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Original Article

Therapeutic value of lymphadenectomy and adjuvant radiotherapy in uterine corpus confined endometrioid-type cancer

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Abstract

Background: To determine the efficacy of lymphadenectomy and adjuvant radiotherapy in patients with endometrioid-type cancer confined to the uterine corpus.
Methods: A total of 323 patients were evaluated. Patients were stratified according to depth of myometrial invasion (DMI) and tumor grade.
Results: Lymphadenectomy was performed in 83% of the entire cohort. Age (<60 vs. ≥60) and DMI affected disease-free survival. Addition of lymphadenectomy improved the disease-specific survival. The improved effect of lymphadenectomy was only observed in DMI ≥½ and grade 2 tumor (78.5% vs. 95.4%). However, that effect in this group was determined in patients with more than 50 removed lymph nodes. Performing adjuvant radiotherapy and the type of the radiotherapy (vaginal brachytherapy vs. external beam radiotherapy) were not significant for disease-free and disease-specific survival. In the entire cohort, loco-regional recurrence occurred in 3.1% and 4.4% of patients with or without adjuvant radiotherapy, respectively. However, these rates were 2.6% and 13.6% for patients with DMI ≥½ and grade 2 who were older than 60 years, respectively.
Conclusion: Lymphadenectomy should be performed in patients with DMI ≥½ and grade 2 to improve survival. Adjuvant vaginal brachytherapy may only be given to patients who are older than 60 years old with moderate differentiation and deep myometrial invasion to reduce loco-regional recurrence.

Keywords: Adjuvant radiotherapy; Endometrial cancer; Intermediate-risk group

1. Introduction

According to GLOBACAN 2012 data endometrium cancer (EC) is the most common sixth malignancy in women, with 320.000 women diagnosed each year.[1] Disease is usually diagnosed in early stages and is confined to the uterus in 80% of patients at the time of diagnosis.[2] Five-year overall survival (OS) is greater than 80% in these patients.[3] This rate increases to 95% in these patients with disease confined to the uterus and with low-risk, defined as having FIGO grade 1 or 2 disease with depth of myometrial invasion less than half (<½).[4–8]

EC has been staged surgically according to the International Federation Obstetricians and Gynecologists (FIGO) since 1988.[9] FIGO revised the staging system in 2009.[10] Evaluation of the pelvic and para-aortic lymph nodes is needed in this new staging system. Additionally, a National Comprehensive Cancer Network (NCCN) guideline recommends lymphadenectomy for all patients with uterine cancer.[11] Nevertheless, routine lymphadenectomy as a part of surgical procedure in EC is still controversial. Discussion continues not

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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only about the indications of lymphadenectomy but also about the definition, limits and sufficiency of the procedure. It was shown that addition of lymphadenectomy to total abdominal hysterectomy and bilateral salpingo-oophorectomy in the low-risk group at early stages did not improve survival.[4–6,12–14] Moreover, the morbidity rate resulting from this surgical procedure is in substantial amounts.[4] Thereby, performing lymphadenectomy on all patients with EC will be over-treatment. In contrast, it is known that lymphadenectomy improves survival in patients with depth of myometrial invasion equal and more than half (≥½), FIGO grade 3 tumor, cervical invasion, and extrauterine spread, all of which were defined as high risk for lymphatic spread.[5,15,16]

Another controversial subject regarding endometrial cancer confined to the uterus is the necessity of adjuvant radiotherapy. However, the group of patients who will take radiotherapy or the technique has not been clarified. Despite that, the necessity of radiotherapy is tried to define according to the clinical situation, pathology, and surgery performed. Reports revealed that external beam radiotherapy (EBRT) decreased loco-regional recurrence in patients with deep myometrial invasion, tumor with poor differentiation, and advanced age, but EBRT couldn't be shown to improve overall survival.[17,18] On the other hand, the costs of loco-regional control obtained with ERBT were an increase in morbidity and poor quality of life.[19] It was shown that vaginal brachytherapy provided almost similar pelvic control and overall survival compared to EBRT; with much lower adverse effects.[20]

The present study investigated the role of lymphadenectomy and adjuvant radiotherapy on recurrence and survival in patients with intermediate risk endometrioid-type endometrial cancer confined to the uterine corpus.

2. Methods

The data of 357 patients with endometrioid-type EC who underwent at least total abdominal hysterectomy and bilateral salpingo-oophorectomy and whose definitive pathology report revealed disease confined to the uterine corpus and intermediate risk for recurrence between January 1993–May 2013 in our gynecologic oncology clinic was evaluated from database and patient files retrospectively. Patients with FIGO grade 1 or 2 tumor without myometrial invasion and FIGO grade 3 tumor with myometrial invasion ≥ ½ at final pathology were excluded. Additionally, patients with non-endometrioid type EC, EC including sarcoma components, invasion of glandular or stromal cervix, adnexal spread, involvement of uterine serosa, positive peritoneal cytology, nodal or non-nodal extra-uterine tumor spread, synchronized tumors and patients undergoing systemic adjuvant therapy were not included. Patients were staged according to FIGO criteria. IRB approval (2016/209; 17) was obtained before the study.

Thirty-three patients were excluded due to the following reasons; (i) having synchronized tumor (n:9); (ii) lost to follow-up after surgery (n:17); (iii) death within a month after the surgery (n:3); (iv) undergoing adjuvant chemotherapy (n:4); and (v) undergoing sandwich therapy (n:1). Finally, the study included 323 patients. The patients were stratified into five groups according to FIGO grade and depth of myometrial invasion. The groups were defined as; Group 1; no myometrial invasion and grade 3 tumor, Group 2; depth of myometrial invasion < ½ and grade 2 tumor, Group 3; depth of myometrial invasion < ½ and grade 3 tumor, Group 4; depth of myometrial invasion ≥ ½ and grade 1 tumor and Group 5; depth of myometrial invasion ≥ ½ and grade 2 tumor.

Frozen-section (F/S) consultation is utilized routinely for patients with EC in our clinic, and staging surgery is performed for those patients whose F/S consultation has revealed non-endometrioid adenocarcinoma, FIGO grade 2 or 3 disease, depth of myometrial invasion ≥ ½, cervical involvement, and tumor size >2 cm. Also, patients with a preoperative diagnosis of FIGO grade 3 disease or high-risk cell type undergo staging surgery directly. Lymphadenectomy is performed in most patients by skeletonizing of the pelvic and paraaortic regions. Nevertheless, there are patients treated by sampling of the suspicious lymph nodes at the discretion of the surgeon. Since patients with positive lymph nodes were evaluated, patients who had lymph node sampling were also included in the study. Bilateral pelvic lymphadenectomy was performed to complete skeletonization, with all lymphatic tissue of the common, external and internal iliac vessels and the obturator fossa removed after visualization of the obturator nerve. The superior surgical dissection margin for the pelvic nodes was aortic bifurcation, and the anterior distal surgical dissection margin was the circumflex iliac vein. The presacral lymphatic tissue was harvested separately. The upper limit of paraaortic lymphadenectomy was renal veins.

The decision for adjuvant radiotherapy was made by the senior surgeon and the gynecologic oncology counsel, and the radiotherapy was performed as external beam radiotherapy and/or vaginal brachytherapy. Both the depth of myometrial invasion and grade were considered in making this decision. Patients were followed up quarterly in the first two years, semi-annually up to five 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 clinically suspicious of disease. Thoracic and/or abdominal computerized tomography was used when needed. Pap-smear test and CA125 level were utilized in the follow-up, even though they were not used routinely.

The period from initial surgery to recurrence or last visit was defined as disease-free survival (DFS), and the period from surgery to death because of the disease (except in the first month after surgery) or last visit was defined as disease-specific survival (DSS). The recurrences occurring at sites that were below the level of the linea terminalis; such as vagina, vaginal vault and pelvic side wall, were defined as loco-regional recurrence; the ones occurring between the linea terminalis and diaphragma were defined as upper abdominal, and the remainder were defined as extra-abdominal recurrence. Recurrences in the liver parenchyma and bone were accepted as extra-abdominal, and cytologically defined ascites and peritonitis carcinomatosa were accepted as upper

abdominal recurrence. Upper abdominal and extra-abdominal recurrences were defined as distant recurrence.

The categorical parameters were compared by chi-square test, and continuous parameters were compared by ANOVA test. Survival analyses on categorical variables were performed using the Kaplan−Meier method, and significant differences were identified using the log-rank test. Multivariate analysis was performed using Cox proportional hazards models. The factors having a p value below 0.25 in the univariate analysis were included in the multivariate analysis. The cut-off for statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS (SPSS, Inc., Chicago, IL, USA) version 17.0.

3. Results

While there were only two patients in Group 1, there were 104 in Group 2, 25 in Group 3, 72 in Group 4 and 120 in Group 5. Group 1 was not included in the statistical analysis due to the small number of patients. Neither of the two patients in Group 1 had adjuvant therapy, and recurrence did not occur during 9 and 44 months' follow-up, respectively.

The mean age of the 321 patients who were evaluated in statistical analysis was 59 years and ranged between 34 and 83 years. Median tumor size was 35 mm (range, 10−335 mm). Depth of myometrial invasion was below ½ in 131 (40.8%) patients (stage IA) and above ½ in 190 (59.2%) patients (stage IB). FIGO grade was grade 1 in 72 (22.4%) patients, grade 2 in 224 (69.8%) and grade 3 in 25 (7.8%) patients. Lymphovascular space invasion was positive in 85 (27.9%) out of 305 patients whose LVSI was reported. Lymphadenectomy was added to surgical procedure for 267 (83.2%) patients. The number median lymph nodes removed was 49 (range, 3−122). Characteristics of the patients are shown in Table 1. There was no difference between groups in the ratio of patients who had lymphadenectomy. Lymphadenectomy was added to the surgical procedure in 81% (n: 84/104) of Group 2 patients, in 88% (n: 22/25) of Group 3, 82% (n: 59/72) of Group 4 and in 85% (n: 102/120) of Group 5 patients ($p = 0.751$).

It was determined that adjuvant radiotherapy was performed in 161 (50.2%) patients. Radiotherapy was applied to 65 patients as EBRT, to 67 patients as vaginal brachytherapy and to 6 patients as EBRT with vaginal brachytherapy. No information was obtained regarding the modality of radiotherapy for 23 patients. The ratio of the patients taking adjuvant radiotherapy varied significantly between the groups. It was determined that adjuvant radiotherapy was performed in 27.9% (n: 29/104) of Group 2, in 72% (n: 18/25) of Group 3, in 47.2% (n: 34/72) of Group 4 and in 67.5% (n: 81/120) of Group 5 ($p < 0.0001$).

The distribution of the risk factors (age, tumor size, lymphovascular space invasion, FIGO grade and depth of myometrial invasion) was not balanced between the groups formed according to the performance of lymphadenectomy and the performance of radiotherapy. The patients who had lymphadenectomy were older, and the presence of lymphovascular space invasion was higher compared to that in patients who did not undergo lymphadenectomy. On the other hand, deep myometrial invasion (≥½) and the presence of lymphovascular space invasion were observed more in the patients who

Table 1
Clinical, surgical and pathological characteristics of patients.

Characteristics		n/Mean	% or Median (range)
Age at initial diagnosis		59	59 (34−83)
Tumor size at initial diagnosis (mm)		39	35 (10−335)
FIGO 2009 stage	IA	131	40.8
	IB	190	59.2
FIGO grade	1	72	22.4
	2	224	69.8
	3	25	7.8
Depth of myometrial invasion	< ½	131	40.8
	≥½[a]	190	59.2
Lymphovascular space invasion	Negative	220	68.5
	Positive	85	26.5
	Not reported	16	5
Lymphadenectomy at initial surgery	Not performed	54	16.8
	Performed	267	83.2
Number of harvested lymph nodes (total)		49	49 (3−122)
Number of harvested para-aortic lymph nodes		18.5	17 (1−48)
Number of harvested pelvic lymph nodes		41	39 (5−92)
Adjuvant radiotherapy	Not received	160	49.8
	Received	161	50.2
Type of adjuvant radiotherapy	External beam radiotherapy	65	20.3
	Brachytherapy	67	20.9
	External beam radiotherapy + brachytherapy	6	1.9
	Unreported	23	7.2

[a] Except the serosal involvement.

Table 2
Distribution of risk factors according to lymphadenectomy performed or not and adjuvant radiotherapy applied or not.

Factors		Lymphadenectomy		p	Adjuvant radiotherapy		p
		Not performed	Performed		Not received	Received	
Age, median (range)		56 years (43–75)	60 years (34–83)	0.028	59 years (34–83)	59 years (39–82)	0.163
Tumor size, median (range)		30 mm (25–60)	35 mm (10–335)	0.657	35 mm (10–335)	35 mm (15–100)	0.636
Positive lymphovascular space invasion, (%)		13	31.1	0.007	19.5	35.9	0.001
FIGO grade	1	18.1	81.9	0.780	52.8	47.2	0.078
	2	17	83		50.9	49.1	
	3	12	88		28	72	
Depth of myometrial invasion, (%)	< ½	17.6	82.4	0.770	64.1	35.9	<0.0001
	≥ ½	16.3	83.7		39.5	60.5	

had adjuvant radiotherapy compared to those not having adjuvant radiotherapy (Table 2).

In the entire cohort, twenty-eight (8.7%) patients had recurrence, and 9 (2.9%) patients died because of disease within a median follow-up time of 40 months (range, 1–178 months). Disease progression was not observed during the therapy. Five-year DFS was 88%, and 5-year DSS was 96% in the entire cohort. While 9 (2.9%) patients had isolated loco-regional recurrences, 19 (5.9%) patients had distant recurrences. Sixteen out of 19 distant recurrences were extra-abdominal, and 13 of those were observed only in the extra-abdominal region (Table 3).

The follow-up time was similar among the groups ($p = 0.258$). There was a significant difference in terms of the rate of recurrences between the groups. Recurrence rate was 1.9% in Group 2, 4% in Group 3, 8.3% in Group 4, 15.8% in Group 5 ($p = 0.002$). However, the site of recurrence did not change according to the groups. Site of the recurrences and the differences within the groups were shown at Table 3 in detail.

3.1. Disease-free survival and disease-specific survival

DFS was significantly different between the groups in the univariant analysis. Five-year DFS that was 97.7% in Group 1 and decreased to 78.4% in Group 5 ($p = 0.002$). However, DSS between groups tended to be significant ($p = 0.095$) (Table 4). Additionally, age and depth of myometrial invasion was significant for DFS, and addition of lymphadenectomy to surgical procedure was significant for DSS. Five-year DFS diminished from 93.3% to 80.9% for the patients older than 60 years old ($p = 0.001$). Five-year DFS was 95.5% for patients with a depth of myometrial invasion below ½ and 81.1% for patients above ½ ($p = 0.001$). 5-year DSS increased from 88.2% to 98.2% in patients who had lymphadenectomy ($p = 0.005$). However, the number of removed lymph nodes was not a significant factor for DFS and DSS (Table 4). Adjuvant radiotherapy application and modality of the radiotherapy (vaginal brachytherapy vs. EBRT) were insignificant for DFS and DSS.

Subgroup survival analysis was performed for Group 4 and Group 5. Groups 2 and 3 were not included into the analysis due to the inadequate number of patients in terms of recurrences (n: 2/104 and n: 1/25, respectively) and death because of the disease (n: 1/104 and n: 0/25, respectively). Five-year DFS and 5-year DSS were 86.4% and 97% for Group 4 and 78.4% and 92.8% for Group 5, respectively (Table 4). While the effects of age on DFS and lymphadenectomy on DSS couldn't be shown in Group 4, the effects of both factors were observed in Group 5. DFS decreased from 85.8% to 70% in Group 5 for the patients older than 60 years old ($p = 0.025$) (Fig. 1). The addition of lymphadenectomy to the surgical procedure improved 5-year DSS 17% (Fig. 2). Five-year DSS that was 78.5% in patients without lymphadenectomy increased to 95.4% in patients who underwent additional lymphadenectomy ($p = 0.039$) (Table 5). That effect of lymphadenectomy in Group 5 was only observed in patients with a higher number of removed lymph nodes. Survival wasn't statistically different between patients who did not

Table 3
Recurrence site according to groups.

Groups	Rekürrens site, n (%)							Percentage of recurrence (recurrent patient/total patient)
	Only pelvic	Only UA	Only EA	Pelvic + UA	UA + EA	Pelvic + UA + EA	p	
Group-2 (Myometrial invasion < ½ + Grade 2)	–	–	–	1 (50)	–	1 (50)	0.062	1.9 (n:2/104)
Group-3 (Myometrial invasion < ½ + Grade 3)	1 (100)	–	–	–	–	–		4 (n:1/25)
Group-4 (Myometrial invasion ≥ ½ + Grade 1)	2 (33.3)	–	4 (66.7)	–	–	–		8.3 (n:6/72)
Group-5 (Myometrial invasion ≥ ½ + Grade 2)	6 (31.6)	2 (10.5)	9 (47.4)	–	1 (5.3)	1 (5.3)		15.8 (n:19/120)
Total	9 (32.1)	2 (7.1)	13 (46.4)	1 (3.6)	1 (3.6)	2 (7.1)		$p = 0.002$

UA = upper abdomen; EA = extra-abdome.

Table 4
Factors that predicted disease-free survival and disease-specific survival in the entire cohort.

Prognostic factor		5-year disease-free survival		5-year disease-specific survival	
		%	p	%	p
Age[a]	≤59	93.5	0.001	97.5	0.149
	≥60	80.9		94.5	
Deep of myometrial invasion	< ½	97.2	0.001	98.9	0.068
	≥ ½	81.1		94.3	
Tumor size (mm)[a]	≤35	95.7	0.160	NE	–
	≥36	85.5		NE	
Grade	1	86.4	0.586	97	0.403
	2	57.1		95.5	
	3	95.5		100	
Lymphovascular space invasion	Negative	85.8	0.425	96.1	0.835
	Positive	92.6		92.6	
Lymphadenectomy	Not performed	82.8	0.363	88.2	0.005
	Performed	88		98.2	
Number of removed lymph node[a]	≤49	87.8	0.806	97.3	0.157
	≥50	88		100	
Adjuvant radiotherapy	No received	89.1	0.437	98.1	0.256
	Received	86.6		95	
Type of adjuvant radiotherapy	Brachytherapy	89.1	0.749	97.9	0.374
	External beam radiotherapy	83.8		92.2	
Groups	Group 2 (myometrial invasion < ½ + Grade 2)	97.7	0.002	99.5	0.095
	Group 3 (myometrial invasion < ½ + Grade 3)	95.5		100	
	Group 4 (myometrial invasion ≥ ½ + Grade 1)	86.4		97	
	Group 5 (myometrial invasion ≥ ½ + Grade 2)	78.4		92.8	

[a] Median value. NE = No event.

have lymphadenectomy and patients from whom up to 50 lymph nodes were removed. Five-year DSS in Group 5 was 78.5% for patients who did not have lymphadenectomy, 97% for patients from whom more than 50 lymph nodes were removed ($p = 0.010$) and 90% for patients from whom up to 50 lymph nodes were removed ($p = 0.165$). Additionally, among patients included in Group 5 and who didn't have lymphadenectomy, 5 recurrences occurred, and only 1 of these recurrences was observed in the pelvic and para-aortic area in addition to systemic recurrence. EBRT was applied as adjuvant therapy for this patient.

Adjuvant radiotherapy did not improve the DFS or DSS in Group 5. By further statistical analysis, the effect of the adjuvant therapy was evaluated for patients in Group 5 who didn't have lymphadenectomy. However, this statistical evaluation could not be made because of the small number of patients in this group (n: 18). Nevertheless, the effect of adjuvant therapy on DFS in Group 5 was evaluated between the subgroups of patients formed according to the age of the patient as being ≤59 years or ≥60 years-old. Adjuvant radiotherapy seemed to be non-effective in both groups ($p = 0.204$ and $p = 0.293$, respectively). Additionally, the modality of radiotherapy was not associated with recurrence and survival for patients older than 60 years old in Group 5. While 5-year DFS was 75.4% in patients who had adjuvant EBRT, the value was 75% in patients who had adjuvant vaginal brachytherapy ($p = 0.537$). These rates were 84% and 83% for 5-year DSS, respectively ($p = 0.550$).

To define the independent factors for DFS in Group 5, multivariate analysis was performed by creating a model with age (≤59 years vs. ≥60 years) and lymphadenectomy (performed vs. not performed), but neither parameter was shown to be an independent prognostic factor for DFS (Table 6). Multivariate analysis for DSS was not performed, since a model couldn't be created due to the correlation between lymphadenectomy (performed vs. not performed) and number of lymph nodes removed.

3.2. Loco-regional recurrence and adjuvant radiotherapy

Loco-regional recurrence was observed in 12 patients, and 9 of them had isolated recurrence. Eight of the isolated recurrences were in the vagina and vaginal vault. Five of 12 patients who had loco-regional recurrence had had adjuvant radiotherapy. The adjuvant radiotherapy was performed as EBRT for 3 patients and as vaginal brachytherapy for 1 patient, and both of these modalities were performed in 1 patient. Loco-regional recurrence was not associated with adjuvant radiotherapy. In the entire cohort, loco-regional recurrence

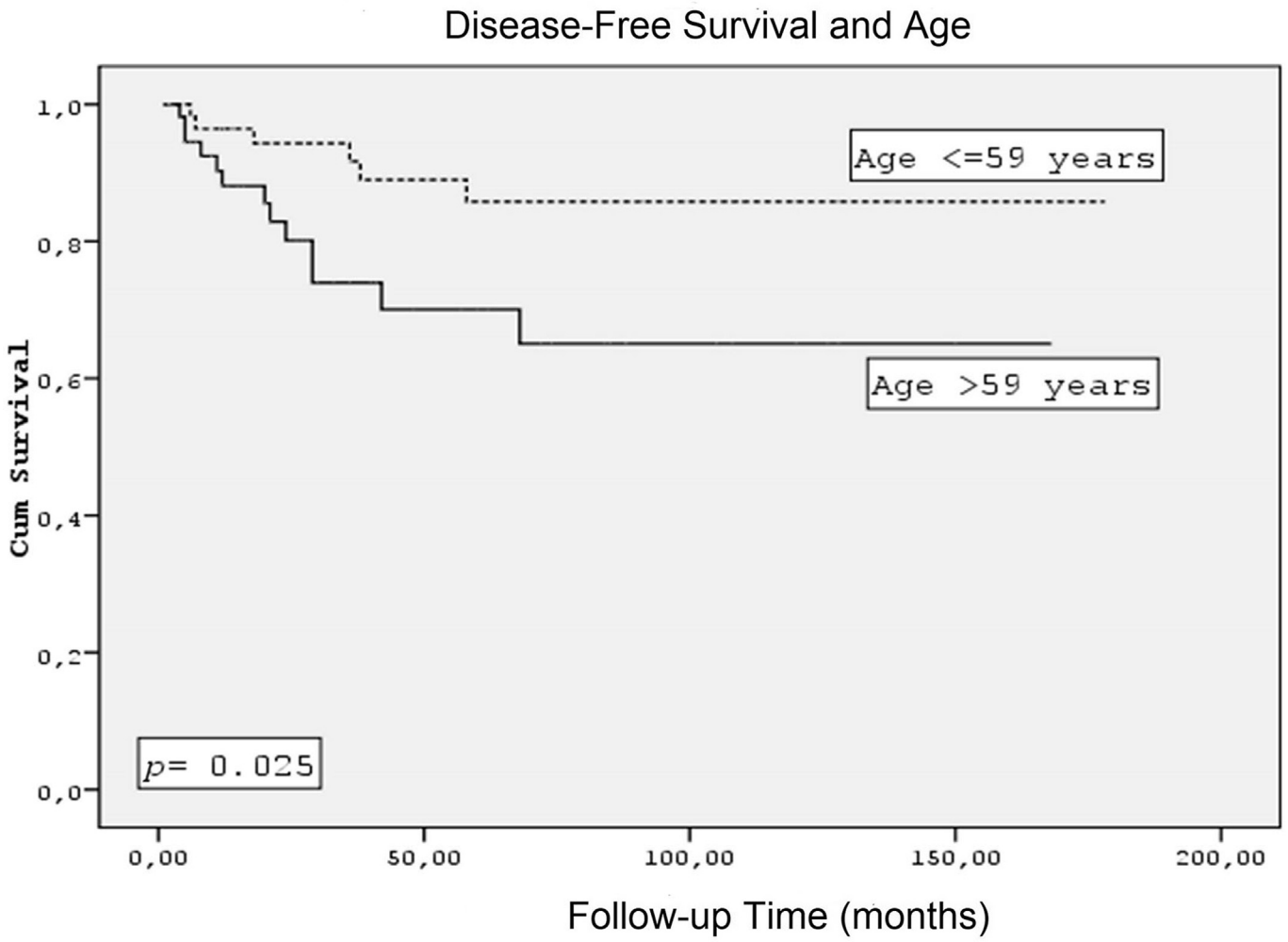

Fig. 1. Effect of age on disease-free survival in Group 5.

occurred in 3.1% of patients who had adjuvant therapy and 4.4% of the patients who did not have adjuvant therapy ($p = 0.534$). These rates were 4.9% and 7.7% in Group 5, respectively $p = 0.547$). For further analysis, patients older than 60 years in Group 5 were evaluated (n: 61 patients, 22 patients without adjuvant therapy and 39 patients with adjuvant therapy). Loco-regional recurrence rates were 13.6% for the patients who received adjuvant radiotherapy and 2.6% for the patients who did not receive radiotherapy in that group ($p = 0.093$). The effect of adjuvant radiotherapy for local control could not be evaluated in the other risk groups because of the small number of patients who had recurrence (2 patients in Group 2, 1 patient in Group 3, 2 patients in Group 4).

4. Discussion

In our study in which patients were stratified according to FIGO grade and depth of myometrial invasion by paraffin block results, it was seen that recurrence rates increased and survival decreased from Group 2 (myometrial invasion $< ½ +$ grade 2) to Group 5 (myometrial invasion $\geq ½ +$ grade 2). Recurrence rates and possibility of distant recurrence were significantly higher in Group 5. Five-year DFS and 5-year DSS were 97.7% and 99.5% in Group 2; and in Group 5 these rates were 78.4% and 92.8%, respectively. In the entire cohort, age and performance of lymphadenectomy were associated with recurrence and survival. However, this association could be shown to be significant only in Group 5 in the subgroup analysis.

4.1. Lymphadenectomy

There are two reasons to add lymphadenectomy to surgical procedure: 1) determining the stage, to offer appropriate therapy; 2) providing tumor debulking. It was shown that the number of removed lymph nodes was directly related to survival. Chan et al. found that the number of removed lymph nodes showed correlation with survival by evaluating 12,333 high-risk (1988 FIGO stage IB and grade 3, stage IC-IV and all grades) patients by using SEER data. Interestingly, this correlation was regardless of metastatic lymph node count. It was shown that the survival improved with the increase in number of removed non-metastatic lymph nodes.[15]

This situation is explained by the existence of metastatic lymph nodes which were removed but could not be defined

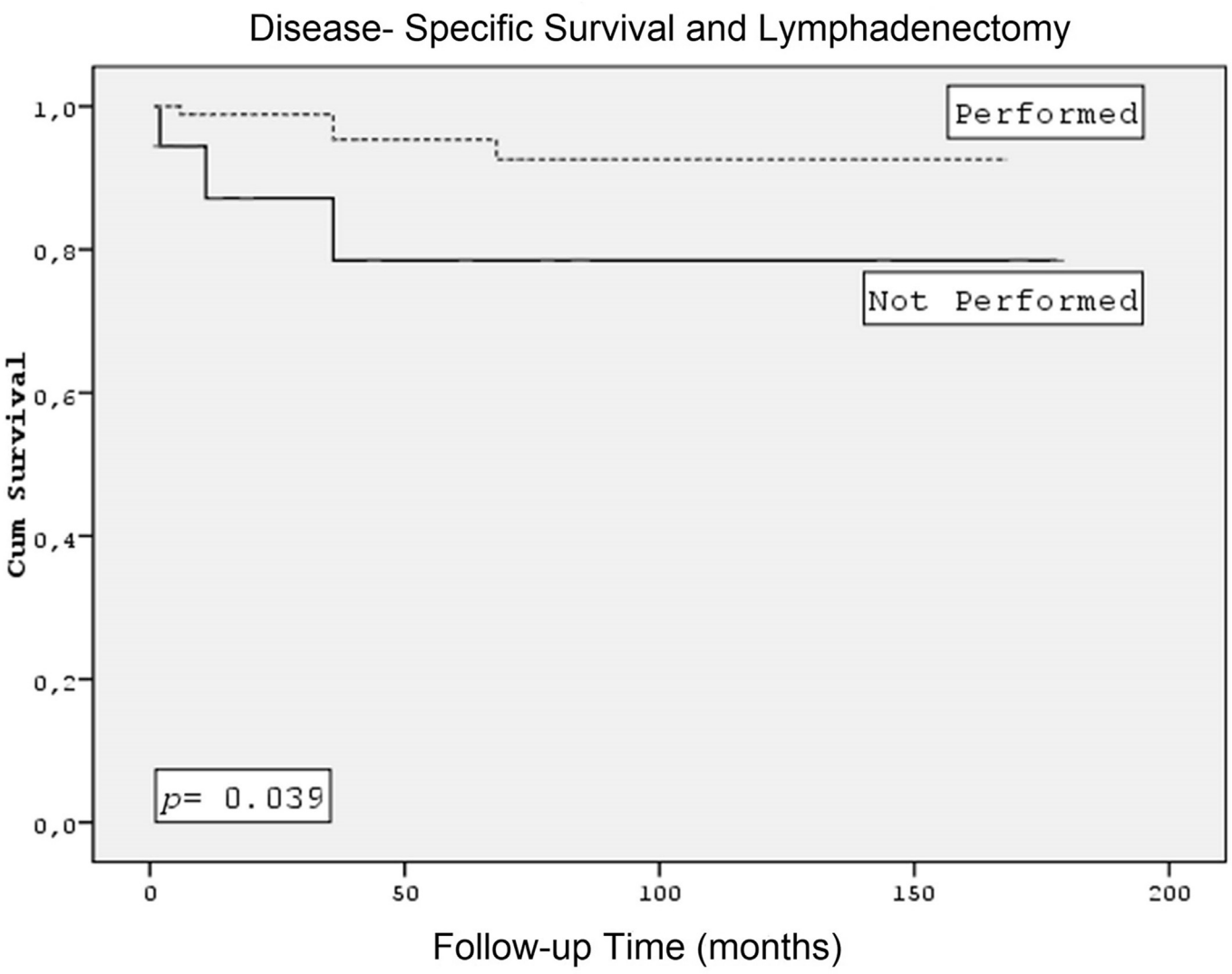

Fig. 2. Effect of adding lymphadenectomy on disease-specific survival in Group 5.

histologically. Routine application of hematoxylin-eosin has a limited effectiveness for determining metastatic lymph nodes. Yabushita et al. revealed that immunohistochemical evaluation by cytokeratin showed occult metastasis in 20 out of 66 (30%) nodes defined as tumor negative by routine staining in patients with stage IIIC endometrial cancer.[21] In our study, removed lymph node count was not associated with recurrence and survival. But performance of lymphadenectomy was the only significant factor for DSS in Group 5 (myometrial invasion $\geq$ ½ + grade 2) which had the highest risk for lymphatic spread, recurrence and survival. Lymphadenectomy improved the 5-year DSS at a rate of 17% in that group. Additionally, this effect occurred in patients who had higher number of removed lymph nodes. Survival wasn't statistically different between patients who did not have lymphadenectomy and patients in whom up to 50 lymph nodes were removed. Consequently, achieved survival advantage can be explained by the tumoral debulking which was provided by lymphadenectomy. However, how can the absence of tumoral debulking effect of lymphadenectomy be explained in other groups? It can be probably explained by the presence of quite lower rates of lymph node spread in those groups. In groups which could be defined as having low risk, presented rates of lymph node metastassis did not exceed 4%.[4,6,22] It was illustrated that adding lymphadenectomy to total abdominal hysterectomy and bilateral salpingo-ooforectomy in patients at low risk in terms of lymphatic spread did not improve the survival. Hidaka et al. found that lymphadenectomy did not improve recurrence and survival rates in patients with FIGO grade 1 or 2 tumor and depth of myometrial invasion < ½. While 5-year DFS was 95.6% in patients who had lymphadenectomy, it was 98.3% in patients who did not. These rates were reported as 98.5% and 98.3% for 5-year OS, respectively.[4] Similar results were reported by Dowdy et al. In their study, it was revealed that the 5-year OS was 97.3% and 99% in low risk group with and without lymphadenectomy, respectively.[6] These results were supported by other studies, too.[5,13] Nevertheless, lymphadenectomy improves survival for the patients at high risk for lymphatic spread. Jeong et al. found that lymphadenectomy improved 5-year OS from 70.6% to 91.6% in patients

Table 5
Factors that predicted disease-free survival and disease-specific survival for Group 4 and Group 5.

Prognostic factor	Group 4 (Myometrial invasion ≥ ½ + Grade 1)				Group 5 (Myometrial invasion ≥ ½ + Grade 2)			
	5-year disease-free survival		5-year disease-specific survival		5-year disease-free survival		5-year disease-specific survival	
	%	p	%	p	%	p	%	p
Age[a]								
≤59	93.8	0.147	100	0.303	85.8	0.025	93.1	0.503
≥60	81.4		93.8		70		92.4	
Tumor size (mm)[a]								
≤35	100	0.290	NE	–	86.2	0.969	NE	–
≥36	83		NE		78.2		NE	
Lymphovascular space invasion								
Negative	81.2	0.487	100	0.105	73.5	0.323	89.9	0.569
Positive	92.9		87.5		87.8		95.7	
Lymphadenectomy								
Not performed	91.7	0.798	88.9	0.102	61.3	0.122	78.5	0.039
Performed	84.9		100		81.8		95.4	
Number of removed lymph node[a]								
≤49	83.1	0.804	NE	–	82.5	0.881	87.5	0.125
≥50	90.9		NE		80		100	
Adjuvant therapy								
Not received	82.5	0.747	100	0.510	72.3	0.766	96.7	0.568
Received	86.1		95.7		79.8		92	
Type of adjuvant radiotherapy								
Brachytherapy	90	0.618	100	0.346	82.9	0.865	95.8	0.592
EBRT	83.3		88.9		79.6		88.9	

[a] Median value. EBRT = external beam radiotherapy; NE = no event.

Table 6
Multivariate analysis for recurrence in Group 5 (Myometrial invasion ≥ ½ + Grade 2).

Factors	Odds Ratio	Confidence Interval	p
Age (≥60 years vs. ≤59 years)	1.365	0.44–4.23	0.590
Lymphadenectomy (not performed vs. performed)	1.309	0.397–4.319	0.658

with FIGO grade 3 tumor, depth of myometrial invasion ≥ ½ and cervical invasion (p = 0.0095).[5] Other studies supported this result.[15,16] Our study showed that lymphadenectomy improved survival only in the intermediate-risk group in patients with depth of myometrial invasion ≥ ½ and FIGO grade 2 tumor.

On the other hand, our results related to lymphadenectomy and survival are only theoretical information rather than guiding for clinical practice, since this study didn't include patients who had the same uterine pathology, were staged surgically and had lymphatic involvement. Therefore, setting up models with different depths of myometrial invasion and FIGO grades to evaluate the necessity of lymphadenectomy was not an end-point that could be obtained by the results of this study. However, the presence of tumoral debulking effect of lymphadenectomy in high-risk patients, improvement of the 5-year DSS by a rate of 17% in this group, and the relation of this effect with the number of removed lymph nodes were important results of this study about lymphadenectomy. Hence, systematic lymphadenectomy should be performed to improve survival results for the patients with myometrial invasion ≥ ½ and FIGO grade 2 tumor.

4.2. Adjuvant radiotherapy

Indication for radiotherapy for EC confined to the uterus is uncertain. Present studies do not offer clear advice for management of these patients. After 2000, there are two crucial randomized controlled studies comparing surgery alone and surgery with EBRT. These are Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) Study No. 1 and Gynecologic Oncology Group (GOG) Study No. 99.[17,18] In these two studies, it was shown that loco-regional recurrence significantly decreased with EBRT, but this effect was not observed in overall survival. In the PORTEC#1 study (patient group: grade 1 with depth of myometrial invasion ≥ ½, grade 2 with any depth of myometrial invasion, and grade 3 with depth of myometrial invasion < ½; patient number: 715; 361 patients received only surgery, and 354 patients received surgery with EBRT; lymphadenectomy was not performed), it was determined that 5-year loco-regional recurrence decreased from 14% to 4% in the treatment arm ($p < 0.001$). But this improvement was not observed in 5-year overall survival. While the 5-year overall survival rate was observed to be as 85% in the control group, it was 81% in the treatment group ($p = 0.310$). It was defined that overall survival was not improved by postoperative radiotherapy in patients with intermediate-risk EC after adjustments were made for age, grade and depth of myometrial invasion.[17] Two-year loco-regional recurrence decreased from 7.4% to 1.6% with adjuvant radiotherapy in the GOG#99 study (patient group: 1988 FIGO stage IB with grade 1–3, IC with grade 1–3, and occult IIA with grade 1–3, occult IIB with grade 1–3; patient number: 392, 202 patients received only surgery, and 190 patients received surgery with EBRT; lymphadenectomy was performed). Additionally it was determined that cumulative recurrence decreased from 12% to 3% ($p = 0.007$). This improvement in cumulative recurrence was more significant for the high-intermediate risk group defined by advanced age, presence of lymphovascular space invasion, moderate and poor differentiation, and deeper myometrial invasion. In this group (grade 2 or 3 with lymphovascular space invasion with depth of myometrial invasion ≥ ½ or age 50 years and older with two of the risk factors or age 70 years and older with one of the risk factors), when patients underwent EBRT after surgery, cumulative recurrence decreased at a rate of 58% (27% *vs.* 13%). However, a significant reduction in distant recurrence couldn't be shown. Therefore, the improvement in cumulative recurrence was mostly related to improvement in loco-regional recurrence. However, reduction in loco-regional recurrence did not result in improvement in overall survival, as shown by the PORTEC#1 study. Four-year overall survival rate was 86% in the control group and was 92% in the therapy group.[18] The absence of improvement in overall survival was also reported by other studies.[19,20,23,24] Rate of loco-regional recurrence did not decrease with

adjuvant radiotherapy in our study. While locoregional recurrence occurred in 4.4% of patients who had adjuvant therapy, the rate was 3.1% for patients who didn't. These rates were 4.9% and 7.7% in Group 5, respectively, but this difference was not statistically significant. However, for patients defined as having high risk (age 60 years and older) in Group 5, loco-regional recurrence rates were 2.6% and 13.6% for those patients given radiotherapy or not, respectively. This difference tended to be statistically significant ($p = 0.093$). Adjuvant radiotherapy did not improve loco-regional recurrence in our study, especially considering the entire cohort. Possible reasons for this may be the application of adjuvant radiotherapy to high-risk patients and performance of lymphadenectomy in most of the patients. Systematic lymphadenectomy rate was observed to be 83% for the entire cohort. The rate was 85% in Group 5. Sterilization obtained by radiotherapy in the lymphatic regions may also be achieved by lymphadenectomy.[25,26] Hence, recurrence possibility, especially pelvic recurrence, may have decreased, since more than 80% of the entire cohort was formed by patients who had undergone lymphadenectomy. Therefore, lower recurrence rates in our study results compared to other studies such as PORTEC#1, which didn't include patients who had undergone lymphadenectomy, and GOG#99, in which systematic lymphadenectomy wasn't performed, could be explained by the higher rate of performance of lymphadenectomy in the present study. In patients who didn't receive adjuvant radiotherapy, 5-year loco-regional recurrence was 14% in the PORTEC#1 study, and 2-year loco-regional recurrence was 7.4% in the GOG#99 study and 4.4% in our study, with a median follow-up time of 40 months.[17,18]

The cost of pelvic control acquired by EBRT which is not observed in overall survival is an increase in morbidity and reduction in quality of life. Patients given EBRT as adjuvant radiotherapy experienced late treatment-related complications at a rate of 25% in the PORTEC#1 study, and complications were mostly related to the gastrointestinal system.[17] This situation was not different for the GOG#99 study.[18] Therefore, vaginal brachytherapy that has an acceptable toxicity profile may be offered as a treatment option. EBRT and vaginal brachytherapy were compared in the second study of the PORTEC group. Five-year loco-regional recurrence rates were 5.1% for vaginal brachytherapy and 2.1% in the EBRT arm of the PORTEC#2 study (patient group: age 60 years and older with FIGO 1988 stage IB with grade 3, age 60 years and older with FIGO 1988 stage IC with grade 1 or 2, FIGO stage IIA with any age except for depth of myometrial invasion $\geq$ ½ with grade 3; patient number: 427; 213 patients received surgery with vaginal brachytherapy and 314 patients received surgery with EBRT; lymphadenectomy: not performed) ($p = 0.170$). In that study, 5-year DFS and 5-year overall survival rates were similar in both treatment arms ($p = 0.740$ and $p = 0.570$, respectively). Five-year DFS and 5-year overall survival were 82.7% and 84.8% in patients given vaginal brachytherapy after surgery, respectively. These rates were 78.1% and 79.6% in the adjuvant EBRT arm, respectively. However, treatment-related toxicity was significantly higher in the EBRT arm.[20] The effect of vaginal brachytherapy was shown in other studies, too.[24,27] Our study revealed no difference in the therapy results regarding modality of adjuvant radiotherapy. In the entire cohort, 5-year DFS was 87.8% for patients given adjuvant EBRT and 89.1% for patients given adjuvant vaginal brachytherapy. These rates were 92.2% and 97.9%, respectively for 5-year DSS. The results were not different in Group 4 and Group 5.

An explanation regarding absence of improvement in overall survival with the reduction of recurrence with adjuvant radiotherapy hasn't been given. Nevertheless, it is suggested that post-recurrence survival is significantly lower in the patients who are given radiotherapy, and so improvement in overall survival cannot be achieved. While 3-year post-recurrence survival was 51% in the PORTEC#1 control group, the rate was 19% in the therapy group.[17,28]

Retrospective study design is the main limitation of our study. Because the doses and radiotherapy machine type could not be achieved for all cases within 20 years, the condition of administering the radiotherapy could not be optimized. It was observed that lymphadenectomy and radiotherapy were performed in the higher-risk groups in this study in which the effect of lymphadenectomy and adjuvant radiotherapy on recurrence was evaluated in the intermediate-risk group. Effort was made to reduce this limitation by stratifying patients into 5 groups and by performing subgroup analysis. The reported results were encouraging for systematic lymphadenectomy to be advised for the patients with depth of myometrial invasion $\geq$ ½ with grade 2 tumor and for adjuvant radiotherapy to be recommended for patients older than 60 years with depth of myometrial invasion $\geq$ ½ with grade 2 tumor in order to reduce loco-regional recurrence. Additionally, being performed in a single center, including a high number of patients, and having a high rate of lymphadenectomy performance are other advantages of this study.

In conclusion, regardless of lymphatic spread results, systematic lymphadenectomy should be performed in the patients with depth of myometrial invasion $\geq$ ½ with grade 2 tumor to improve survival. Adjuvant therapy wasn't associated with improved overall survival in intermediate-risk patients. It should only be given to patients who are older than 60 years old with moderate differentiation and deep myometrial invasion to reduce loco-regional recurrence. Vaginal brachytherapy may be performed as the radiotherapy modality in these patients. Despite three important randomized controlled studies reported after 2000, there is a need for multicenter randomized controlled studies to show the necessity for adjuvant radiotherapy in the high-intermediate-risk group for patients who have received systematic lymphadenectomy.

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