plus VBT group, all patients received a platinum-based regimen (carboplatin plus paclitaxel), and 45 (65.2%) received six cycles. The median body mass index (BMI) was 24.65. Ninety-eight patients (45.8%) had underlying diseases, which were hypertension (95 patients), diabetes mellitus (49 patients), and dyslipidemia (56 patients). One hundred percent of patients in the VBT alone group were stage I, while only 28.2% of patients in the EBRT plus VBT group were stage I. Forty-two patients had pelvic LN, and 13 patients had paraaortic LN. The total characteristic data is shown in Table 1. The median overall treatment times of VBT alone, EBRT plus VBT, and chemotherapy plus EBRT plus VBT were 8, 38.5, and 41 days, respectively.

The 5-year overall survival rate for the entire cohort was 67.3%, with a median follow-up time of 67 months (IQR, 56–78 months). Treatment failure was found in 17 patients (5 in loco-regional and 12 in distant relapses). The 5-year LRFS of VBT alone, EBRT plus VBT, and ACT plus EBRT plus VBT were 93.3%, 95.6%, and 95.6%. The 5-year RRFS of VBT alone, EBRT plus VBT, and ACT plus EBRT plus VBT were 100.0%, 99.1%, and 99.1%, respectively. The 5-year DMFS of VBT alone, EBRT plus VBT, and ACT plus EBRT plus VBT were 100.0%, 92.5%, and 92.5%, respectively. The 5-year overall survival rates of VBT alone, EBRT plus VBT, and ACT plus EBRT plus VBT were 84.4%, 65%, and 57.4%, respectively. In univariate analysis, statistical significance was shown for age >65, type II histology, substantial lympho-vascular invasion (LVSI), advanced stage, high grade, the presence of lymph nodes, a greater pelvic lymph node ratio >10%, and involvement of the cervix in the whole group. Figure 2 shows selected Kaplan-Meier curves for the entire group

Table 1. Patient Characteristic Data

Parameters	VBT alone (n:65)		EBRT plus VBT (n:80)		ACT plus EBRT plus VBT (n:69)	
	n	(%)	n	(%)	n	(%)
Age, median (IQR)	58	(54 – 63)	59	(54 – 65.5)	58	(54 – 62)
BMI, median (IQR)	25.2	(16.9 – 27.7)	23.1	(20.23 – 26.25)	24.2	(21.8 – 27.8)
Underlying disease						
Yes	27	41.5	38	47.5	33	47.8
No	38	58.5	42	52.5	36	52.2
Stage						
IA	35	53.8	10	12.5	0	0
IB	30	46.2	31	38.8	1	1.4
	0	0	18	22.5	0	0
IIB	0	0	0	0	0	0
IIIA	0	0	10	12.5	25	36.2
IIIB	0	0	1	1.3	2	2.9
IIIC	0	0	0	0	1	1.4
IIIC1	0	0	7	8.8	26	37.7
IIIC2	0	0	2	2.5	13	18.8
IVB	0	0	0	0.7	1	1.4
N/A	0	0	1	1.3	0	0
Histology						
Endometrioid type	65	100	64	80	52	75.4
Non-endometrioid type	0	0	14	17.5	16	23.2
N/A	0	0	2	2.5	1	1.4
Grade						
Grade 1	23	35.4	23	28.8	26	37.7
Grade 2	20	30.8	16	20	13	18.8
Grade 3	22	33.8	36	45	14	34.8
N/A	0	0	5	6.3	6	8.7
Myometrial invasion						
No	1	1.5	1	1.3	3	4.3
Less than half	37	56.9	26	32.5	8	11.6
More than half	25	38.5	48	60	39	56.5
N/A	2	3.1	5	6.3	19	27.5
LVSI						
Yes	28	43.1	57	71.3	55	79.7
No	35	53.8	22	27.5	13	18.8
N/A	2	3.1	1	1.3	1	1.4
LVSI spaces						
Focal LVSI (0-3)	49	75.4	37	46.3	22	31.9
Substantial LVSI (4+)	12	18.5	34	42.5	35	50.7
N/A	4	6.2	9	11.3	12	17.4
Cervix involvement						
No	58	89.2	49	61.3	40	58
Endocervical gland	5	7.7	7	8.8	3	4.3
Cervical stroma	1	1.5	24	30	25	36.2
N/A	1	1.5	0	0	1	1.4
Pelvic LN						
Yes	0	0	8	10	34	49.3
No	59	90.8	53	66.3	27	39.1
N/A	6	9.2	19	23.8	8	11.6

Table 1. Continued

Parameters	VBT alone (n:65)		EBRT plus VBT (n:80)		ACT plus EBRT plus VBT (n:69)	
	n	(%)	n	(%)	n	(%)
Paraaortic LN						
Yes	0	0	3	3.8	10	14.5
No	27	41.5	28	35	18	26.1
N/A	38	58.5	49	61.3	41	59.4
Chemotherapy						
No	65	100	80	100	0	0
Yes	0	0	0	0	69	100
Dose (Gy), means ± SD.						
Vaginal cuff	29.1±3.0		60.1±3.3		60.2±1.7	
Bladder	21.0±10.8		58.0±4.8		58.3±3.3	
Rectum	31.2±8.9		58.0±3.8		59.8±3.5	
OTT (days), median (IQR)	8	(7 – 11)	38.5	(36 – 43)	41	(37 – 43)
FU times (months), median (IQR)	70	(58 – 79)	67	(56 – 78)	65	(46 – 77)

ACT, adjuvant chemotherapy; BMI, body mass index; N/A, not accessible; EBRT, external beam radiotherapy; FU, follow-up; LN, lymph node; LVSI, lympho-vascular invasion, OTT, overall treatment time; SD, standard deviation; VBT, vaginal brachytherapy

and parameters. In a multivariate analysis, there were strong links between the overall survival rate and being over 65 years old, having cancer in the cervix, having lymph nodes (LN), and having a lot of LVSI (4+ spaces). However, stages and grade which is widely considered as high-risk factors show no significant relation with OS in our study. This might be due to a small size of samples in our center. Table 2 shows this information. In VBT alone and EBRT plus VBT, none of the parameters were statistically significant. However, in ACT plus EBRT plus VBT, the prognosis was worse for non-endometrioid histology (p = 0.016), grade 3 (p = 0.018), substantial LVSI (p = 0.006), and less than 6 cycles of chemotherapy (p = 0.009) (Table 3).

Toxicity

According to our findings, grade 3–4 acute and late toxicities affected 25 patients and 6 patients, respectively. The most common acute toxicity and the most typical late toxicity in our population were diarrhea and proctitis, respectively, while 11% of ACT plus EBRT plus VBT group developed grade 3-4 neutropenia. Most toxicities emerged in the EBRT with VBT with ACT group due to combined modalities. Table 4 presents all the information on toxicities.

Discussion

Many large randomized controlled studies of adjuvant radiotherapy for stage I endometrial cancer demonstrated that EBRT ± VBT decreased only locoregional relapse (vagina and pelvic) without any benefits in distant metastasis or overall survival [11, 12] (Table 5). The patients with intermediate risk who received VBT alone

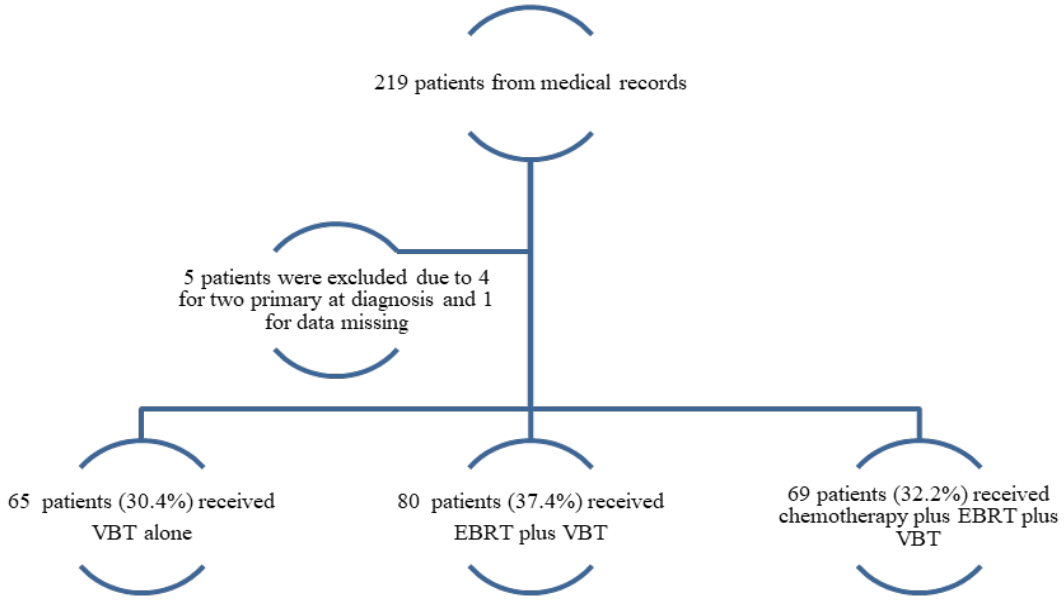

Figure 1. Consort Diagram of This Study

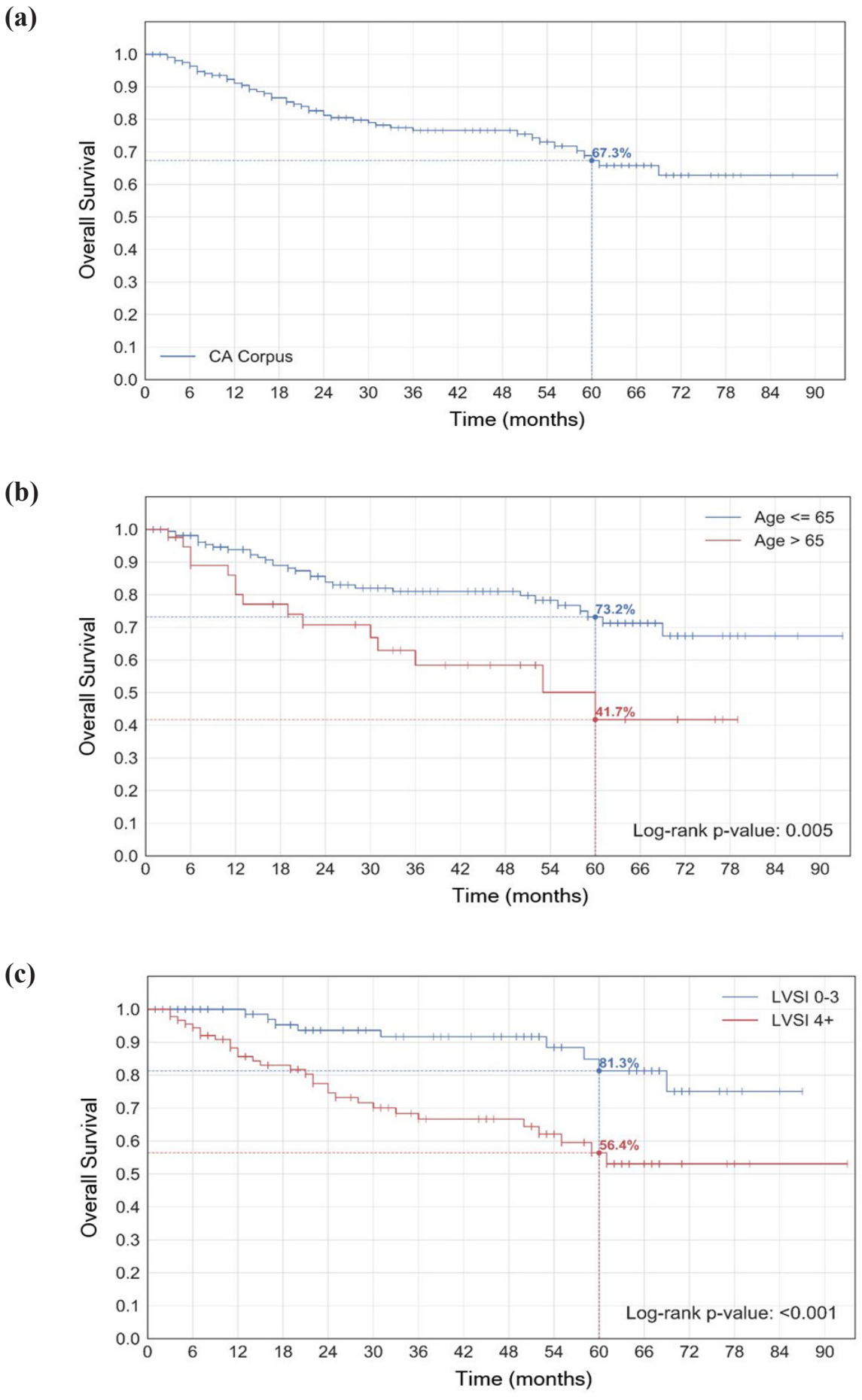

Figure 2. Selected Kaplan-Meier Curves Demonstrated Overall Survival of the whole Group (a), age >65 years (b), substantial lympho-vascular invasion (c), cervical involvement

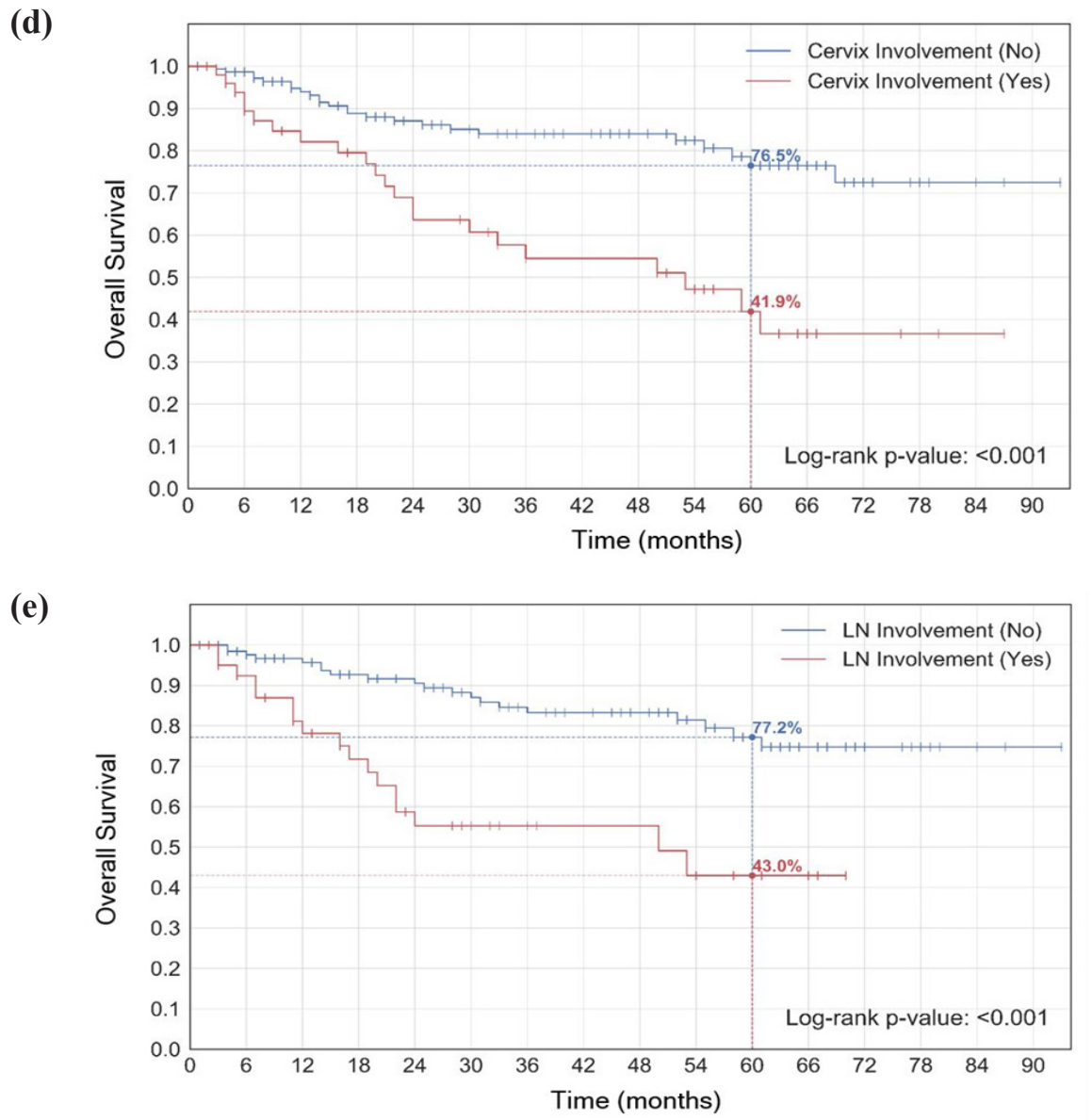

Figure 2. Selected Kaplan-Meier Curves Demonstrated Overall Survival of the whole Group (d), and presented Lymph nodes (e) in the whole group (N = 214).

in the PORTEC-2 study had similar results in vaginal relapse but better quality of life [8]. EBRT plus VBT is recommended for intermediate- to high-risk stage I patients (IBG3). Adding chemotherapy to adjuvant EBRT ±VBT was recommended for locally advanced disease (stage III) [5].

The practice in our center is also in line with clinical practice guidelines [5, 10]. The patients who received VBT alone were in stages IA and IB, and most patients (98.6%) who received adjuvant chemotherapy plus EBRT plus VBT were in stages IIIA-IVB. Patients who received adjuvant EBRT plus VBT varied from stage IA to IVB. The schema of VBT alone in our center was the same as in the PORTEC2 study, 21 Gy in 3 fractions [8]. A single fraction of 7 Gy VBT after EBRT was chosen due to our high workload. This schema of a single dose of 7 Gy was also reported by the Spanish group, which had similar efficacy and safety to multiple fractions and was more convenient for the patients [13].

In factor analysis, PORTEC-1 and PORTEC-2 demonstrated that substantial LVSI was the worst prognostic factor [14]. Many studies have reported the significance of age [15-17, 12]. The multivariate analysis in our study was in line with these studies. We found that older age (>65), advanced stage (stage II-IV), lymph node metastasis, and substantial LVSI (≥4) were the poorest prognostic factors. Moreover, in ACT plus EBRT plus VBT, histology (type 2), grade (grade 3), LVSI (>3), and chemotherapy (less than 6 cycles) showed poor prognostic factors. As expected, the treatment outcome and toxicity profiles of the patients who received VBT alone showed better overall survival than the other two groups since there were only stage I diseases. As a result of chemotherapy, patients in the EBRT plus VBT and ACT plus EBRT plus VBT groups had more toxicities than patients receiving VBT alone due to combined modality, with the most common late side effects occurring in the gastrointestinal tract like those of PORTEC-1, PORTEC-2, and GOG99 [7,

Table 2. Univariate and Multivariate Analysis in Overall Survival for Overall Patients (N:214)

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (>65 vs <65)	2.353	1.267-4.368	0.007	6.151	1.432-26.428	0.015
BMI (>25 vs <:25)	0.672	0.349-1.294	0.235	1.89	0.543-6.583	0.317
Stage (1 vs 2-4)	2.218	1.180-4.170	0.013	0.217	0.023-2.057	0.183
Myometrial Invasion (2 vs 0-1)	1.876	0.896-3.925	0.095	0.827	0.208-3.280	0.787
Grade (3 vs 1-2)	2.045	1.086-3.850	0.027	2.057	0.625-6.767	0.235
LVSI (>3 vs ≤3)	3.485	1.651-7.356	0.001	21.464	2.537-181.598	0.005
LN Involvement (present vs absent)	3.623	1.890-6.943	<0.001	6.665	1.097-40.486	0.039
Cervix Involvement (yes vs no)	3.288	1.842-5.871	<0.001	10.603	1.270-88.543	0.029
Histology (non-endometrioid vs endometrioid)	4.363	2.373-8.023	<0.001	1.34	0.305-5.885	0.698
LN Involvement (2+ vs 0-1)	2.019	0.919-4.433	0.08	0.345	0.066-1.794	0.206

ACT, adjuvant chemotherapy; BMI, body mass index; CI, confidence interval; EBRT, external beam radiotherapy; HR, hazard ratio; LN, lymph node; LVSI, lympho-vascular space invasion; UD, underlying disease; VBT, vaginal brachytherapy.

11, 12]. Our study's 5-year survival rates for VBT alone, EBRT plus VBT, and ACT plus EBRT plus VBT were 84.4%, 65%, and 57.4%, respectively. The locoregional control and overall survival rates in our study were nearly identical to those in other studies [18-20]. In the VBT alone group, in comparison to the PORTEC II study, our study showed a 5-year overall survival rate of 84.4% vs. 84.8% in PORTEC-2 [8]. For the advanced group that received EBRT plus VBT, our results had a slightly lower overall survival rate (65%) than the PORTEC-3 study (69.1% in the RT alone arm) [21]. This is because, in our study, 7 patients with stage IIIC were included in the EBRT plus VBT group, and all of them were unsuitable for ACT. For the ACT plus EBRT plus VBT group, the 5-year overall survival rate of our study (57.4%) was in line with the chemoradiotherapy group of the GOG 258 study (59%) [18]. According to our data, acute and late toxicities of grade 3-4 impacted 25 and 6 patients, respectively. In our population, the most prevalent acute and late toxicities were diarrhea and proctitis. The incidences of toxicities in our analysis are not different to other studies. .

However, our study had some limitations. First, it was retrospectively performed in a single center, resulting in a rather small number of patients. Although our study had a long median follow-up time of 67 months, some data was lost throughout the data collection procedure due to the COVID-19 outbreak. Moreover, the molecular profiles were not performed in our routine clinical practice. Despite all these limitations, our report shared similar outcomes for adjuvant radiotherapy for endometrial cancer as other studies [8, 18, 19]. According to the TIME-C study, intensity-modulated radiation therapy (IMRT) showed better results than three-dimensional conventional radiotherapy (3D-CRT) in terms of toxicity and quality of life [20]. According to PORTEC 4a, molecular profiles of endometrial cancer are implemented in the international guidelines to define the risk groups of patients, which later help define the treatment options (observation, radiotherapy, or a combination of chemotherapy and radiotherapy) [22, 23]. Additionally, the new stage of endometrial cancer was published by FIGO this year with many changes in terms of definition [24]. This analysis will be planned to be our baseline in treating endometrial cancer, and we have a future plan to integrate radiotherapy treatment with the new FIGO stage and molecular profiles.

In conclusion, our study's 5-year survival rate for

Table 3. Univariate and Multivariate Analysis in Overall Survival for Patients who Received EBRT Plus ACT (N:69)

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (>65 vs <65)	0.571	0.226-1.440	0.235	1.802	0.103-31.654	0.687
BMI (>25 vs <:25)	1.264	0.545-2.932	-	-	-	-
Stage (1-3b vs 3c+)	2.58	1.011-6.580	0.047	9.671	0.010-9232.080	0.517
Myometrial Invasion (2 vs 0-1)	0.176	0.023-1.341	0.094	1.392	0.030-65.021	0.866
Grade (3 vs 1-2)	0.355	0.144-0.877	0.025	0.03	0.002-0.556	0.018
LVSI (>3 vs ≤3)	0.398	0.133-1.196	0.101	0.001	0.000-0.124	0.006
LN Involvement (present vs absent)	3.066	1.186-7.925	0.021	189.237	0.223-162506.0	0.128
Cervix Involvement (yes vs no)	0.317	0.139-0.726	0.007	5.457	0.132-225.647	0.372
Histology (non-endometrioid vs endometrioid	0.163	0.072-0.371	0	0.011	0.000-0.124	0.006
Chemotherapy (0-5 vs 6)	3.295	1.452-7.477	0.004	309.686	4.128-22931.800	0.009

ACT, adjuvant chemotherapy; BMI, body mass index; CI, confidence interval; EBRT, external beam radiotherapy; HR, hazard ratio; LN, lymph node; LVSI, lympho-vascular space invasion; UD, underlying disease; VBT, vaginal brachytherapy.

Table 4. Acute and Late Toxicities in VBT Alone, EBRT plus VBT, and ACT plus EBRT plus VBT

Toxicity	VBT alone (n:65)		EBRT plus VBT (n:80)		ACT plus EBRT plus VBT (n:69)	
	n	%	n	%	n	%
Acute toxicity						
Anemia						
0-2	65	100.0%	77	96.3%	67	97.1%
3-4	0	0.0%	2	2.5%	2	2.9%
N/A	0	0.0%	1	1.3%	0	0.0%
Total	65		80		69	
Neutropenia						
0-2	65	100.0%	78	97.5%	61	88.4%
3-4	0	0.0%	2	2.6%	8	11.5%
N/A	0	0.0%	0	0.0%	0	0.0%
Total	65		80		69	
Thrombocytopenia						
0-2	65	100.0%	78	97.6%	66	95.7%
3-4	0	0.0%	1	1.3%	2	2.9%
N/A	0	0.0%	1	1.3%	1	1.4%
Total	65		80		69	
Dermatitis						
0-2	65	100.0%	79	98.8%	68	98.6%
3-4	0	0.0%	0	0.0%	0	0.0%
N/A	0	0.0%	1	1.3%	1	1.4%
Total	65		80		69	
Diarrhea						
0-2	64	98.4%	74	92.6%	66	95.7%
3-4	0	0.0%	6	7.5%	2	2.9%
N/A	1	1.5%	0	0.0%	1	1.4%
Total	65		80		69	
Cystitis						
0-2	65	100.0%	79	98.8%	68	98.6%
3-4	0	0.0%	0	0.0%	0	0.0%
N/A	0	0.0%	1	1.3%	1	1.4%
Total	65		80		69	
Late toxicity						
Hematuria						
0-2	58	89.2%	78	97.5%	65	94.2%
3-4	0	0.0%	0	0.0%	0	0.0%
N/A	7	10.8%	2	2.5%	4	5.8%
Total	65		80		69	
Proctitis						
0-2	58	89.2%	77	96.3%	62	89.8%
3-4	0	0.0%	1	1.3%	3	4.3%
N/A	7	10.8%	2	2.5%	4	5.8%
Total	65		80		69	
Vaginal stricture						
0-2	58	89.2%	76	95.1%	65	94.2%
3-4	0	0.0%	2	2.5%	0	0.0%
N/A	7	10.8%	2	2.5%	4	5.8%
Total	65		80		69	

ACT, adjuvant chemotherapy; EBRT, external beam radiotherapy; N/A, not accessible; VBT, vaginal brachytherapy.

Table 5. Comparative Studies of Outcome and late Toxicities

Studies	N	Patients	Modalities	Results	Late Toxicities
PORTEC-1 [11]	429	Stage IC G1-2 or Stage IB G 2-3 EC	Observation	5yr LRR 14% 5yr OS 85%	-
			Adjuvant EBRT	5yr LRR 4% 5yr OS 81%	GI Grade 3+ 3%
GOG99 [12]	392	Stage IB, IC, IIA	Observation	2yr LRR 12% 2yr OS 86%	-
			Adjuvant EBRT	2yr LRR 3% 2yr OS 92%	GI Grade 3+ 8%
PORTEC 2 [8]	427	Stage IBG3 or ICG1-2	Adjuvant EBRT	5yr LRR 2.1% 5yr OS 79.6%%	GI Grade 3+ <1%
		(Age 60+) of previous FIGO stage	Adjuvant VBT	5yr LRR 5.1% 5yr OS 84.8%	GI Grade 3+ 2%
PORTEC 3 [19]	686	Stage I high risk, stage II-III	Adjuvant RT	5yr pelvic/paraaortic recurrences 11.3% 5yr OS 69.1%	GI Grade 3+ 1% GI Grade 3+ 1%
			Adjuvant CCRT	5yr pelvic/paraaortic recurrences 7% 5yr OS 76.5%	
Zhang, et al [13]	325		EBRT plus		
			VBT 4-6Gy x 3 fractions (125 pts)	LR 3 pts (FU 95months)	GI Grade 1+ 6.4%
			VBT 5-6Gy x 2 fractions (93 pts)	LR 2 pts (FU 67months)	GI Grade 1+ 8.6%
			VBT 7Gy x 1 fractions (107 pts)	LR 1 pts (FU 51 months)	GI Grade 1+ 1.9%
GOG 258[20]	736	Stage III/IVA	Chemoradiotherapy	5-yr LR 2% 5-yr alive and relapse-free 59%	Grade 3+ 58%
			Chemotherapy alone	5-yr LR 7% 5-yr alive and relapse-free 58%	Grade 3+ 63%
Our study	214	Stage IAG3, IBG1-2 IBG3, II	VBT (7Gy x3 fractions) EBRT plus VBT (7Gy x 1 fraction boost)	5-yr LRC 93.8% and 5-yr OS 84.4%	GI Grade 3+ 0% GU Grade 3+ 0%
		IBG3, II with type II histology and stage III-IVA	ACT plus EBRT plus VBT (7Gy x 1 fraction boost)	5-yr LRC 94.9% and 5-yr OS 65%	GI Grade 3+ 1.3%, GU Grade 3+ 0%
				5-yr LRC 94.9% and 5-yr OS 57.4%	GI grade 3+ 4.3% GU grade 3+ 0%

ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; EC, endometrial cancer; EBRT, external beam radiotherapy; G, grade; GI, gastrointestinal; GU, genitourinary; GOG, Gynecologic Oncology Group; LR, local recurrence rate; LRC, locoregional control; LRR, locoregional recurrence; OS, overall survival; PORTEC, Post-Operative Radiation Therapy in Endometrial Cancer; VBT, vaginal brachytherapy

adjuvant radiotherapy was 67.4%. The 5-year survival rates for VBT alone, EBRT plus VBT, and ACT plus EBRT plus VBT were 84.4%, 65%, and 57.4%, respectively. Treatment failure was found in 17 patients. The grade 3–4 proctitis rate in our study was 1.9%. Older age, advanced stage, substantial LVSI, and presented LN showed statistical significance for worse prognostic factors.

Author Contribution Statement

NC: concept design, data collection, data grouping, and manuscript writing; ET: concept design, data grouping, data calculation, data analysis, and manuscript writing; KK: data analysis; PM: data collection; SC: data collection; PK: data collection; WO: data collection; BJ: data collection; PT: data collection; and IC: consultant. This manuscript was reviewed by all authors.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Uharcek P. Prognostic factors in endometrial carcinoma. J Obstet Gynaecol Res. 2008;34(5):776-83. https://doi.org/10.1111/j.1447-0756.2008.00796.x.
2. Zhang S, Gong TT, Liu FH, Jiang YT, Sun H, Ma XX, et al. Global, regional, and national burden of endometrial cancer, 1990-2017: Results from the global burden of disease study, 2017. Front Oncol. 2019;9:1440. https://doi.org/10.3389/fonc.2019.01440.
3. Wilailak S, Lertchaipattanakul N. The epidemiologic status of gynecologic cancer in thailand. J Gynecol Oncol. 2016;27(6):e65. https://doi.org/10.3802/jgo.2016.27.e65.
4. Saeaib N, Sriplung H, Pichatechaiyoot A, Bilheem S. Trends in incidence of uterine cancer in songkhla, southern thailand. J Gynecol Oncol. 2019;30(2):e22. https://doi.org/10.3802/jgo.2019.30.e22.
5. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. Esgo/estro/esp guidelines for the management of patients with endometrial carcinoma. Radiother Oncol. 2021;154:327-53. https://doi.org/10.1016/j.radonc.2020.11.018.
6. Nout RA, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, van der Steen-Banasik EM, et al. Five-year quality of life of endometrial cancer patients treated in the randomised post operative radiation therapy in endometrial cancer (portec-2) trial and comparison with norm data. Eur J Cancer. 2012;48(11):1638-48. https://doi.org/10.1016/j.ejca.2011.11.014.

7. Wortman BG, Creutzberg CL, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens L, et al. Ten-year results of the portec-2 trial for high-intermediate risk endometrial carcinoma: Improving patient selection for adjuvant therapy. Br J Cancer. 2018;119(9):1067-74. https://doi.org/10.1038/s41416-018-0310-8.
8. Nout RA, Smit VT, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (portec-2): An open-label, non-inferiority, randomised trial. Lancet. 2010;375(9717):816-23. https://doi.org/10.1016/s0140-6736(09)62163-2.
9. Amant F, Mirza MR, Koskas M, Creutzberg CL. Cancer of the corpus uteri. Int J Gynaecol Obstet. 2018;143 Suppl 2:37-50. https://doi.org/10.1002/ijgo.12612.
10. Koskas M, Amant F, Mirza MR, Creutzberg CL. Cancer of the corpus uteri: 2021 update. Int J Gynaecol Obstet. 2021;155 Suppl 1(Suppl 1):45-60. https://doi.org/10.1002/ijgo.13866.
11. Creutzberg CL, Nout RA, Lybeert ML, Wárlám-Rodenhuis CC, Jobsen JJ, Mens JW, et al. Fifteen-year radiotherapy outcomes of the randomized portec-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys. 2011;81(4):e631-8. https://doi.org/10.1016/j.ijrobp.2011.04.013.
12. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, 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(3):744-51. https://doi.org/10.1016/j.ygyno.2003.11.048.
13. Zhang Y, Ascaso C, Herreros A, Sánchez J, Del Pino M, Torné A, et al. Is one brachytherapy fraction of 7 gy similar to more fractions after external beam irradiation in postoperative endometrial carcinoma? Clin Transl Oncol. 2020;22(8):1295-302. https://doi.org/10.1007/s12094-019-02255-z.
14. Bosse T, Peters EE, Creutzberg CL, Jürgenliemk-Schulz IM, Jobsen JJ, Mens JW, et al. Substantial lymph-vascular space invasion (lvsi) is a significant risk factor for recurrence in endometrial cancer--a pooled analysis of portec 1 and 2 trials. Eur J Cancer. 2015;51(13):1742-50. https://doi.org/10.1016/j.ejca.2015.05.015.
15. Jolly S, Vargas CE, Kumar T, Weiner SA, Brabbins DS, Chen PY, et al. The impact of age on long-term outcome in patients with endometrial cancer treated with postoperative radiation. Gynecol Oncol. 2006;103(1):87-93. https://doi.org/10.1016/j.ygyno.2006.01.038.
16. Mundt AJ, Waggoner S, Yamada D, Rotmensch J, Connell PP. Age as a prognostic factor for recurrence in patients with endometrial carcinoma. Gynecol Oncol. 2000;79(1):79-85. https://doi.org/10.1006/gyno.2000.5917.
17. Sun S, Zou L, Wang T, Liu Z, He J, Sun X, et al. Effect of age as a continuous variable in early-stage endometrial carcinoma: A multi-institutional analysis in china. Aging (Albany NY). 2021;13(15):19561-74. https://doi.org/10.18632/aging.203367.
18. Matei D, Filiaci V, Randall ME, Mutch D, Steinhoff MM, DiSilvestro PA, et al. Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer. N Engl J Med. 2019;380(24):2317-26. https://doi.org/10.1056/NEJMoa1813181.
19. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (portec-3): Patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 2019;20(9):1273-85. https://doi.org/10.1016/s1470-2045(19)30395-x.
20. Klopp AH, Yeung AR, Deshmukh S, Gil KM, Wenzel L, Westin SN, et al. Patient-reported toxicity during pelvic intensity-modulated radiation therapy: Nrg oncology-rtog 1203. J Clin Oncol. 2018;36(24):2538-44. https://doi.org/10.1200/jco.2017.77.4273.
21. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (portec-3): Final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(3):295-309. https://doi.org/10.1016/s1470-2045(18)30079-2.
22. Wortman BG, Bosse T, Nout RA, Lutgens L, van der Steen-Banasik EM, Westerveld H, et al. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: Evaluation of the pilot phase of the portec-4a trial. Gynecol Oncol. 2018;151(1):69-75. https://doi.org/10.1016/j.ygyno.2018.07.020.
23. Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, et al. Endometrial cancer: Esmo clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(9):860-77. https://doi.org/10.1016/j.annonc.2022.05.009.
24. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. Figo staging of endometrial cancer: 2023. Int J Gynaecol Obstet. 2023;162(2):383-94. https://doi.org/10.1002/ijgo.14923.