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Analysis of the relapse patterns and risk factors of endometrial cancer following postoperative adjuvant chemotherapy in a phase III randomized clinical trial

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HIGHLIGHTS

- Analysis of relapse of endometrial cancer was done using a phase III randomized trial data.
- Local relapse and distant relapse are similar in frequency after adjuvant chemotherapy.
- Median disease-free interval is about 12 months.
- Post-relapse overall survival is correlated with disease-free interval and para-aortic lymphadenectomy.

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ABSTRACT

Objective: This study was to analyze patterns and risk factors of relapse after postoperative adjuvant chemotherapy for endometrial cancer.
Methods: Among patients enrolled in a randomized phase III trial (JGOG2043) investigating the efficacy of adjuvant chemotherapy for endometrial cancer at a high risk of progression, the recurrent patients were studied. Clinical information were collected, and correlation between relapse-related factors and clinicopathological factors were analyzed.
Results: Among 193 patients analyzed, 50% had local relapse and 63% had distant relapse. Local relapse involved regional lymph nodes in 30%, while distant relapse involved the abdominal cavity in 42%. Imaging was used to confirm relapse in 83%, and the median disease-free interval (DFI) was 11.5 months. Factors showing a significant correlation with DFI $\leq$12 months were residual tumor at surgery ($p < 0.01$), Grade 3 histology ($p < 0.01$), and lymph node metastasis ($p = 0.03$). In contrast, treatment with paclitaxel and carboplatin showed a significant correlation with DFI >12 months ($p = 0.04$). The median post-relapse overall survival (RS) was 23.9 months. In multivariate analysis, CA125 $\geq$ 100 U/mL prior to relapse ($p < 0.01$), distant metastasis ($p < 0.01$), DFI $\leq$ 12 months ($p = 0.02$), and not performing para-aortic lymphadenectomy ($p = 0.01$) were independently related to poor RS.

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Conclusions: Relapse of endometrial cancer following adjuvant chemotherapy often occurs by 1 year after treatment, with common relapse sites of the abdominal cavity and regional lymph nodes. Among treatment-related factors, RS was correlated with DFI and para-aortic lymphadenectomy.

1. Introduction

After initial surgery is considered to have achieved complete resection of endometrial cancer, some patients subsequently develop relapse of disease. Postoperative adjuvant therapy is indicated both for early staged patients with high risk of recurrence and for advanced staged patients [1]. Common sites for relapse of endometrial cancer are the vaginal stump, intra-pelvic, intra-abdominal, and distant organs [2]. A meta-analysis of patients with stage I endometrial cancer demonstrated favorable control of local relapse by adjuvant radiotherapy compared with no adjuvant therapy, but there was no difference in distant metastasis and no improvement of survival [3–5]. On the other hand, among patients with advanced disease, the GOG122 study demonstrated better survival with adjuvant chemotherapy than whole abdominal irradiation [6]. Accordingly, it is expected that the efficacy of chemotherapy as adjuvant therapy for patients with an intermediate or high risk of recurrence will be evaluated further and its clinical use will increase.

Standard follow-up after treatment of endometrial cancer is recommended to include periodic medical examination, vaginal cytology, measurement of tumor markers, and diagnostic imaging, but the optimal approach is unclear [7]. These methods for detection of relapse have been adopted on the basis of the patterns of recurrence identified in retrospective clinical studies of adjuvant radiotherapy, while information about relapse patterns and outcomes following adjuvant chemotherapy is still insufficient. To develop individualized follow-up procedures, large-scale clinical data need to be acquired from patients with homogenous background and treatment factors.

The Japanese Gynecologic Oncology Group (JGOG) previously conducted a clinical trial at 118 Japanese institutions (JGOG2043 study: "A randomized phase III trial of docetaxel plus cisplatin or paclitaxel plus carboplatin compared with doxorubicin plus cisplatin as adjuvant chemotherapy for endometrial cancer at a high risk of progression") [8]. The main objective of that study was to compare efficacy among several types of adjuvant chemotherapy using progression-free survival (PFS) as the endpoint. Patients indicated for adjuvant therapy were enrolled and all of them received adjuvant chemotherapy, excluding those with a low risk of recurrence who could be cured by surgery alone and those with metastatic lesions who did not achieve complete remission after initial treatment. This study was an analysis using the collected data in the phase 3 randomized clinical trial, the JGOG2043 study. The aim was to analyze the patterns and risk factors of relapse in endometrial cancer patients who received adjuvant chemotherapy, as well as the correlations between relapse and various clinicopathological factors.

2. Patients and methods

This study enrolled patients with confirmed relapse among those registered in the JGOG2043 study, excluding patients who did not receive chemotherapy and those lost to follow-up.

The JGOG2043 study investigated patients with histopathological confirmation of endometrial cancer who were considered to have a high risk of progression following surgery. A high risk of progression was defined as FIGO1988 surgical stage I-II with myometrial invasion exceeding 50% and Grade 2 or 3 histology (including serous, clear cell, and undifferentiated), or surgical stage III-IV without distant metastasis beyond the abdominal cavity. Other inclusion criteria were patients who had undergone total hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and maximum residual tumor diameter $\leq$2 cm, as well as no prior anticancer therapy, age $\geq$20 years to <75 years at registration, ECOG Performance Status (PS) of 0–2, adequate of vital organ function (bone marrow, heart, liver, and kidneys), no serious complications, and no history of other cancer within the past 5 years. Para-aortic lymphadenectomy was optional, and it was done by the investigator's decision depending on the estimated risk of recurrence. Para-aortic lymphadenectomy was performed in 58% of the patients. The JGOG2043 study received approval from the institutional review board at each institution, and written informed consent was obtained from all patients.

Patients were enrolled from November 24, 2006, through January 7, 2011. A total of 788 eligible patients were randomly allocated to one of the following treatments at a 1:1:1 ratio: doxorubicin + cisplatin (AP therapy, 263 patients), docetaxel + cisplatin (DP therapy, 263 patients), or paclitaxel + carboplatin (TC therapy, 262 patients). All patients were scheduled to receive 6 cycles of treatment. After completion of scheduled treatment, further anticancer therapy including radiotherapy was not given until relapse or progression was observed. Follow-up investigation including physical findings, serum CA125, and imaging was performed every 6 months for at least 5 years according to the study protocol. The median follow-up period was 7.0 years.

The following demographic information was collected: age at initiation of treatment, surgical stage (FIGO1988), CA125 before therapy, histological type, tumor grade, myometrial invasion, lymph-vascular space invasion, lymph node metastasis, ascites cytology, para-aortic lymphadenectomy, size of the residual tumor, chemotherapy regimen, and number of chemotherapy cycles. Prognostic information included the following: site of relapse, method of detecting relapse, CA125 prior to relapse, disease-free interval (DFI), and treatment following relapse. DFI was calculated from the last day of chemotherapy to the day of detecting relapse or progression, while the post-relapse overall survival (RS) was calculated from the day when relapse was confirmed to the day of death from any cause. Patients lost to follow-up were censored on the last day when survival was confirmed.

The pattern of relapse (including the timing and site of relapse) and the correlations of that with clinicopathological factors were analyzed. Local relapse was defined as involvement of the vagina, vulva, intra-pelvic sites, or regional lymph nodes, while relapse at other sites was defined as distant relapse. For statistical analysis, the chi-square test was used to assess independence. Correlations between RS and clinicopathological factors were investigated by Cox proportional hazards analysis. RS was estimated by the Kaplan-Meier method with stratification by various factors and differences in survival between groups were assessed by the log-rank test. P values < 0.05 were considered statistically significant.

3. Results

Among 788 patients registered in the JGOG2043 study, relapse occurred in 196 patients during the observation period (median: 7.0

Table 1
Patient characteristics. 1A Summary of all patient characteristics in the JGOG2043 study (N = 788). 1B Summary of relapsed patient characteristics in this analysis (N = 193).

A

Characteristics	No.	(%)
Age, years		
Median	59	
Range	22-74	
Surgical stage (FIGO 1988)		
IC	171	(22)
II	71	(9)
III	494	(63)
IV	52	(7)
Histological type		
Endometrioid carcinoma	633	(80)
Serous carcinoma	57	(7)
Clear cell carcinoma	25	(3)
Mucinous carcinoma	7	(1)
Mixed carcinoma	31	(4)
Others	35	(4)
Tumor grade		
Grade 1	191	(24)
Grade 2	311	(39)
Grade 3	210	(27)
Unknown/Not applicable	76	(10)
Para-aortic lymphadenectomy		
No	334	(42)
Yes	454	(58)
Size of residual tumor		
No residual	757	(96)
Residual (≤2 cm)	31	(4)
Chemotherapy regimen		
Doxorubicin + Cisplatin (AP)	263	(33)
Docetaxel + Cisplatin (DP)	263	(33)
Paclitaxel + Carboplatin (TC)	262	(33)

B

Characteristics		No.	(%)
Patients factor	Age, years		
	Median	60.5	
	Range	22-74	
	Surgical stage (FIGO 1988)		
	IC	16	(8)
	II	9	(5)
	III	133	(69)
	IV	35	(18)
	CA125 pretreatment, U/mL		
	Median	47.2	
	Range	0.7-541	
Pathological factor	Histological type		
	Endometrioid carcinoma	133	(69)
	Serous carcinoma	28	(15)
	Clear cell carcinoma	10	(5)
	Mucinous carcinoma	3	(2)
	Mixed carcinoma	10	(5)
	Others	9	(5)
	Tumor grade		
	Grade 1	28	(15)
	Grade 2	62	(32)
	Grade 3	69	(36)
	Unknown/Not applicable	34	(18)
	Myometrial invasion		
	<50%	44	(23)
	≥50%	149	(77)
	Lymph-vascular space invasion		
	No	46	(24)
	Yes	140	(73)
	Unknown	7	(4)
	Peritoneal cytology positive		
	No	100	(52)
	Yes	90	(47)
	Not done	3	(2)
	Lymph node metastasis		
	No	89	(46)
	Yes	102	(53)
	Unknown	2	(1)
Therapeutic factor	Para-aortic lymphadenectomy		
	No	75	(39)
	Yes	118	(61)
	Size of residual tumor		
	No residual	175	(91)
	Residual (≤2 cm)	18	(9)
	Chemotherapy regimen		
	Doxorubicin + Cisplatin (AP)	67	(35)
	Docetaxel + Cisplatin (DP)	55	(28)
	Paclitaxel + Carboplatin (TC)	71	(37)
	No. of chemotherapy cycles		
	Median	6	
	Range	1-6	

years). Among them, 3 patients did not receive chemotherapy, and the remaining 193 patients were analyzed in this study. The demographic profiles of all patients in the JGOG2043 study and these relapsed 193 patients in this study are shown in Table 1.

The patterns of relapse are listed in Table 2. Local relapse occurred in 50% of the patients (96/193) and distant relapse occurred in 63% (121/193), with both types of relapse in 12% (24/193). Local relapse only was seen in 37% (72/193) of the patients, while 50% (97/193) had distant metastasis only. The most common site of local relapse was the regional lymph nodes (30%), followed by the vagina and vulva (18%). Distant relapse was most common in the abdominal cavity (42%), followed by the lungs (25%) and the non-regional lymph nodes (13%). Median DFI was 11.5 months (0–86.3 months) and there were two peaks of relapse (≤12 months and >1.5 years). It was 9.7 months with AP therapy, 9.5 months

Table 2
Relapse status.

Factors		No.	(%)
Site of relapse	Local	96	(50)
	vagina, vuvla	35	(18)
	pelvis	17	(9)
	regional lymph node	57	(30)
	Distant	121	(63)
	abdominal cavity	47	(42)
	liver	15	(8)
	lung	49	(25)
	bone	18	(9)
	non-regional lymph node	25	(13)
	others	8	(4)
	Local only	72	(37)
	Distant only	97	(50)
	Local and distant	24	(12)
Disease-free interval	refractory	1	(1)
	≤3 months	30	(16)
	>3 months, ≤ 6 months	26	(13)
	>6 months, ≤ 12 months	42	(22)
	>1 year, ≤ 1.5 years	13	(7)
	>1.5 years, ≤ 2 years	31	(16)
	>2 years, ≤ 3 years	23	(12)
	>3 years	27	(14)
	Median (range), months	11.5 (0–86.3)	
Diagnosis	Method		
	Imaging	160	(83)
	Clinical	2	(1)
	Biopsy	31	(16)
	CA125 prior to relapse, U/mL		
	Median (range), U/mL	24.9 (3.4-6,968)	

Table 3
Correlation between relapse status and clinicopathological factors.

Factors	Site of relapse			Disease-free interval			CA125 prior to relapse		
	Local only (n = 72)	Distant (n = 121)	p value	>12 M (n = 94)	≤12 M (n = 99)	p value	<100 U/mL (n = 118)	≥100 U/mL (n = 33)	p value
Age, years									
≤60	36	67		52	51		64	17	
>60	36	54	0.47	42	48	0.60	54	16	0.78
Surgical stage (FIGO 1988)									
I-II	10	15		16	9		20	2	
III-IV	62	106	0.77	78	90	0.10	98	31	0.12
CA125 before therapy, U/mL									
≤100	47	73		61	59		76	14	
>100	12	24	0.53	16	20	0.50	21	10	0.04
Histological type									
endometrioid	53	80		70	63		86	18	
non-endometrioid	19	41	0.28	24	36	0.10	32	15	0.04
Tumor grade									
Grade 1/2	32	58		55	35		53	17	
Grade 3	29	40	0.41	27	42	<0.01	48	8	0.16
Myometrial invasion									
<50%	11	33		23	21		24	9	
≥50%	61	88	0.05	71	78	0.59	94	24	0.39
Lymph-vascular space invasion									
No	8	38		27	19		22	10	
Yes	62	78	<0.01	63	77	0.12	90	23	0.19
Peritoneal cytology positive									
No	44	56		51	49		74	5	
Yes	28	62	0.07	41	49	0.45	42	28	<0.01
Lymph node metastasis									
No	28	61		51	38		53	17	
Yes	44	58	0.10	42	60	0.03	64	15	0.43
Para-aortic lymphadenectomy									
No	26	49		35	40		41	18	
Yes	46	72	0.55	59	59	0.65	77	15	0.04
Size of residual tumor									
No residual	66	109		91	84		108	28	
Residual (≤2 cm)	6	12	0.71	3	15	<0.01	10	5	0.26
Chemotherapy regimen									
Doxorubicin + Cisplatin (AP)	30	37		27	40		44	10	
Docetaxel + Cisplatin (DP)	17	38	0.11	26	29	0.44	35	10	0.65
Doxorubicin + Cisplatin (AP)	30	37		27	40		44	10	
Paclitaxel + Carboplatin (TC)	25	46	0.25	41	30	0.04	39	13	0.42
No. of chemotherapy cycles									
= 6	58	83		71	70		92	22	
≤5	14	38	0.07	23	29	0.45	26	11	0.18

with DP therapy, and 18.8 months with TC therapy. Thus, the longer DFI was obtained with TC therapy. Relapse was mainly detected by imaging, including CT scanning, and median CA125 prior to relapse was not elevated (24.9 U/mL).

Correlations among the site of relapse, DFI, CA125 prior to relapse, and various clinicopathological factors are shown in Table 3. Lymph-vascular space invasion was associated with local relapse ($p < 0.01$), but no other significant factors were identified in the site of relapse. Factors showing a significant correlation with DFI ≤12 months were residual tumor at surgery ($p < 0.01$), Grade 3 histology ($p < 0.01$), and lymph node metastasis ($p = 0.03$). In contrast, the only factor significantly correlated with DFI >12 months was TC therapy ($p = 0.04$). CA125 > 100U/mL prior to relapse was significantly correlated with positive peritoneal cytology ($p < 0.01$), not performing para-aortic lymphadenectomy ($p = 0.04$), CA125 > 100U/mL before therapy ($p = 0.04$), and non-endometrioid ($p = 0.04$).

Median RS of all patients was 23.9 months (728 days) (Fig. 1A). Treatment after relapse included chemotherapy 59.6% (115/193), radiotherapy 16.6% (32/193), surgery 9.3% (18/193), other therapy 5.2% (10/193), and no treatment 9.3% (18/193). When RS was stratified by the site of relapse, DFI, and CA 125 prior to relapse, it was significantly better in patients with local relapse only ($p < 0.01$), patients with DFI > 12 months ($p < 0.01$), and patients whose CA125 was ≤100 U/mL prior to relapse ($p < 0.01$) (Fig. 1B–D). Correlations between RS and clinicopathological factors are shown in Table 4. According to univariate analysis, CA125 > 100 U/mL prior to relapse ($p < 0.01$), distant relapse ($p < 0.01$), positive peritoneal cytology ($p < 0.01$), DFI ≤ 12 months ($p < 0.01$), residual tumor at surgery ($p < 0.01$), not performing para-aortic lymphadenectomy ($p = 0.02$), stage III–IV disease ($p = 0.02$), non-endometrioid ($p = 0.02$), and ≤5 chemotherapy cycles ($p = 0.03$) were significantly correlated with poor RS. In multivariate analysis, the following factors were independent determinants of poor RS: CA125 > 100 U/mL prior to relapse ($p < 0.01$), distant relapse ($p < 0.01$), DFI ≤ 12 months ($p = 0.02$), and not performing para-aortic lymphadenectomy ($p = 0.01$). During the observation period, 46% of local relapse patients (33/72) could be salvaged, while 25% of distant relapse patients (30/121) could be salvaged. In local relapse, patients who could choose radiotherapy were significantly salvaged compared to those who received other therapies ($P < 0.01$).

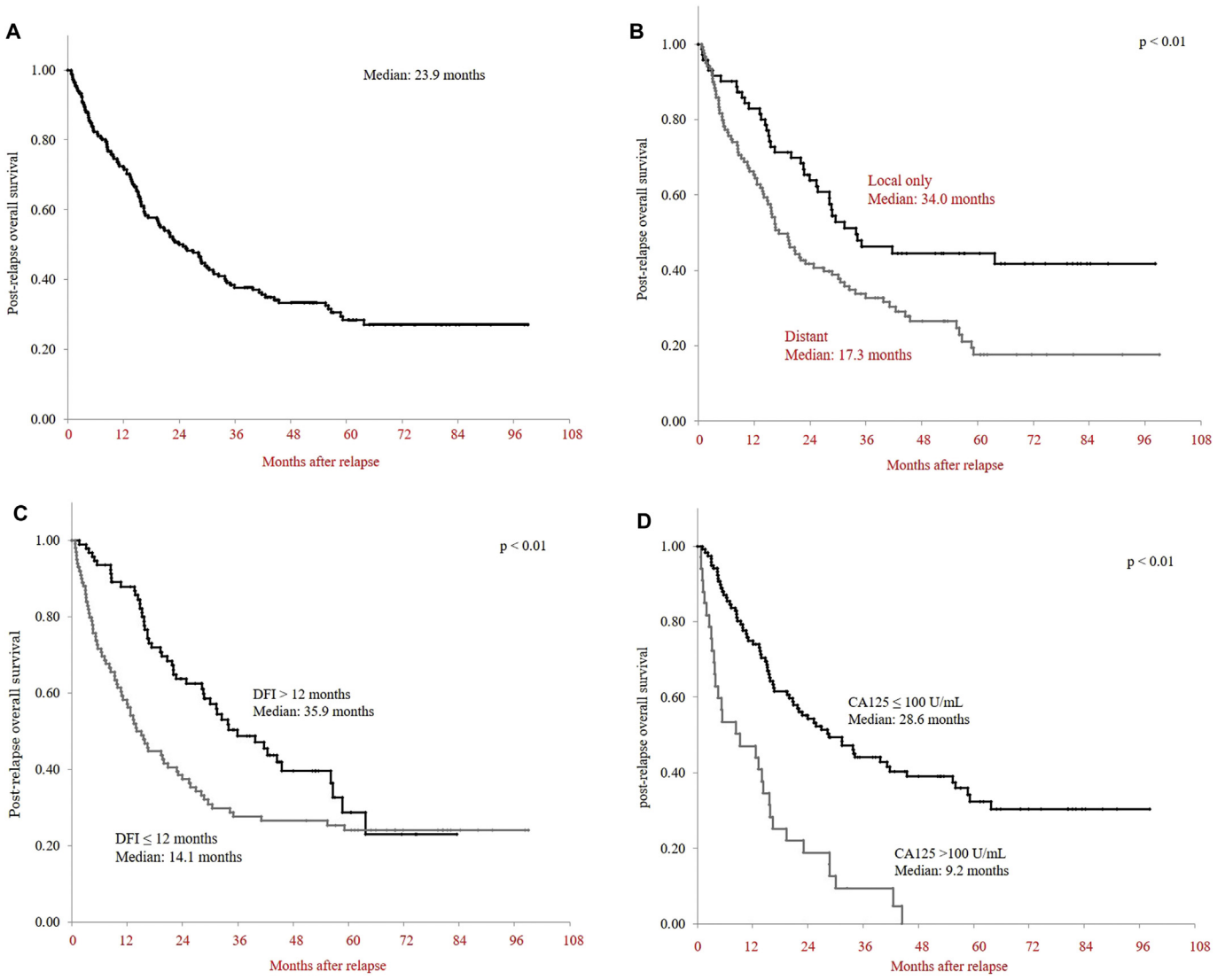

Fig. 1. Post-relapse overall survival curve (A) All patients with relapse (B) Patients with relapse divided by site of relapse (C) Patients with relapse divided by DFI (D) Patients with relapse divided by CA125 value prior to relapse.

4. Discussion

We found that the rates of local relapse and distant relapse were similar, while RS differed at a threshold DFI of approximately 12 months. This study analyzed clinical data obtained prospectively, but had the limitations of only being conducted in Japan and enrolling patients who underwent extensive surgical procedures including pelvic lymphadenectomy.

In this study, 37% of the patients only had local relapse, while 62% had distant relapse with/without local relapse. The abdominal cavity and regional lymph nodes were frequent sites of relapse. In the JGOG2033 study, pelvic relapse alone was found in 43% of the radiotherapy group and 42% of the chemotherapy group [9]. In an Italian study, pelvic relapse alone occurred in 18% of the radiotherapy group versus 34% of the chemotherapy group [10]. The GOG122 study revealed pelvic relapse in 24%, peritoneal relapse in 30%, and relapse at other sites in 41% with radiotherapy, while the corresponding results for chemotherapy were 35%, 28%, and 35%, respectively [6]. According to integrated analysis of the NSGO EC-9501/EORTC-55991 study and the MaNGO ILIADE-III study, local relapse occurred in 14% and distant relapse in 86% [11]. The PORTEC-3 study showed local relapse in 6% and distant relapse in 94% [12]. The GOG258 study showed local relapse in 26% and distant relapse in 74% with chemoradiotherapy among the relapsed patients, while 52% and 48% with chemotherapy, respectively [13]. Furthermore, the GOG184 study revealed local relapse in 24% and distant relapse in 76% [14]. The results of the present study were similar to previous findings. Based on these reports, adjuvant chemotherapy inhibits distant relapse better than radiotherapy, but local relapse is more frequent with chemotherapy. The salvage rate after local relapse was not poor as shown in this study. Because local relapse could be controlled by radiotherapy, there may be a clinical significance of prior adjuvant chemotherapy for controlling distant relapse.

All patients in the JGOG2043 study underwent pelvic lymphadenectomy and 58% also received para-aortic lymphadenectomy. However, the regional lymph nodes were involved in 31% of the patients with relapse. The clinical significance of performing lymphadenectomy in patients with early endometrial cancer was not demonstrated by two randomized controlled studies [15,16], and a meta-analysis also reached the same conclusion [17]. In the MRC ASTEC study, local relapse occurred in 39% of patients without lymphadenectomy versus 35% with lymphadenectomy [15], while the corresponding results were 32% and 30% in an Italian study [16].

Table 4
Univariate and multivariate analysis on post-relapse overall survival time.

Factors	No.	univariate				multivariate			
		Hazard ratio	(95% CI)		p value	Hazard ratio	(95% CI)		p value
Age, years									
≤60	103								
>60	90	1.22	0.86	1.73	0.28				
Surgical stage (FIGO 1988)									
I-II	25								
III-IV	168	2.14	1.12	4.09	0.02				
Histological type									
endometrioid	133								
non-endometrioid	60	1.52	1.06	2.19	0.02				
Peritoneal cytology positive									
No	100								
Yes	90	1.73	1.21	2.48	<0.01				
Lymph node metastasis									
No	89								
Yes	102	1.17	0.82	1.68	0.38	1.37	0.89	2.11	0.15
Para-aortic lymphadenectomy									
No	75								
Yes	118	0.66	0.46	0.94	0.02	0.58	0.38	0.88	0.01
Size of residual tumor									
No residual	175								
Residual (≤2 cm)	18	2.15	1.28	3.62	<0.01				
Chemotherapy regimen									
Doxorubicin + Cisplatin (AP)	67								
Taxane + Platinum	126	1.03	0.71	1.49	0.88				
No. of chemotherapy cycles									
= 6	141								
≤5	52	1.53	1.04	2.25	0.03	1.43	0.90	2.27	0.13
Disease-free interval, months									
>12	94								
≤12	99	1.74	1.22	2.49	<0.01	1.67	1.10	2.53	0.02
CA125 prior to relapse, U/mL									
≤100	118								
>100	33	3.21	2.08	4.96	<0.01	2.50	1.56	4.01	<0.01
Site of relapse									
Loccal only	72								
Distant	121	1.84	1.25	2.69	<0.01	1.95	1.24	3.08	<0.01

Based on these reports, it seems that lymphadenectomy may not contribute to controlling local relapse.

In this study, the most common method of detecting relapse was imaging. The median value of CA125 was not above the reference range at the time of relapse. It was reported that tumor markers are of limited usefulness for detecting relapse, except in patients with high pretreatment levels, but it was also reported that CT and measurement of CA125 are better for detecting asymptomatic relapse than other methods [7,18]. While some studies have shown that patients with asymptomatic relapse may have a better prognosis than those with symptomatic relapse [19–21], it has also been reported that early diagnosis of relapse does not contribute to improve prognosis [7,22,23]. Although physical examination and CT are recommended for follow-up, frequent evaluation may not be needed, given that the impact of early detection of relapse on prognosis was not consistent in previous studies.

Chemotherapy was often selected for treatment of relapse in this study. There were several clinicopathological factors that showed a significant correlation with RS, among which the factors that could be modified by treatment were para-aortic lymphadenectomy and DFI. DFI was also correlated with residual tumor at surgery and with TC therapy. Para-aortic lymphadenectomy was previously reported to be clinically useful for extending overall survival in intermediate to high risk patients, corroborating our finding [24,25]. And the phase 3 trial to investigate the survival benefit of para-aortic lymphadenectomy is in progress [26]. DFI is considered to be an important factor when deciding to perform chemotherapy following relapse. According to pooled analysis of second-line chemotherapy performed by the Gynecologic Oncology Group, DFI >3 months is associated with a decreased risk of death [27]. Other retrospective analyses have shown that DFI of 6 months to > 12 months may be associated with a better prognosis [28–31]. It seems appropriate to consider that DFI of 12 months is related to a better prognosis following relapse of endometrial cancer. In addition, TC therapy is consistent with the current standard treatment strategy. The GOG209 study showed the non-inferiority of paclitaxel plus carboplatin to paclitaxel with doxorubicin plus cisplatin [32]. From its correlation with longer DFI, using TC therapy as adjuvant therapy could have a clinical significance. A meta-analysis of cytoreductive surgery for advanced endometrial cancer demonstrated that achieving complete resection prolonged overall survival [33], suggesting that no residual tumor following surgery may be correlated with a more favorable prognosis through extension of DFI.

In summary, relapse frequently occurred at 1 year after treatment in patients receiving adjuvant chemotherapy, and distant metastasis was less frequent, while local relapse was more frequent than reported previously after adjuvant radiotherapy. DFI >12 months was correlated with no residual tumor at surgery and with use of TC therapy, while the factors correlated with better RS were performing para-aortic lymphadenectomy and DFI >12 months.

Conflicts of interest

Daisuke Aoki reports grants from Chugai Pharmaceutical, Sanofi, and Taiho Pharmaceutical; personal fees from AstraZeneca, Chugai

Pharmaceutical, Daiichi Sankyo, Janssen Pharmaceutical, Kyowa Hakko Kirin, MSD, Nippon Kayaku, Ono Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical, and Yakult Honsha, outside the submitted work. Kazuhiro Takehara reports personal fees from AstraZeneca, Chugai Pharmaceutical, Eisai, and Ono Pharmaceutical, outside the submitted work. All other authors declare that they have no conflicts of interest.

Author contribution section

All of the authors take responsibility for data analysis and interpretation.

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References

[1] N. Colombo, C. Creutzberg, F. Amant, et al., ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up, Int. J. Gynecol. Cancer 26 (2016) 2–30.
[2] E. Sartori, B. Laface, A. Gadducci, et al., Factors influencing survival in endometrial cancer relapsing patients: a Cooperation Task Force (CTF) study, Int. J. Gynecol. Cancer 13 (2003) 458–465.
[3] A. Kong, I. Simera, M. Collingwood, et al., Adjuvant radiotherapy for stage I endometrial cancer: systematic review and meta-analysis, Ann. Oncol. 18 (2007) 1595–1604.
[4] ASTEC/EN5 Study Group, P. Blake, A.M. Swart, et al., Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis, Lancet 373 (2009) 137–146.
[5] A. Kong, N. Johnson, H.C. Kitchener, et al., Adjuvant radiotherapy for stage I endometrial cancer: an updated Cochrane systematic review and meta-analysis, J. Natl. Cancer Inst. 104 (2012) 1625–1634.
[6] M.E. Randall, V.L. Filiaci, H. Muss, et al., Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group study, J. Clin. Oncol. 24 (2006) 36–44.
[7] R. Salani, F.J. Backes, M.F. Fung, et al., Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: society of Gynecologic Oncologists recommendations, Am. J. Obstet. Gynecol. 204 (2011) 466–478.
[8] H. Nomura, D. Aoki, H. Michimae, et al., Effect of taxane plus platinum regimens vs doxorubicin plus cisplatin as adjuvant chemotherapy for endometrial cancer at a high risk of progression: a randomized clinical trial, JAMA Oncol 5 (2019) 833–840.
[9] N. Susumu, S. Sagae, Y. Udagawa, et al., Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study, Gynecol. Oncol. 108 (2008) 226–233.
[10] R. Maggi, A. Lissoni, F. Spina, et al., Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial, Br. J. Canc. 95 (2006) 266–271.
[11] T. Hogberg, M. Signorelli, C.F. de Oliveira, et al., Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer - results from two randomised studies, Eur. J. Cancer 46 (2010) 2422–2431.
[12] S.M. de Boer, M.E. Powell, L. Mileshkin, et al., Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial, Lancet Oncol. 19 (2018) 295–309.
[13] D. Matei, V. Filiaci, M.E. Randall, et al., Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer, N. Engl. J. Med. 380 (2019) 2317–2326.
[14] H.D. Homesley, V. Filiaci, S.K. Gibbons, et al., A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: a Gynecologic Oncology Group study, Gynecol. Oncol. 112 (2009) 543–552.
[15] ASTEC study group, H. Kitchener, A.M. Swart, et al., Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study, Lancet 373 (2009) 125–136.
[16] P. Benedetti Panici, S. Basile, F. Maneschi, et al., Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial, J. Natl. Cancer Inst. 100 (2008) 1707–1716.
[17] H.S. Kim, D.H. Suh, M.K. Kim, et al., Systematic lymphadenectomy for survival in patients with endometrial cancer: a meta-analysis, Jpn. J. Clin. Oncol. 42 (2012) 405–412.
[18] J.Y. Lee, J.H. Kim, J.W. Seo, et al., Detecting asymptomatic recurrence in early-stage endometrial cancer: the value of vaginal cytology, imaging studies, and CA-125, Int. J. Gynecol. Cancer 26 (2016) 1434–1439.
[19] C.J. Smith, M. Heeren, J.L. Nicklin, et al., Efficacy of routine follow-up in patients with recurrent uterine cancer, Gynecol. Oncol. 107 (2007) 124–129.
[20] Y. Ueda, T. Enomoto, T. Egawa-Takata, et al., Endometrial carcinoma: better prognosis for asymptomatic recurrences than for symptomatic cases found by routine follow-up, Int. J. Clin. Oncol. 15 (2010) 406–412.
[21] L. Carrara, A. Gadducci, F. Landoni, et al., Could different follow-up modalities play a role in the diagnosis of asymptomatic endometrial cancer relapses?: an Italian multicentric retrospective analysis, Int. J. Gynecol. Cancer 22 (2012) 1013–1019.
[22] M. Fung-Kee-Fung, J. Dodge, L. Elit, et al., Follow-up after primary therapy for endometrial cancer: a systematic review, Gynecol. Oncol. 101 (2006) 520–529.
[23] I. Otsuka, M. Uno, A. Wakabayashi, et al., Predictive factors for prolonged survival in recurrent endometrial carcinoma: implications for follow-up protocol, Gynecol. Oncol. 119 (2010) 506–510.
[24] Y. Todo, H. Kato, M. Kaneuchi, et al., Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis, Lancet 375 (2010) 1165–1172.
[25] Y. Todo, H. Kato, S. Minobe, et al., Initial failure site according to primary treatment with or without para-aortic lymphadenectomy in endometrial cancer, Gynecol. Oncol. 121 (2011) 314–318.
[26] H. Watari, H. Katayama, T. Shibata, et al., Phase III trial to confirm the superiority of pelvic and para-aortic lymphadenectomy to pelvic lymphadenectomy alone for endometrial cancer: Japan Clinical Oncology Group Study 1412 (SEPAL-P3), Jpn. J. Clin. Oncol. 47 (2017) 986–990.
[27] K.N. Moore, C. Tian, D.S. McMeekin, et al., Does the progression-free interval after primary chemotherapy predict survival after salvage chemotherapy in advanced and recurrent endometrial cancer?: a Gynecologic Oncology Group ancillary data analysis, Cancer 116 (2010) 5407–5414.
[28] S. Nagao, S. Nishio, H. Michimae, et al., Applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer: the SGSG-012/GOTIC-004/Intergroup study, Gynecol. Oncol. 131 (2013) 567–573.
[29] Y. Ueda, T. Miyake, T. Egawa-Takata, et al., Second-line chemotherapy for advanced or recurrent endometrial carcinoma previously treated with paclitaxel and carboplatin, with or without epirubicin, Cancer Chemother. Pharmacol. 67 (2011) 829–835.
[30] T. Ninomiya, W. Yamagami, N. Susumu, et al., Retrospective analysis on the feasibility and efficacy of docetaxel-cisplatin therapy for recurrent endometrial cancer, Anticancer Res. 36 (2016) 1751–1758.
[31] T. Odagiri, H. Watari, M. Hosaka, et al., Multivariate survival analysis of the patients with recurrent endometrial cancer, J Gynecol Oncol 22 (2011) 3–8.
[32] D. Miller, V. Filiaci, G. Fleming, et al., Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study, Gynecol. Oncol. 125 (2012) 771–773 (Abstract).
[33] J.N. Barlin, I. Puri, R.E. Bristow, Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis, Gynecol. Oncol. 118 (2010) 14–18.