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Original Article

Pulmonary recurrence in patients with endometrial cancer

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Abstract

Background: In this article, we aimed to define the clinical, pathological, and surgical factors predicting pulmonary recurrence (PR) and determining survival after PR in patients with endometrial cancer.

Methods: Thirty-six (2.7%) patients were analyzed who suffered pulmonary failure in the first recurrence out of 1345 patients who had at least extrafascial hysterectomy plus bilateral salpingo-oophorectomy for endometrial cancer between January 1993 and May 2013. The recurrence was designated as an isolated PR in cases of the presence of recurrence only in the lung, while it was called a synchronized PR if the patient had extrapulmonary recurrence in addition to PR.

Results: In the multivariate analysis in the entire cohort, only International Federation of Gynecology and Obstetrics stage was an independent prognostic factor for PR. Two-year overall survival (OS) was 52% in patients with PR. In the univariate analysis, early International Federation of Gynecology and Obstetrics stage, absence of lymphatic metastasis, negative lymphovascular space invasion, absence of cervical invasion, negative adnexal spread, negative peritoneal cytology, negative omental metastasis, adjuvant radiotherapy after initial surgery, isolated PR, and chemotherapy upon recurrence were associated with improved OS after PR. The OS was 54 months for patients with isolated PR, while it was 10 months for patients who had synchronized PR. Furthermore, OS was 43 months and 13 months for the patients who took chemotherapy and radiotherapy, respectively.

Conclusion: Advanced stage is associated with PR. If recurrence is only in the lung, survival is better. Systemic treatment after PR is associated with improved survival. However, multi-center studies are required to standardize the treatment for PR.

Keywords: endometrial cancer; pulmonary recurrence; survival

1. Introduction

Endometrial cancer is the sixth most frequent cancer in women worldwide and 320,000 women are annually diagnosed with this challenging disease according to 2012 GLOBOCAN data.[1] Endometrial cancer is usually diagnosed in the early stages; however, 20% of patients have extrauterine disease.[2] The 5-year overall survival (OS) rate is above 80% for patients in the early stages.[3] Recurrence develops in 11–13% of all patients with endometrial cancer in the first 2 years following initial treatment, depending on the clinical factors, stage, previous surgery, and pathological factors.[4–6] In the presence of poor prognostic factors, recurrence is observed in up to 60% of the patients.[7–9] Additionally, extrapelvic failure is detected in >75% of the patients with recurrence.[6,10,11]

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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The lung is a common site for endometrial cancer metastasis, and pulmonary metastasis is primarily the result of hematogeneous spread. Pulmonary failure was reported to be observed in 1.9–9% of patients with first recurrence.[11–17] There is limited data about the factors predicting pulmonary recurrence (PR). However, PR was reported to be associated with Stage IV disease and deep myometrial invasion.[15] Earlier reports stated that PR was associated with poor prognosis. In these reports, 75% of patients with PR were shown to expire from cancer in the 1st year.[14] However, in a recent paper, patients with isolated lung metastasis that was ≤2 cm and low grade were detected to have 98-months OS following recurrence.[16] Additionally, the 5-year OS of patients with endometrial cancer who had pulmonary metastasectomy after the initial recurrence was reported to be up to 76%.[18–21]

The factors predisposing patients to PR, how PR progresses, and what its treatment should be have not been clarified. The data regarding PR in endometrial cancer is limited and it is not without limitations. Usually, PR was included in distant recurrences in previous reports and not analyzed separately. Patients with sarcomas in addition to epithelial tumors were generally included or patients with endometrial cancer were evaluated with patients who had cancer of other primary sites in those reports.

In the present study, we aimed to define the clinical, pathological, and surgical factors predicting PR and determining survival after PR.

2. Methods

A total of 1640 patients with diagnosed epithelial endometrial cancer were treated in our clinic between January 1993 and May 2013. The data of 1413 patients who had at least extrafascial hysterectomy plus bilateral salpingo-oophorectomy were obtained from the Gynecological Oncology Clinic (Ankara, Turkey) electronic database and patient files. Among these 1413 patients, 68 patients either were deemed lost to follow-up or died of surgery-related complications in the early postoperative period. Clinical, surgical, and pathological data of the remaining 1345 patients was collected. The patients who had a sarcomatous component in their final pathology report and who were treated for pulmonary failure in the second or subsequent recurrences were not included. The first recurrence was in the lung in 36 of the 1345 patients who were retrospectively evaluated. The entire cohort was analyzed in order to define the factors determining PR. In this group, patients with recurrence except PR and patients who had no recurrence were defined as PR negative group.

The clinical, surgical, and pathological factors determining OS in patients with PR ($n = 36$) were defined. The recurrence was labeled as an isolated PR in cases of the presence of recurrence only in the lung, while it was called synchronized PR if the patient had extrapulmonary recurrence in addition to PR. The extent of disease in the lung was stratified as single pulmonary nodule (1 nodule) and multiple pulmonary nodules (>1 nodule) according to the number of tumoral nodules in the lung. Recurrence tumor size was accepted as the largest diameter of the tumor in the lung or other sites, while the largest diameter of tumor in the lung was defined as pulmonary tumor size. Disease-free interval (DFI) was the period between initial surgery and PR, and OS was defined as the period between PR and death or the last contact with the patients. Institutional Review Board (Ankara, Turkey) approval was obtained.

The patients were staged according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) criteria. Serous, clear cell, and undifferentiated tumors were accepted as Grade 3 tumors in the pathological evaluation following initial surgery.

PR and extrapulmonary recurrence was diagnosed by the clinical and radiological signs obtained from the pelvic and systemic examination, chest X-ray, abdominopelvic and thoracic computerized tomography, or magnetic resonance imaging. Additionally, tissue diagnosis was available in five patients. The decision of the treatment that would be performed was taken by the gynecologic oncology council. The status of disease after treatment was evaluated according to the World Health Organization.[22] According to the assessment made in the 1st month after treatment, we defined clinical response as the following: (1) complete clinical response: disappearance of the macroscopic tumor; (2) partial clinical response: shrinkage over 50% in the macroscopic tumor; (3) stable disease: macroscopic tumor shrinkage less than 50% or not less than 25% growth; and (4) progressive disease: > 25% growth in the macroscopic tumor or macroscopic appearance of new tumor foci.

Patients who had complete clinical response after the therapy for recurrence were followed-up every 3 months for 2 years, every 6 months until the 5th year following treatment, and yearly thereafter. In the follow-up, pelvic examination, abdominopelvic ultrasonography, complete blood count, and blood chemistry were performed. At every patient visit, chest X-ray was performed. Thoracic and/or abdominal computerized tomography was used when there was an abnormality in the pelvic examination or ultrasonography or chest X-ray or when there was clinical suspicion. Ca-125 level was utilized in the follow-up, even though it was not routinely used. The same follow-up protocol except for the chest X-ray had been performed after the initial treatment that the patients had received, subsequent to the initial diagnosis of endometrial cancer. In the follow-up after treatment following the initial diagnosis of endometrial cancer, chest X-ray was utilized yearly or more commonly in cases of clinical suspicion such as the presence of cough and/or dyspnea.

In the entire cohort, the factors determining PR were compared using Chi-square test. Factors having a p value < 0.25 in univariate analyses were included as candidate variables in multivariate analyses with logistic regression analysis. The isolated PR group was compared with the synchronized PR group with Chi-square test for the categorical parameters and by analysis of variance table test for continuous parameters. In the PR group, OS estimates were determinated by using the Kaplan–Meier method, and survival

curves were compared using the log-rank test. The factors determining OS after PR could not be evaluated in multivariate analysis due to the small study population and the interdependence of predictors. Statistical analyses were performed using SPSS (SPSS Inc., Chicago IL, USA) version 17.0. The cut-off for statistical significance was set at $p < 0.05$.

3. Results

3.1. Entire cohort

The median age of the 1345 patients was 58 years, ranging between 23 years and 92 years of age. The median uterine tumor size was 41 mm (range, 1–335 mm). Two hundred and fifty-seven patients had Stages III and IV disease. The tumor type of 1161 patients was endometrioid and 696 patients had FIGO Grade 1 disease (Table 1). Myometrial invasion was ≥1/2 in 480 patients and 165 patients had cervical involvement. Lymphovascular space invasion, adnexal involvement, peritoneal cytology, and omental spread were positive in 311 patients, 92 patients, 64 patients, and 59 patients, respectively. The median lymph node number in the 827 patients who underwent staging surgery was 48 (range, 2–122) and 190 patients had lymphatic involvement. Overall, a total of 593 patients had adjuvant therapy following surgery. Among these, 396 patients had only radiotherapy and 112 patients had only chemotherapy. Furthermore, 83 patients received both therapies. Additionally, two patients received hormonal therapy.

Among all cohort with a median follow-up time of 36 months (range, 1–249 months), 162 (12%) patients had recurrence and 36 (2.7%) had PR. In the univariate analysis, advanced age, nonendometrioid tumor type, advanced FIGO stage, performance of lymphadenectomy, presence of lymph node metastasis, high FIGO grade, increased depth of myometrial invasion, positive lymphovascular space invasion, adnexal metastasis, positive peritoneal cytology, omental metastasis, and taking adjuvant therapy were associated with PR (Table 2). Since lymphadenectomy was performed on patients with a high risk of lymph node metastasis, advanced stage disease, nonendometrioid tumor type, deep myometrial invasion, high FIGO grade, cervical invasion, adnexal metastasis, lymphovascular space invasion, and positive peritoneal cytology were more common in these patients. This was also the case for those who received adjuvant therapy.

The correlation between prognostic factors was detected with logistic regression analysis; according to this assessment, age at diagnosis (≤58 years vs. > 58 years), FIGO grade (Grade 1 and 2 vs. Grade 3), lymphovascular space invasion (negative vs. positive), and stage (Stage I and II vs. Stage III &

Table 1
Clinical, surgical, and pathological characteristics of the entire cohort.

Characteristics		
Age at initial diagnosis (y)		58 (23–92)
Tumor size at initial diagnosis (mm)		41 (1–335)
FIGO 2009 stage	Stages I & II	1088 (81)
	Stages III & IV	257 (19)
FIGO grade[a]	1–2	1055 (78.4)
	3	280 (21)
Treatment	Staging surgery performed	827 (62)
	Staging surgery not performed	518 (38)
Adjuvant therapy	Not performed	752 (56)
	Performed	593 (44)
Type of adjuvant therapy	Radiotherapy	396 (66.7)
	Chemotherapy	112 (19)
	Chemotherapy & radiotherapy	83 (14)
	Hormonal therapy	2 (0.3)

Data are presented as *n* (%) or median (range).
FIGO = International Federation of Gynecology and Obstetrics.
[a] The grade of 10 patients could not be obtained.

Table 2
Factors determining pulmonary recurrence: univariate analysis.

Characteristics		Pulmonary recurrence (%)	*p*
Age at initial diagnosis (y)[a]	≤58	1.9	0.004
	>58	5.3	
2009 FIGO stage	I & II	1.5	<0.0001
	III & IV	7.8	
Tumor type	Endometrioid	2.1	0.001
	Nonendometrioid	6.5	
Lymphadenectomy at initial surgery	Not performed	0.4	<0.0001
	Performed	4.1	
No. of removed lymph nodes[a]	≤48	4.4	0.901
	>48	4.2	
Lymph node metastasis	Negative	3	0.003
	Positive	7.9	
Metastatic lymph node site	Isolated pelvic	4.9	0.149
	Isolated paraaortic	16.1	
	Pelvic & paraaortic	7.9	
FIGO grade	1	0.6	<0.0001
	2	3.6	
	3	6.8	
Depth of myometrial invasion	≤1/2	0.9	<0.0001
	>1/2	5.8	
Lymphovascular space invasion	Negative	1.3	<0.0001
	Positive	5.5	
Cervical invasion	Negative	2.3	0.056
	Positive	5.5	
Adnexal metastasis	Negative	2.3	<0.0001
	Positive	8.8	
Peritoneal cytology	Negative	2.2	<0.0001
	Positive	12.5	
Omental metastasis	Negative	2	<0.0001
	Positive	17	
Adjuvant therapy at initial diagnosis	Not performed	0.5	<0.0001
	Performed	5.7	
Type of adjuvant therapy	Radiotherapy	5.4	0.160
	Chemotherapy	8.9	
	Radiotherapy & chemotherapy[b]	1.9	
Uterine tumor size (mm)[a]	≤40	2.6	0.280
	>40	4.2	

FIGO = International Federation of Gynecology and Obstetrics.
[a] Median value.
[b] Chemotherapy followed by radiotherapy or radiotherapy followed by chemotherapy or sandwich therapy (3 cycles of paclitaxel and carboplatin followed by radiotherapy followed by 3 cycles paclitaxel and carboplatin).

Table 3
Multivariate analysis of selected clinicopathological variables regarding pulmonary recurrence.

Parameter	*p*	HR	95% CI
Age at initial diagnosis (≤58 y vs. >58 y)	0.061	2.207	0.963−5.057
FIGO grade (Grades 1 & 2 vs. Grade 3)	0.077	1.628	0.948−2.798
Lymphovascular space invasion (negative vs. positive)	0.348	1.531	0.629−3.729
2009 FIGO stage (Stages I & II vs. Stages III & IV)	0.023	2.842	1.158−6.975

CI = confidence interval; FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio.

IV) were further entered into the multivariate analysis. Only stage was found to be an independent prognostic factor for PR (Table 3). The risk of development of PR was 2.842 times higher in patients with Stages III and IV disease (95% confidence interval, 1.158−6.975; $p = 0.023$).

3.2. PR group

The median age of the patients with PR at the initial diagnosis was 62 years, ranging between 48 years and 81 years. Median DFI was 17 months (range, 1−54 months) and the median age at recurrence was 63 years (range, 48−83 years). Median recurrence tumor size was 27.5 mm (range, 10−110 mm) and median pulmonary tumor size was 20.5 mm (range, 10−100 mm). Eleven patients had a single nodule in the lung and 20 patients had multiple nodules. The data of five patients regarding the number of pulmonary tumor nodules could not be obtained. Twelve patients had symptoms at the time of diagnosis of recurrence. The main symptom was dyspnea in five patients, gastrointestinal symptoms in two patients, abdominal distension in two patients, coughing in one patient, vaginal bleeding in one patient, and severe fatigue in one patient.

The median CA-125 level at initial diagnosis was 49 IU/mL and ranged between 1 IU/mL and 915 IU/mL. Median CA-125 level at recurrence was 110 IU/mL (range, 1−3150 IU/mL). Three patients had Stage IA disease, 11 patients had Stage IB disease, two patients had Stage II, two patients had Stage IIIA, three patients had Stage IIIC1, four patients had Stage IIIC2, and 11 patients had Stage IVB disease, according to FIGO 2009 criteria. Twenty-four patients had endometrioid type carcinoma and 19 patients had FIGO Grade 3 disease. Myometrial invasion was ≥1/2 in 28 patients, and seven of these had uterine serosal invasion. Cervical invasion was observed in nine patients and invasion was stromal in these patients. Positive peritoneal cytology, lymphovascular space invasion, adnexal metastasis, and omental spread were detected in eight patients, 17 patients, eight patients, and 10 patients, respectively. Clinical, surgical, and pathological data at the initial diagnosis are shown in Table 4 in detail.

Thirty-four patients had lymphadenectomy in the initial surgery. The median lymph node number harvested in these patients was 45 (range, 4−99); it was 13 (range, 5−36) for the para-aortic region and 41 (range, 4−65) for the pelvic region.

Table 4
Clinical and pathological characteristics of patients with pulmonary recurrence.

Characteristics		*n*	%	Mean	Median (range)
Age at initial diagnosis (y)				62.7	62 (48−81)
Age at recurrence (y)				63.8	63 (48−83)
Disease free interval (mo)				19	17 (1−54)
CA 125 level at initial diagnosis (IU/mL)				149	49 (1−915)
CA 125 level at recurrence (IU/mL)				346	110 (1−3150)
2009 FIGO stage	IA	3	8.3		
	IB	11	30.6		
	II	2	5.6		
	IIIA	2	5.6		
	IIIC1	3	8.3		
	IIIC2	4	11.1		
	IVB	11	30.6		
Tumor type	Endometrioid	24	66.7		
	Clear cell	4	11.1		
	Serous	5	13.9		
	Undifferentiated	2	5.6		
	Mixed	1	2.8		
FIGO grade	1	4	11.1		
	2	13	36.1		
	3	19	52.8		
Depth of myometrial invasion	No invasion	1	2.8		
	<1/2	7	19.4		
	≥1/2[a]	21	58.3		
	Serosal invasion	7	19.4		
Lymphovascular space invasion	Negative	12	33.3		
	Positive	17	47.2		
	Not reported	7	19.4		
Cervical invasion	Negative	27	75		
	Positive	9	25		
Peritoneal cytology	Negative	28	78.2		
	Positive	8	22.2		
Adnexal metastasis	Negative	28	78.2		
	Positive	8	22.2		
Omental metastasis	Negative	23	63.9		
	Positive	10	27.8		
	Not reported[b]	3	8.3		
Lymphadenectomy at initial surgery	Not performed	2	5.6		
	Performed	34	94.4		
No. of harvested lymph nodes				47.3	45 (4−99)
Lymph node metastasis	Negative	19	52.8		
	Isolated pelvic	4	11.1		
	Isolated paraaortic	5	13.9		
	Pelvic & paraaortic	6	16.7		
Adjuvant therapy at initial treatment	Not performed	3	8.3		
	Performed	33	91.7		
Type of adjuvant therapy	Radiotherapy	22	66.7		
	Chemotherapy	10	30.3		
	Sandwich therapy[c]	1	3		

FIGO = International Federation of Gynecology and Obstetrics.
[a] Except for uterine serosal invasion.
[b] Omentectomy was not preformed.
[c] Three cycles of paclitaxel and carboplatin followed by radiotherapy followed by three cycles of paclitaxel and carboplatin.

Among the patients having lymphadenectomy, lymph node involvement was detected in 15 patients. Lymph node metastasis was in the paraaortic region in five patients, in the pelvic region in four patients, and in both regions in six patients (Table 4). Median metastatic lymph node number was six and ranged between one and 53.

None of the patients had residual tumor following the initial surgery. Thirty-three patients received adjuvant therapy. Among these, 22 had radiotherapy only, 10 had chemotherapy only, and one had sandwich therapy (3 cycles of paclitaxel and carboplatin followed by radiotherapy followed by 3 cycles of paclitaxel and carboplatin). Chemotherapy was applied as paclitaxel and carboplatin in six patients, cisplatin and adriamycin in two patients, adriyamisin in one patient, and dosetaxel and carboplatin in one patient. Four patients had thoracic surgery and there was no residual tumor in three of these patients. Complete clinical response was achieved in three of these four patients who took chemotherapy following surgery (2 patients megestrol acetate, 1 patient paclitaxel and carboplatin, and 1 patient cisplatin and epirubicin). Stable disease was obtained in the patient who had residual tumor following surgery and took megestrol acetate.

Recurrence was isolated PR in 21 (58.3%) patients. Among the 15 (41.7%) patients with synchronized PR, four had recurrence in the lung and pelvis, four had recurrence in the lung and upper abdomen, three had recurrence in the lung and liver parenchyma, one had recurrence in the lung, liver parenchyma, surrenal gland, and pelvis, one had recurrence in the lung, upper abdomen, and pelvis, one had recurrence in the lung and bone, and one had recurrence in the lung, upper abdomen, bone, and brain.

The patients with synchronized PR had advanced stage disease at the initial diagnosis compared with patients with isolated PR (80% vs. 31.1%, respectively; $p = 0.013$). In this group, median DFI was shorter (23.5 months vs. 12.7 months, respectively; $p = 0.015$). Additionally, lymph node involvement, omental metastasis, and positive peritoneal cytology were more common in this group (Table 5). However, both groups were similar in terms of age at primary diagnosis, age at recurrence, CA-125 level at recurrence, number of harvested lymph nodes, recurrence tumor size, pulmonary tumor size, pulmonary nodule number, tumor type, FIGO grade, depth of myometrial invasion, presence of cervical invasion, adnexal metastasis, appliance of adjuvant therapy, and type of adjuvant therapy.

Median follow-up time after PR was 23.5 months (range, 4−108 months). Fifteen patients died. Estimated 2-year OS was 52% in the study population. Early FIGO stage, no lymphatic metastasis, negative lymphovascular space invasion, no cervical invasion, negative adnexal spread, negative peritoneal cytology, negative omental metastasis, adjuvant radiotherapy after initial surgery, isolated pulmonary recurrences, and chemotherapy at recurrence were associated with improved survival after PR (Table 6). All these factors associated with good prognosis were present in eight patients. Median follow-up time after recurrence was 35 months (range, 6−108 months) in these patients and none of them died of disease.

The appliance of chemotherapy after initial surgery was associated with a reduction in OS compared with radiotherapy (15 months vs. 44 months, respectively; $p = 0.020$). However, the patients who received adjuvant chemotherapy were at advanced stages. Ninety percent of the patients having chemotherapy and 43.5% of the patients having radiotherapy had FIGO Stages III and IV disease ($p = 0.013$). OS was poorer in the patients with advanced stage disease. OS was 17 months in patients with Stages III and IV disease, while it was 55 months in the patients with Stages I and II disease ($p = 0.011$). Type of PR was associated with OS. OS was 54 months and 10 months in patients with isolated PR and synchronized PR, respectively ($p = 0.005$; Fig. 1).

Table 5
Clinical, pathological characteristics, and type of pulmonary recurrence.

Characteristics	Isolated pulmonary recurrence	Synchronized pulmonary recurrence	p
Age at initial diagnosis (y)	63 (61; 53−77)	62.3 (63; 48−91)	0.826
Age at recurrence (y)	64.8 (62.5; 55−80)	62.4 (63; 48−83)	0.403
CA 125 level at recurrence (IU/mL)	349 (66.5; 1−1350)	344 (300; 2−1205)	0.986
No. of removed lymph nodes	46.1 (48; 4−93)	49.3 (43; 5−99)	0.769
Disease free interval from initial diagnosis (mo)	23.5 (19; 1−54)	12.7 (14; 2−24)	0.015
Pulmonary tumor size (mm)	34.2 (25; 10−100)	26 (17; 10−62)	0.387
Recurrence tumor size (mm)	34.2 (25; 10−100)	35 (30; 10−110)	0.770
2009 FIGO Stages III & IV	38.1	80	0.013
Lymph node metastasis	28.6	69.2	0.020
Omental metastasis	10	61.5	0.002
Positive peritoneal cytology	9.5	40	0.030
Nonendometrioid tumor type	23.8	46.7	0.151
FIGO Grade 3	57.1	46.7	0.535
Depth of myometrial invasion $\geq$ 1/2	81	73.3	0.588
Positive lymphovascular space invasion	47.1	75	0.132
Cervical invasion	19	33.3	0.329
Adnexal metastasis	14.3	33.3	0.175
Adjuvant therapy was performed	95.2	86.7	0.359
Adjuvant chemotherapy	21.1	42.9	0.178
Multiple pulmonary nodule	68.4	58.3	0.567

Data are presented as mean (median; range) or %.
FIGO = International Federation of Gynecology and Obstetrics.

Table 6
Clinical, pathological, surgical factors, and overall survival in patients with pulmonary recurrence.

Characteristics		*n*	Overall survival (mo), mean	*p*
Age at initial diagnosis (y)[a]	≤62	14	39	0.144
	>62	14	24	
Age at recurrence (y)[a]	≤63	19	34	0.515
	>63	15	27	
Disease free interval (mo)[a]	≤17	19	28	0.976
	>17	17	27	
2009 FIGO stage	I & II	16	55	0.011
	III & IV	20	17	
Tumor type	Endometrioid	24	44	0.086
	Nonendometrioid	12	17	
Lymphadenectomy at initial surgery	Not performed	2	–	NC[b]
	Performed	34	–	
No. of removed lymph nodes[a]	≤45	15	43	0.906
	>45	14	28	
Lymph node metastasis	Negative	19	55	0.014
	Positive	15	16	
FIGO grade	1 & 2	17	40	0.296
	3	19	21	
Depth of myometrial invasion	≤1/2	8	26	0.925
	>1/2	28	32	
Lymphovascular space invasion	Negative	12	58	0.048
	Positive	17	22	
Cervical invasion	Negative	27	39	0.024
	Positive	9	16	
Adnexal metastasis	Negative	28	44	0.001
	Positive	8	7	
Peritoneal cytology	Negative	28	45	0.008
	Positive	8	8	
Omental metastasis	Negative	23	49	<0.0001
	Positive	10	7	
Adjuvant therapy at initial treatment	Not performed	3	–	NC[c]
	Performed	33	–	
Type of adjuvant therapy at initial treatment	Radiotherapy	23	44	0.020
	Chemotherapy	10	15	
Recurrence tumor size (mm)[a]	≤28		18	0.706
	>28		41	
Pulmonary tumor size (mm)[a]	≤21		17	0.441
	>21		45	
Ca 125 at recurrence (IU/mL)[a]	≤110	13	50	0.061
	>110	11	13	
Symptom at recurrence	Negative	24	29	0.431
	Positive	12	32	
Type of recurrence	Isolated pulmonary recurrence	21	54	0.005
	Synchronized pulmonary recurrence	15	10	
No. of pulmonary nodules	Single pulmonary nodule	11	30	0.424
	Multiple pulmonary nodules	20	40	
Pulmonary surgery at recurrence	Not performed	32	9	0.059
	Performed	4	37	
Salvage treatment for recurrence	Radiotherapy	5	13	0.025
	Chemotherapy	18	43	

FIGO = International Federation of Gynecology and Obstetrics.
[a] Median value.
[b] NC = not compared because two patients did not have lymphadenectomy.
[c] NC = not compared because three patients did not take adjuvant chemotherapy.

Eighteen patients took chemotherapy, five patients took radiotherapy, two patients took megestrol acetate, and 11 patients were managed palliatively at recurrence. Among the patients having chemotherapy, seven took paclitaxel and carboplatin, four took cisplatin and epirubicin, two took cisplatin and adriamycin, one took carboplatin, one took cisplatin, one took adriamycin, one took topotecan, and one took paclitaxel, cisplatin, and farmorubicin. The efficiency of treatment applied at recurrence was analyzed excluding the patients taking hormonal therapy and the patients who were managed

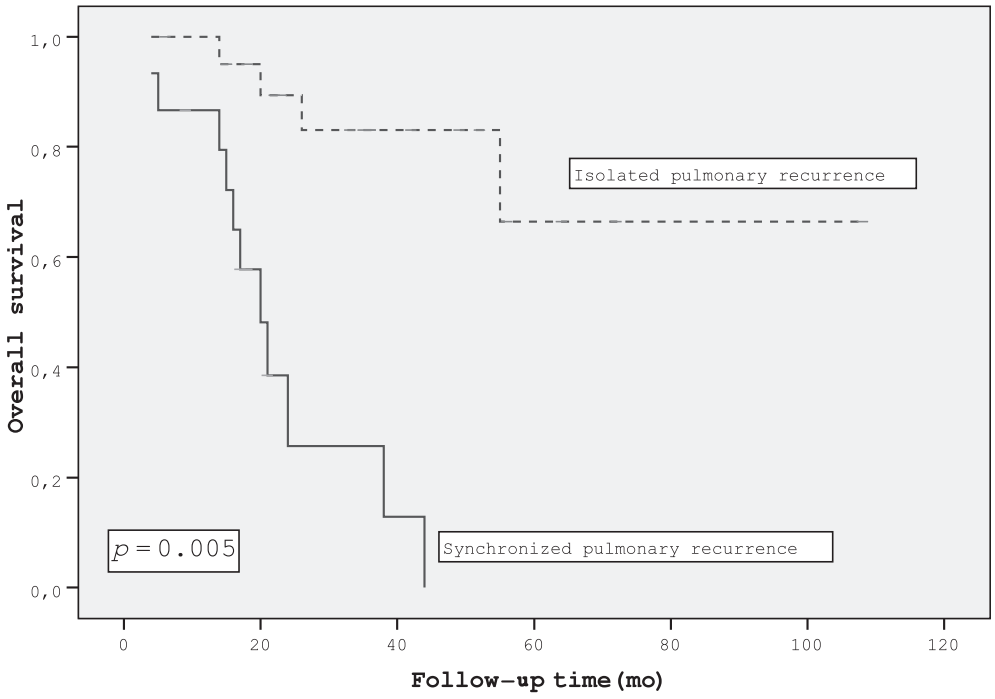

Fig. 1. Type of pulmonary recurrence.

palliatively. Systemic therapy at recurrence was associated with improved OS. OS was 43 months in the patients taking chemotherapy, while it was 13 months in the patients who took radiotherapy ($p < 0.025$; Fig. 2).

Endometrioid type tumor and having thoracic surgery were borderline predictors for improved prognosis ($p = 0.086$ and $p = 0.059$, respectively). CA-125 level at the time of recurrence had a tendency to be significant to predict OS ($p = 0.061$). However, age at diagnosis and age at recurrence, DFI, number of harvested lymph nodes, FIGO grade, depth of myometrial invasion, recurrence tumor size, pulmonary tumor size, number of tumoral nodules in the lung, and presence of symptoms were not associated with OS.

4. Discussion

PR developed in 2.7% of 1345 patients whose median follow-up time was 36 months. In the univariate analysis, advanced age, advanced FIGO stage, performance of

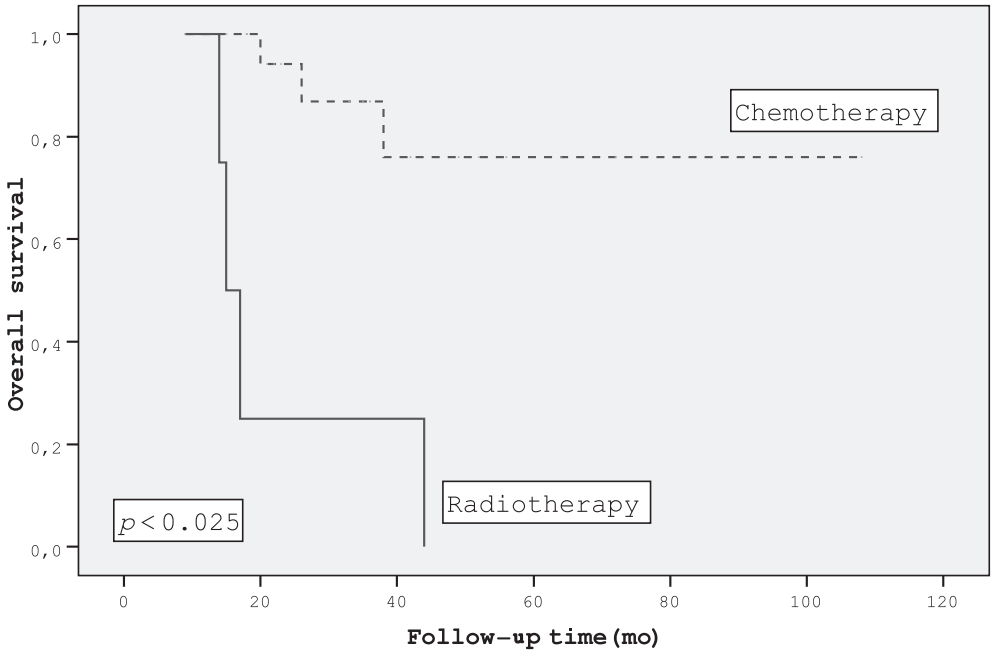

Fig. 2. Treatment of recurrence.

lymphadenectomy, high FIGO grade, increased depth of myometrial invasion, positive lymphovascular space invasion, extrauterine disease (adnexal metastasis, positive peritoneal cytology, omental metastasis, and lymph node metastasis), and receiving adjuvant therapy were associated with PR. Only FIGO stage was an independent prognostic factor for PR development in logistic regression analysis. PR developed in 7.8% of the patients with Stages III and IV disease and 1.5% of the patients with Stages I and II disease ($p < 0.0001$). Similar results were reported by Mariani et al.[15] In that study, advanced age (>65 years), advanced stage (Stage IV), deep myometrial invasion (>1/2), high FIGO grade (Grade 3), adnexal metastasis, positive peritoneal cytology, lymphovascular space invasion, adjuvant chemotherapy or radiotherapy, and uterine tumor size were associated with PR in the univariate analysis. However, in the multivariate analysis, only Stage IVB disease and deep myometrial invasion were independent prognostic factors for PR. These results were supported by other studies.[13,17]

Two-year OS after recurrence was 52% in the present study. Survival was associated with FIGO stage, lymphovascular space invasion, cervical invasion, extrauterine disease at initial diagnosis (lymph node metastasis, adnexal metastasis, positive peritoneal cytology, and omental metastasis), type of adjuvant therapy, site of recurrence (isolated vs. synchronized), and salvage treatment at recurrence. OS was 44 months and 15 months in the patients who received radiotherapy and chemotherapy, respectively. Nevertheless, the relationship between adjuvant therapy and survival depended on what chemotherapy was given to which patient. The patients who received chemotherapy were at more advanced stages than the patients taking radiotherapy. Ninety percent of patients taking chemotherapy had Stages III and IV disease, while it was 43.5% for the patients who had radiotherapy, and OS was significantly lower in the patients who had advanced stage disease. OS was 55 months and 17 months for the patients with Stages I and II disease and Stages III and IV disease, respectively. Similar results regarding survival after recurrence and adjuvant chemotherapy were also reported in the study by Huang et al[6] in which recurrent endometrial cancer was evaluated. However, in the present study, cytotoxic therapy as the salvage therapy improved OS in the patients with PR. OS was 43 months in patients receiving salvage chemotherapy, while it was 13 months in the patients who received salvage radiotherapy. However, it must be mentioned that this result was based on only five patients who received salvage radiotherapy. Nevertheless, lower FIGO grade, smaller pulmonary tumor size (≤2 cm), and the presence of estrogen receptor were associated with better survival, while salvage chemotherapy was related to poorer survival compared with other treatment modalities in patients with isolated PR in the study by Dowdy et al.[16] In that study, OS was 14 months and 28 months in patients who received chemotherapy and other treatment modalities, respectively. The authors explained this result with the presence of poorer prognostic factors in the patients receiving chemotherapy. However, in the same study, hormonal therapy was shown to be efficient in selected patients. In the present study, megestrol acetate was given to the two patients who underwent pulmonary metastasectomy as salvage therapy. Complete clinical response could be achieved in the patients who had no residual tumor following the surgery performed for the recurrence 36 months after the initial therapy and she has been free of disease for 108 months. The second patient had recurrence 21 months after the initial therapy and there was gross residual tumor following thoracic surgery and she has been using megestrol acetate since then. She has had stable disease for 23 months.

Earlier reports stated a low survival after PR. Bouros et al[14] showed that 75% of the patients died of disease in the 1st year after the diagnosis of PR. However, in that study, in 21% of the patients with PR who were analyzed, the tumor type was uterine sarcoma. OS was reported to be 98 months after the diagnosis of PR in the patients who had low grade tumor only in the lung, equal or lower than 2 cm in the study by Dowdy et al.[16] Nevertheless, in their study, 2-year OS was found to be 22%. This is much lower than the 2-year OS that we found. This difference may be explained by the higher rate of progressive disease during the initial treatment (22% vs. no progressive disease in our study), the lower rate of isolated PR (34% vs. 58% in our study), presence of higher rate of abdominal disease (33% vs. 19.4% in our study), and the lower DFI in that study (median 9 months vs. 17 months).

In the present study, site of recurrence was important. OS was significantly lower in the patients with synchronized PR compared with the patients who had isolated PR (10 months vs. 54 months, respectively). However, pulmonary tumor size and number of tumoral nodules in the lung were not associated with OS. Similar results were also reported by other studies. OS was 27 months and 7 months in the patients with isolated PR and synchronized PR, respectively, in the study by Dowdy et al.[16] In that study, pulmonary tumor size was associated with OS in the patients with isolated PR, while number of pulmonary tumoral nodules were not. By contrast, Otsuka et al[17] showed that survival after PR was lower in the presence of extensive pulmonary tumor.

In our study, synchronized PR developed earlier than isolated PR (median DFI 14 months vs. 19 months, respectively), at more advanced stages (Stages III and IV 80% vs. 38.1%, respectively), and synchonized PR was observed more commonly in patients who had lymph node metastasis, positive peritoneal cytology, and omental metastasis compared with patients having isolated PR. These results were similar to the results of the study by Dowdy et al.[16] Additionally, in that study, adnexal metastasis and nonendometrioid tumor type were more common in the patients with synchronized PR. Although the type of PR (synchronized vs. isolated) was associated with DFI in both studies, it was not associated with survival after recurrence. However, Otsuka et al[17] reported that DFI was associated with OS (≤24 months vs. > 24 months). Other studies also showed that DFI was associated with survival after recurrence in patients with endometrial cancer.[18,19,21,23]

Resection of the pulmonary tumor had borderline significance for OS. OS was 37 months and 9 months in patients who had resection and those who did not, respectively. Nevertheless, it should be kept in mind that this was the result of only four patients who had thoracic surgery. Similarly, in other studies, pulmonary metastasectomy was shown to be associated with survival.[18−21] In the study by Anraku et al,[18] they analyzed 133 patients who had metastasectomy for uterine tumor related PR and the 5-year OS was 76% in the 23 patients whose primary site were endometrium. However, this superior survival could not be shown by Calvero et al.[21] In that study, 3-year OS after thoracic surgery for PR was 28% in patients with endometrial cancer.

The retrospective nature of the present study resulted in bias in patient selection. Additionally, it prevented the homogenization of the patient population. The small number of patients was another limitation. However, the present study is one of the few studies that analyzed only the patients with PR in detail. Furthermore, this was a study that evaluated the largest number of patients in 20 years.

In conclusion, in the presence of poor clinical, surgical, and pathological factors at initial diagnosis, it should be known that PR may develop. In this cohort, 50% of who survive for at least 2 years, systemic therapy should be performed after recurrence and thoracic surgery should be kept in mind for selected patients. However, multi-center studies are required for the standardization of the treatment that will be performed after PR.

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