Recurrence Pattern after Adjuvant Radiotherapy for Endometrioid Type Endometrial Cancer

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ABSTRACT

OBJECTIVE: To define recurrence pattern of endometrioid type endometrium cancer performed adjuvant radiotherapy.

STUDY DESIGN: 351 patients who underwent at least total abdominal hysterectomy with bilateral salpingo-oophorectomy and followed by adjuvant radiotherapy (vaginal brachytherapy or pelvic radiotherapy or both) for endometrioid type endometrium carcinoma were included. The patients who received systemic adjuvant treatment after surgery were excluded from the study except for 18 patients who received concomitant chemo-radiotherapy. Recurrence was categorized as pelvic recurrence included areas distal to the pelvic inlet, as abdominal recurrence included areas between pelvic inlet and diaphragm and findings such as ascites and peritonitis carcinomatosa, and the rest of recurrences including lung, cutaneous, liver parenchyma and bone as extra-abdominal recurrence.

RESULTS: The median age was 57 years (range; 29-82). 236 patients had stage I, 25 had stage II, 63 had stage III and 14 had stage IV disease (by FIGO 2009). Lymph node metastasis was determined in 21.8% of patients who underwent lymphadenectomy (n: 289). The median follow-up time was 46 months (range; 1-190). Throughout follow-up, recurrence was developed in 55 (15.7%) patients. Only pelvic recurrence was determined in 11 (3.1%) patients. There was recurrence beyond the pelvis in 44 (80%) of the recurrent patients. Thirty-five (%63.6) of recurrent patients had extra-abdominal recurrence. Twenty-three (41.8%) of recurrent patients had stage IB disease. The recurrence developed in 10% of patients with stage I&II, whereas it was occurred in 31% of patients with stage III&IV (p<0.0001).

CONCLUSION: Radiotherapy provides local control of the disease, but recurrence is likely to be extra-pelvic and extra-abdominal in this patient group.

Key words: Endometrioid type endometrial cancer, Adjuvant radiotherapy, Recurrence

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Introduction

According to the 2012 GLOBACAN data, endometrium cancer (EC) is the sixth most common cancer among women (1). EC is mostly diagnosed at an early stage with over the 80% 5-year survival in low grade disease (2). Recurrence rate varying according to clinical factors, stage and pathologic findings; is approximately 11-13% within 2 years after initial treatment in EC patients (3-5). Extra-pelvic disease was present in 70% of recurrent patients' diagnosed high grade EC (6-10).

Primary treatment of endometrium cancer is the surgery that was mostly recommended as an extra facial hysterectomy with bilateral salpingo-oophorectomy. The insertion of lymphadenectomy into the surgical procedure is controversial and it is considered to be a more accurate management of the lymphatic spread in the risky group. The necessity of adjuvant therapy such as chemotherapy, radiotherapy, hormonal therapy and combination of those; was identified according to stage and pathologic findings in postoperative period (11).

Adjuvant radiotherapy can be performed in 4 forms for endometrial cancer patients; (i) vaginal vault brachytherapy (VBT), (ii) external beam pelvic radiotherapy (EBRT), (iii) extended field radiotherapy and (iv) whole abdominal radiotherapy. Sterilization of the tumor within the region performed radiotherapy was obtained in an effective manner. As a result, recurrence usually occurs outside the area of radiotherapy, as in

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the cases with EC patients receiving radiotherapy. Recurrence was developed mostly in outside of the pelvis and extra-abdominal localization in EC patients treated with adjuvant radiotherapy (12-14). However, detailed identification of the recurrence pattern in these patients is not made sufficiently.

The main aim of this study is to identify recurrence pattern of the endometrioid type EC performed adjuvant radiotherapy. Second goal is to determine the survival and the predictive factors of survival.

Material and Method

351 patients who underwent at least total abdominal hysterectomy and bilateral salpingo-oophorectomy and followed by received adjuvant radiotherapy due to the endometrioid type endometrium carcinoma between January 1993 and May 2013 were included to the study. Data of the patients were obtained from electronic database of gynecological oncology clinic and from patients' files. Patients with secondary primer malignancy, with final pathological results including non-endometrioid type tumors or sarcoma components, who received neo-adjuvant therapy or adjuvant systemic therapy (chemotherapy, sandwich therapy *[chemotherapy followed by radiotherapy followed by chemotherapy],* hormonal therapy) and who did not receive adjuvant therapy following surgery were excluded. However, 18 patients received concomitant chemo-radiotherapy modalities that were performed as a weekly low dose cisplatin, because of benefit from its radio-sensitization effect rather than systemic effects; with radiotherapy were included in the study. Patients were staged according to the 2009 FIGO criteria. IRB approval was obtained before the study.

Frozen/section is utilized routinely for patients with endometrial cancer in our clinic and staging surgery is performed for all patients without FS results included the endometrioid type grade 1 & 2 histology, less than ½ myometrial invasion and less than 2 cm tumor size. Staging surgery standardly involves total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic-para aortic lymphadenectomy, omentectomy and cytologic sampling. In case of intraoperative identification of macroscopic disease, cytoreductive surgical techniques are used in addition to staging surgery. Lymphadenectomy is performed in the majority of patients as skeletonization of the pelvic and paraaortic vessels.

The type of both adjuvant therapy (radiotherapy or concomitant chemo-radiotherapy) and radiotherapy (VBT or EBRT or both of them) were decided by the gynecological oncology council. Disease that recurred within 1 month after initial adjuvant therapy and progression of disease during the initial adjuvant therapy was accepted as a refractory disease and those were excluded. Disease developed one month after the end of the adjuvant treatment in patients whose absence of disease approved according to physical examination and necessary imaging techniques that was shown in patients, was defined as recurrence. The period from surgery to recurrence or last visit was defined as disease-free survival (DFS) and the period from surgery to death or last visit was defined as overall survival (OS). Recurrence was categorized as a pelvic recurrence included areas distal to the pelvic inlet, as an abdominal recurrence included areas between pelvic inlet and diaphragm and findings such as ascites and peritonitis carcinomatosa, and the rest of recurrences including lung, cutaneous, liver parenchyma and bone as an extra-abdominal recurrence.

Presence of recurrence was decided according to findings of clinical, imaging techniques; such as chest X-ray, abdomino-pelvic and thoracic computerized tomography or magnetic resonance imaging; and pathologic evaluation tissue if necessary. Decision of treatment type after recurrence was taken by gynecologic oncology council. Response to therapy evaluated according to World Health Organization criteria (15). According to the assessment made in the first month after treatment, we defined clinical response as following: (i) complete clinical response; disappearance of the macroscopic tumor, (ii) partial clinical response; shrinkage over %50 in the macroscopic tumor, (iii) stable disease; macroscopic tumor shrinkage less than 50% or not less than 25% growth, (iv) progressive disease; more than 25% growth in the macroscopic tumor or macroscopic appearance of new tumor foci.

Patients who had complete clinical response after adjuvant therapy were followed up quarterly in the first 2 years, semi-annually up to 5 years and annually later on. Pelvic examination, abdomino-pelvic ultrasonography, complete blood count and blood chemistry were performed in the follow up. Chest X-ray was utilized yearly unless there was a clinical suspicion. Thoracic and/or abdominal computerized tomography was used when needed. Ca-125 level were utilized in the follow-up, even though they weren't used routinely.

Categorical variables were analyzed with Kaplan-Meier Survival Analysis using Log-Rank Test to determine whether they had statistically significant effects on DFS and OS. Whether the continuous and discrete numeric variables had statistically significant effects on DFS and OS were calculated using univariate Cox Proportional Hazard Regression Analysis. Multivariate Backward Stepwise Cox Proportional Hazard Regression Analysis was used to determine the effects of variables effective on PRS after univariate statistical analysis. Factors having a p value of <0.25 in univariate analyses were included as candidate variables in multivariate analyses. p value <0.05 was considered statistically significant for the results. Data analyses were performed by using SPSS for Windows 11.5 package program.

Results

Initial therapy

The median age of all cohort was 57 years and ranged from 29 to 82 years. The mean tumor size was 45 mm (range; 7-130). The mean preoperative CA125 level was 49 IU/mL (range: 1-500). According to FIGO 2009, 236 patients had

stage I, 25 had stage II, 63 had stage III and 14 had stage IV disease. FIGO grade was grade-3 in 89 patients. The myometrial invasion was absent in 9 patients, whereas serosal invasion was determined in 13 patients. Cervical invasion was detected in 71 patients and 59 of them were stromal invasion. Malign peritoneal cytology was present in 15 patients. There was lympho-vascular invasion in 144, adnexal metastasis in 26, omental spread in 10 and extra-uterine non-nodal metastasis in 40 patients. Clinical, surgical and pathologic data of the patients are shown in table 1 in detail.

Lymphadenectomy was performed to 289 patients at initial surgery. The number of median lymph nodes removed was 40 (range: 3-118). Lymph node metastasis was detected in 63 (21.8%) of those patients. Lymph node metastases were in paraaortic region in 13 patients, in pelvic region in 29 patients and in both regions in 21 patients.

No residual tumor was present in 349 patients after initial surgery. However, larger than 1 cm the residual tumor was present after completed surgery in 2 patients. Cisplatin was given as a chemotherapy agent in 18 patients who received concomitant chemo-radiotherapy.

Recurrence and Survival

Median follow-up time was 46 months (range; 1-190). Recurrence developed in 55 (15.7%) patients and 20 (5.7%) patients died due to the disease during the follow-up. Mean CA125 level was 226 IU/mL (range: 2-3150) at recurrence. Eighteen (32.7%, n = 18/55) patients had recurrences in the pelvic region and 11 (20%, n = 11/55) of recurrent patients had only pelvic recurrence. Eighty percent (n: 44/55) of recurrent patients had disease beyond the pelvis. Extra-abdominal recurrence was present in 63.6% of recurrent patients. Recurrence location could not be identified in 1 patient. Twenty-three (41.8%) of recurrent patients had stage IB disease. However, recurrence was observed in 15% of IB cases. In contrast, recurrence developed in 70% of patients with stage IVB (n=7/10). Recurrence rate was significantly increased in the advanced stage. The recurrence developed in 10% of patients with early stage (stage I & II), whereas it was occurred in 31% of patients with advanced stage (stage III & IV) (p<0.0001). There was no relationship between the presence of extra-pelvic recurrence and stage. Seventy-eight percent and 82% of the recurrences was in the extra-pelvic region among the patients with stage I & II and stage III & IV, respectively (p = 0.735). Association between location of recurrence and stage is detailed in table 2.

Table 1: Clinical, surgical and pathological characteristics of patients

Characteristics		n / Mean	% / Median (range)
Age at initial diagnosis		57.3	57 (29-82)
Disease free interval (month) 1		19.5	17 (2-68)
CA 125 level at initial diagnosis (IU/ml)		49	15 (1-500)
CA 125 level at recurrence (IU/ml)		226	35 (2-3150)
Tumor size at initial diagnosis (mm)		45.1	40 (7-130)
FIGO 2009 stage	IA	83	23.6
	IB	153	43.6
	II	25	7.1
	IIIA	13	3.7
	IIIB	1	0.3
	IIIC1	29	8.3
	IIIC2	33	9.4
	IVA	4	1.1
	IVB	10	2.8
FIGO grade	1	93	26.5
	2	165	47
	3	89	25.4
	Not reported	4	1.1
Depth of myometrial invasion	No invasion	9	2.6
	< ½	109	31.1
	≥ ½ 2	219	62.4
	Serosal invasion	13	3.7
	Not reported	1	0.3
Lymphovascular space invasion	Negative	165	47
	Positive	144	41
	Not reported	42	12
Cervical invasion	Negative	279	79.5
	Glandular	12	3.4
	Stromal	59	16.8
	Not reported	1	0.3
Peritoneal cytology	Negative	327	93.2
	Positive	15	4.3
	Not reported	9	2.6
Adnexal metastasis	Negative	325	92.6
	Positive	26	7.4
Omental metastasis	Negative	278	79.2
	Positive	10	2.8
	Not performed	63	17.9
Non-nodal extra-uterine tumor[3]	Negative	311	88.6
	Positive	40	11.4
Lymphadenectomy at initial surgery	Not performed	62	17.7
	Performed	289	82.3
Number of harvested lymph node		41.6	40 (3-118)
Lymph node metastasis[4]	Negative	226	78.2
	Isolated pelvic	29	10
	Isolated paraaortic	13	4.5
	Pelvic & paraaortic	21	7.3
Type of adjuvant therapy	Radiotherapy	333	94.9
	Concomitant chemoradiotherapy	18	5.1

Table 2: Findings of recurrence sites according to FIGO stage

2009 FIGO stage	Only pelvic	Only upper-abdominal	Only extra-abdominal	Pelvic + upper-abdominal	Pelvic + extra-abdominal	Upper-abdominal + extra-abdominal	Pelvic + upper-abdominal + extra-abdominal	Unknown	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n
IA	-	1 (33.3)	1 (33.3)	1 (33.3)	-	-	-	-	3
IB	6 (26.1)	1 (4.3)	14 (60.9)	-	-	1 (4.3)	1 (4.3)	-	23
II	-	-	1 (100)	-	-	-	-	-	1
IIIA	1 (25)	-	2 (50)	1 (25)	-	-	-	-	4
IIIC1	2 (25)	2 (25)	3 (37.5)	-	-	-	1 (12.5)	-	8
IIIC2	2 (28.6)	-	5 (71.4)	-	-	-	-	-	7
IVA	-	-	1 (50)	1 (50)	-	-	-	-	2
IVB	-	1 (14.3)	1 (14.3)	-	1 (14.3)	2 (28.6)	1 (14.3)	1 (14.3)	7
Total	11 (20)	5 (9.1)	28 (50.9)	3 (5.5)	1 (1.8)	3 (5.5)	3 (5.5)	1 (1.8)	55

A palliative approach was offered to 8 patients with recurrent disease and 1 patient lost to follow-up after recurrence. Recurrence therapy was performed as an only salvage chemotherapy in 26, an only radiotherapy in 7, surgery followed by additional therapy in 13 patients (chemotherapy, n=8; radiotherapy, n=3; chemo-radiotherapy, n=1; hormonal therapy, n=1). Recurrence was developed at outside of the initial radiotherapy performed field in 7 patients performed only radiotherapy and 3 patients underwent surgery followed by radiotherapy for recurrence. In 13 patients who underwent curative surgery for recurrent disease; there were no residual disease in 8 (61.5%), ≤1 cm residual tumor in 3 (23.1%) and >1 cm residual tumor in 2 (15.4%) patients.

5-year DFS and OS of all cohort were 80% and 93%, respectively. In univariate analysis, age *(<65 vs. ≥65 year)*, stage *(stage I&II vs. III&IV),* lymph node metastasis (negative vs. positive), depth of myometrial invasion (<%50 vs. ≥%50), uterine serosal involvement (negative vs. positive), lympho-vascular space invasion *(negative vs. positive)*, adnexal metastasis *(negative vs. positive)*, peritoneal cytology *(negative vs. positive*) and non-nodal extra-uterine tumor *(negative vs. positive)* was significantly associated with DFS (Table 3). Time to recurrence *(<12 months vs. ≥12 months)*, stage (stage I&II vs. III&IV), tumor size *(<40 vs. ≥40mm)*, uterine serosal involvement *(negative vs. positive)*, adnexal metastasis *(negative vs. positive)*, peritoneal cytology *(negative vs. positive)* and non-nodal extra-uterine tumor (negative vs. positive) was significantly related with OS

Table 3: The factors predicting disease-free survival and overall survival, univariate analysis

Factors		5-year disease-free survival, (%)	p value	5-year overall survival, (%)	p value
Age at initial diagnosis	< 65 years	82	*0.043*	94	*0.074*
	≥ 65 years	71		87	
Time to recurrence	< 12 months	-	-	52	***0.011***
	≥ 12 months	-		80	
2009 FIGO stage	I and II	87	***<0.0001***	96	***<0.0001***
	III and IV	62		85	
Tumor size 1	< 40 mm	84	*0.832*	No death	***0.038***
	≥ 40 mm	84		96	
Lymphadenectomy	Not performed	79	*0.993*	88	*0.193*
	Performed	80		95	
Lymph node metastasis	Negative	84	***0.012***	95	*0.160*
	Positive	67		90	
FIGO grade	1 and 2	81	*0.413*	94	*0.474*
	3	78		91	
Depth of myometrial invasion	< 1/2	90	***0.013***	97	*0.072*
	≥ 1/2 2	75		92	
Uterine serosal involvement	Negative	82	***<0.0001***	95	***<0.0001***
	Positive	32		61	
Lymphovascular space invasion	Negative	87	***0.013***	97	*0.174*
	Positive	78		93	
Cervical invasion	Negative	80	*0.846*	94	*0.669*
	Positive	83		93	
Adnexal metastasis	Negative	84	***<0.0001***	96	***<0.0001***
	Positive	40		67	
Peritoneal cytology	Negative	84	***<0.0001***	96	***<0.0001***
	Positive	22		58	
Non-nodal extra uterine metastasis 3	Negative	85	***<0.0001***	96	***<0.0001***
	Positive	43		71	
Type of adjuvant therapy	Radiotherapy	80	*0.929*	93	*0.334*
	CCRT	80		94	
Type of adjuvant radiotherapy 4	Brachytherapy	92	*0.177*	97	*0.669*
	EBRT	84		97	
	Bracytherapy+EBRT	76		100	
Recurrence type	Only pelvic	-	-	73	*0.202*
	Extra-pelvic	-		63	

(Table 3). The type of adjuvant therapy (radiotherapy vs. concomitant chemo-radiotherapy) and radiotherapy *(VBT vs. EBRT vs. EBRT plus VBT)* were not associated with both recurrence and survival. Recurrence localization *(only pelvic vs. extra-pelvic)* did not determine the survival.

Variables that had p-value under the 0.25 in univariate analysis were selected for multivariate analysis. After the correlation between the factors was defined, a model was set up for recurrence and death, separately (Table 4). Advanced age was an independent prognostic factor for only recurrence (OR: 2.263, 95% confidence interval: 1.217-4.210, *p=0.010*), whereas the presence of non-nodal extra-uterine tumor was an independent prognostic factor for both recurrence and death (OR: 6.243, 95% confidence interval: 3.505-11.122, *p<0.001* and OR: 4.241, 95% confidence interval: 1.549-11.613, *p=0.005*; respectively) (Figure 1,2,3).

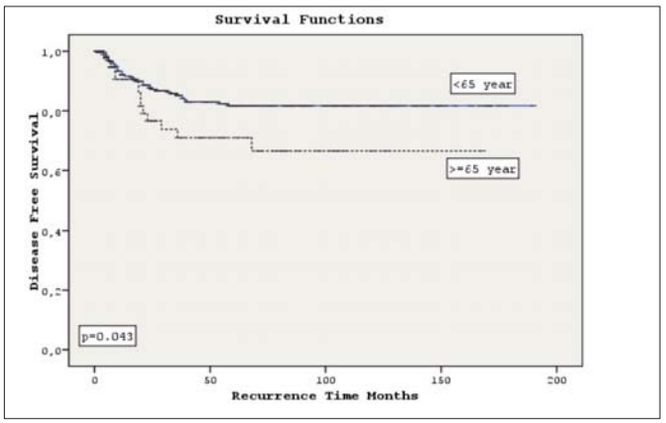

Figure 1: Association between age (<65 vs. 65≤) and DFS

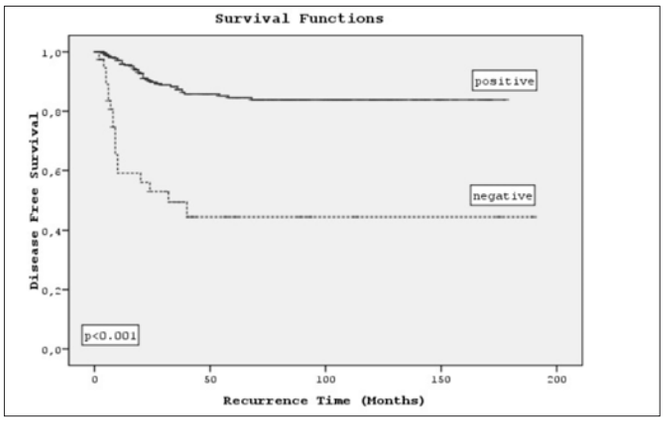

Figure 2: Association between presence of non-nodal extra uterine disease (positive vs. negative) and DFS

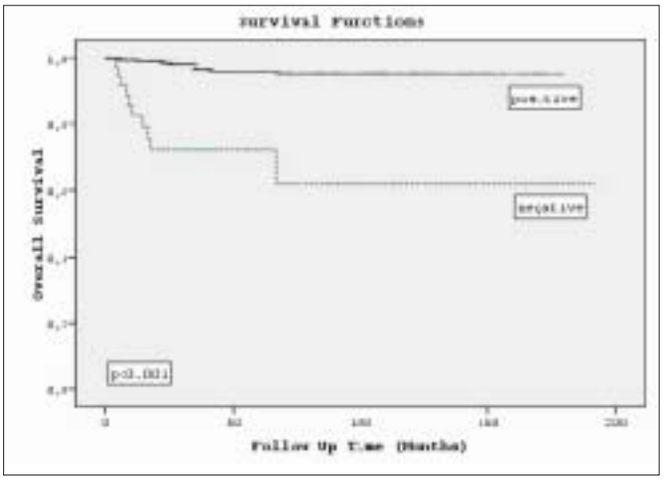

Figure 3: Association between presence of non-nodal extra uterine disease (positive vs. negative) and OS

Discussion

The role of adjuvant radiotherapy for EC especially in early stage disease, has been evaluated in several studies (12-14). Although the success of adjuvant radiotherapy in loco-regional control has been demonstrated; in patients receiving radiotherapy, no change was observed in the incidence of distant recurrences which affected the survival. So the recurrence pattern for those patients should be determined.

In the 15-year outcomes of the PORTEC-1 trial, in which the effect of pelvic radiotherapy on recurrence and survival was assessed in the intermediate-risk group with disease limited to uterine corpus, recurrence in the EBRT receiving group was significantly out of the radiotherapy field. Recurrence rates were 2.5% for vagina, 3.4% for pelvic region and 9.3% for distant recurrence in the radiotherapy group; whereas these rates were 11%, 4.5% and 7.1% in the group without adjuvant treatment, respectively (12). Eighty percent of the recurrences were outside the pelvis in our study that evaluates only patients receiving adjuvant radiotherapy. In addition, 63.6% of the recurrences were in the extra-abdominal region. However, 32.7% of the recurrences were in the radiotherapy performed field.

The only reason is not the efficacy of the applied therapy for why developing recurrences are outside the radiotherapy performed field. Surgical pathologic factors are the primary causes of extra-abdominal recurrences. Bosse et al. identified the grade 3 histology and positivity of lympho-vascular space

Table 4: Factors predicting recurrence and death, multivariate analysis

Factors	OR	95%Confidence Interval	*p* value
Recurrence			
Age (≥65 years vs. <65years)	2.263	1.217-4.210	*0.010*
Non-nodal extra uterine tumor (positive vs. negative)	6.243	3.505-11.122	*<0.001*
Death			
Age (≥65 years vs. <65years)	1.436	0.479-4.307	*0.519*
Non-nodal extra uterine tumor (positive vs. negative)	4.241	1.549-11.613	***0.005***
Lymphadenectomy (not performed vs. performed)	1.800	1.800-0.570	*0.317*
Recurrence site (extra pelvic recurrence vs. pelvic recurrence)	2.168	0.472-9.961	*0.320*

invasion as an important risk factor for distant metastasis in early stage endometrial cancer (16). Besides the surgical pathologic factors, the stage is the most important factor determining distant recurrence (17,18). In our study, 26% and 74% of recurrences were found in stage IB at the pelvic region and in the extra-pelvic region that was outside the radiotherapy performed field, respectively; whereas all of the recurrences were out of the pelvis in stage IV disease.

In our study, it was observed that approximately 80% of the recurrences were extra-pelvic in the cases having extra-uterine disease as an only nodal spread. In patients having para-aortic lymph node metastases, all of the extra-pelvic recurrences were determined as extra-abdominal recurrences. On the other hand, only adjuvant chemotherapy in stage IIIC is associated with higher rates of pelvic recurrence (19,20). For this reason, it is thought that multimodal treatment should be applied in this stage tumor and addition of systemic agent to radiotherapy is thought to be a correct management.

Age, histologic type, grade, depth of myometrial invasion, cervical involvement, lympho-vascular space invasion, presence or area of lymph node metastasis, the amount of the both removed and metastatic lymph nodes, presence of non-nodal extra-uterine disease and addition or type of adjuvant therapy were found to be important for survival (9,17,18,21-27). In our study, it was found that independent prognostic factors in the patients receiving adjuvant radiotherapy were age for only recurrence and non-nodal extra-uterine disease for both recurrence and death. In the presence of non-nodal extra-uterine disease, recurrence and death increased 6.2-fold and 4.2-fold, respectively. Age is known to be associated with poor prognosis in EC. The likelihood of poor prognostic factors and the recurrence increases with increasing of the age and survival in this group of patients is significantly reduced (28-30). The probability of recurrence increased 2.2-fold with age in our study. In addition, the 5-year OS decreased from 97% to 94% in patients with age over the 65 years. However, this difference was not statistically significant. The underlying causes of the relation between aging and carcinogenesis attributed to exposition duration of carcinogenesis and alterations in body composition or structure because of the tissue aging (31,32). Immune senescence, mutations, translocations, hyper methylation of anti-proliferative genes and hypo methylation of oncogenes can appear with tissue aging (33). It is asserted that proliferative and endocrine senescence are related with increased tumor growth stimulating factors and insulin resistance that cause to increase in insulin levels which is one of the important mitotic and tumor growth factor, respectively (31, 34). Accordingly; carcinogenetic, proliferative, endocrine and immune changes is likely to be related with worse prognosis of aging group in EC.

Retrospective design is the most important limitation of this study. The strong-looking features of the study are including the only endometrioid-type endometrium cancer patients and the considerable amount of the study group.

In conclusion, our study showed that radiotherapy provided local control, but the probability of developing the extra-pelvic and extra-abdominal recurrence increased. The probability of extra-abdominal recurrence, especially in the presence of risk factors, increased significantly in this patient group. In addition, survival significantly decreased in the presence of non-nodal extra-uterine disease. Therefore, at high risk endometrioid type endometrium cancer patients, especially in cases that have the disease spread out of the uterus, addition of chemotherapy to the radiotherapy will be the correct choice of treatment.

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