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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 ☆

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Abstract

Objective. To establish an optimal adjuvant therapy for intermediate- and high-risk endometrial cancer patients, we conducted a multi-center randomized phase III trial of adjuvant pelvic radiation therapy (PRT) versus cyclophosphamide–doxorubicin–cisplatin (CAP) chemotherapy in women with endometrioid adenocarcinoma with deeper than 50% myometrial invasion.

Methods. Among 385 evaluated patients, 193 patients received PRT and 192 received CAP. The PRT group received at least 40 Gy. The CAP group received cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m^2) and cisplatin (50 mg/m^2) every 4 weeks for 3 or more courses.

Results. No statistically significant differences in progression-free survival (PFS) and overall survival (OS) were observed. The 5-year PFS rates in the PRT and CAP groups were 83.5% and 81.8% respectively, while the 5-year OS rates were 85.3% and 86.7% respectively. These rates were also not significantly different in a low- to intermediate-risk group defined as stage IC patients under 70 years old with G1/2 endometrioid adenocarcinoma. However, among 120 patients in a high- to intermediate-risk group defined as (1) stage IC in patients over 70 years old or with G3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology), the CAP group had a significantly higher PFS rate (83.8% vs. 66.2%, log-rank test $P=0.024$, hazard ratio 0.44) and higher OS rate (89.7% vs. 73.6%, log-rank test $P=0.006$, hazard ratio 0.24). Adverse effects were not significantly increased in the CAP group versus the PRT group.

Conclusion. Adjuvant chemotherapy may be a useful alternative to radiotherapy for intermediate-risk endometrial cancer.

Keywords: Endometrial cancer; Intermediate risk; Adjuvant radiotherapy; Adjuvant chemotherapy; Cisplatin-based chemotherapy

Introduction

The number of patients with endometrial cancer is increasing in Japan as well as in the United States and other countries [1]. The number of patients with recurrent endometrial cancer is also increasing. Approximately, 10% to 15% of patients with early-stage endometrial cancer will experience recurrences [2,3]. To reduce the recurrence rate, adjuvant chemotherapy or radiotherapy has been applied, but a definite standard therapy has not yet been established.

For stage III–IV endometrial cancer, Randall et al. [4] reported the results of a Gynecologic Oncology Group (GOG) randomized Phase III trial of whole abdominal irradiation (WAI)

☆ The participating institutions for all studies described in this report are listed in the Appendix.

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and platinum–doxorubicin (AP) chemotherapy. This study had a large impact on treatment since adjuvant therapy for advanced endometrial cancer had been limited mainly to radiotherapy, such as whole abdominal irradiation, pelvic irradiation, and vaginal brachytherapy.

Adjuvant therapy for early-stage endometrial cancer has also been limited mainly to radiation therapy. In the National Comprehensive Cancer Network (NCCN) Guidelines for 2006, Version 2 [5], adjuvant therapy was selected based on a combination of characteristics such as surgical staging, grade and risk factors (advanced age, lymphovascular space invasion, tumor size, depth of invasion, etc.). Radiation therapy was recommended for all patients except those with IA/G1 or G2 lesions and those with IB/G1 lesions without risk factors. Chemotherapy was also not included as an adjuvant therapy for stage I/II endometrial cancers. In the FIGO annual report [1], adjuvant radiotherapy was selected roughly twice as often as adjuvant chemotherapy for patients with stage IC, IIA, or IIB endometrial carcinoma.

Recently, some large series of randomized studies regarding adjuvant radiotherapy for early-stage endometrial cancers were performed by Aalders et al. (NRH study) [6], Creutzberg et al. (PORTEC study) [2,7] and Keys et al. (GOG 99 study) [8]. In these three series, the loco-regional recurrence rate was significantly lower in the pelvic irradiation group versus the no adjuvant therapy or brachytherapy groups. However, none of the studies recognized a significant survival benefit. Moreover, the rate of adverse gastrointestinal effects was higher in the pelvic irradiation group after pelvic lymphadenectomy or lymph node sampling in both the PORTEC study [7] and the GOG study [8].

In view of this background, physicians have been concerned as to whether adjuvant therapy is effective for improving the progression-free survival (PFS) and overall survival (OS) of patients with early-stage endometrial cancer. The GOG began a randomized study (GOG 156 study, data not published) consisting of pelvic radiation and chemotherapy (doxorubicin plus cisplatin) treatment groups for patients with stage IB, IC, IIA, and IIB endometrial cancer. However, this trial was closed due to low accrual rates. The Japanese Gynecologic Oncology Group (JGOG) began a randomized study comparing pelvic radiotherapy to platinum-based combined chemotherapy to clarify which modality was more effective for improving the PFS and OS of endometrial cancer patients with deeper than 50% myometrial invasion, including FIGO stage IC to IIIC. Most of the enrolled patients had IC, IIA, IIB, or IIIA intermediate-risk endometrial cancer.

Methods

Patient selection and eligibility criteria

Patient accrual for this study occurred from 1994 to 2000 at 103 member institutions of the JGOG. The eligibility criteria for this study were International Federation of Gynecology and Obstetrics (FIGO) stage IC–IIIC endometrial carcinoma with deeper than 50% myometrial invasion and absence of any prior chemotherapy, irradiation, or surgery for the treatment of any other cancer. Patients with stage II or III without deeper than 50% myometrial invasion were ineligible for this study. Patients were required to be under 75 years old, to have a WHO performance status of 0 to 3, and to have undergone an initial surgery, including total abdominal hysterectomy and bilateral salpingo-oophorectomy, with no residual tumor. Patients with other active cancers or without adequate liver, renal, or bone marrow functions were excluded. All patients agreed to the randomized study design and provided informed consent. Surgical staging consisted ideally of pelvic and/or paraaortic lymphadenectomy. A central pathology review was not performed. Treatment was initiated within 4 weeks of surgery. Treatment was initiated within 4 weeks of surgery.

Pelvic irradiation was given in an open field using the anterio-posterior parallel opposing technique. The scheduled dose of irradiation was 45 to 50 Gy within 4 to 6 weeks, with 9 to 10 Gy of irradiation administered per week (5 working days per week). Subsequently, additional irradiations were performed in 11 cases (5.7%) with paraaortic lesions and in 6 patients (3.1%) who received brachytherapy.

The chemotherapy group received cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m^2), and cisplatin (50 mg/m^2) (CAP chemotherapy) every 4 weeks for 3 or more courses. Dose modifications of doxorubicin and cisplatin were as follows: a 25% reduction of both drugs was allowed for body weight less than 40 kg or age greater than 70 years old, and a 50% reduction was allowed in patients with G3 or G4 myelosuppression.

Study design and randomization

This trial utilized a straightforward randomization among two groups: pelvic radiation and chemotherapy. An allocation table was prespecified based on a

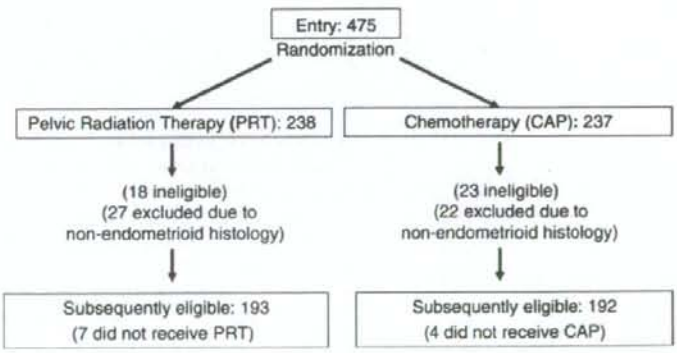

Fig. 1. Flow chart of patients in JGOG study 2033. The initial enrollment was 475 patients, 41 of whom were ineligible due to myometrial invasion of less than 50%, histological diagnosis of sarcoma, or rapid progression of disease after enrollment. An additional 49 patients with non-endometrioid histology were excluded.

Table 1
Patient characteristics

		Pelvic radiation therapy (PRT) (%)		Chemotherapy (CAP) (%)		Total	Univariate P (%)
	n	193		192		385	
Age	Average	58.7		59.3		59.0	P=0.431
	SD	7.5		8.6		8.1	
Menopause	Premenopause	35	18.1	35	18.2	70	P=0.981
	Postmenopause	158	81.9	157	81.8	315	
Co-morbidity	None	123	63.7	127	66.1	250	P=0.619
	Any	70	36.3	65	33.9	135	
Performance status	0	169	87.6	165	85.9	334	P=0.562
	1	22	11.4	19	9.9	41	
	2	2	1.0	6	3.1	8	
	3	0	0.0	2	1.0	2	
Hysterectomy	Simple	55	28.5	40	20.8	95	P=0.298
	Extended	94	48.7	108	56.3	202	
	Radical	43	22.3	42	21.9	85	
	Other	1	0.5	2	1.0	3	
Postoperative stage	IC	123	63.7	112	58.3	235	P=0.387
	IIA	10	5.2	8	4.2	18	
	IIB	10	5.2	25	13.0	35	
	IIIA	28	14.5	22	11.5	50	
	IIIB	0	0.0	1	0.5	1	
	IIIC	22	11.4	24	12.5	46	
Tumor grade	G1	107	55.4	106	55.2	213	P=0.542
	G2	53	27.5	64	33.3	117	
	G3	33	17.1	20	10.4	53	
	Unknown	0	0.0	2	1.0	2	
Myometrial invasion	>1/2, <2/3	113	58.5	104	54.2	217	P=0.317
	>2/3, <serosa	72	37.3	76	39.6	148	
	Serosa	7	3.6	7	3.6	14	
	Beyond serosa	1	0.5	5	2.6	6	
Lymphovascular space invasion	Negative	100	51.8	103	53.6	203	P=0.892
	Positive	72	37.3	72	37.5	144	
	Unknown	21	10.9	17	8.8	38	
Cervical involvement	Negative	156	80.8	142	74.0	298	P=0.128
	Positive	37	19.2	49	25.5	86	
Parametrial invasion	Negative	176	91.2	172	89.6	348	P=0.334
	Positive	7	3.6	11	5.7	18	
	Unknown	10	5.2	9	4.7	19	
Peritoneal cytology	Negative	169	87.6	171	89.1	340	P=0.749
	Positive	23	11.9	21	10.9	44	
	Unknown	1	0.5	0	0.0	1	
Adnexal metastasis	Negative	181	93.8	178	92.7	359	P=0.675
	Positive	12	6.2	14	7.3	26	
Pelvic LN metastasis	Negative	163	84.4	164	85.4	327	P=0.901
	Positive	21	10.9	22	11.5	43	
	n.d.	9	4.7	6	3.1	15	
Paraaortic LN metastasis	Negative	51	26.4	55	28.6	106	P=0.363
	Positive	1	0.5	3	14.9	4	
	n.d.	141	73.1	134	7.8	275	

CAP: cyclophosphamide, doxorubicin, and cisplatin.
n.d.: not done.

simple randomization. Each participant was assigned by central telephone system. The primary endpoint was OS and secondary endpoints were PFS and the incidence of toxicity.

The required sample size was estimated as 173 for each group, with a significance level of 5% and a power level of 80% using Schoenfeld's sample size formula [9] for the log-rank test and assuming a 13% difference in the OS rate at 5 years (5-year OS rates of 80% for the CAP group and 67% for the PRT group). These figures for the 5-year OS rate were calculated based on data from the FIGO annual report [10], assuming an eligible case distribution of 60% stage I patients, 20% stage II patients, and 20% stage III patients.

Statistical methods

Statistical analyses were performed for all eligible patients on an intent-to-treat principle. All statistical analyses were performed using SAS Release 8.02 (Statistical Analysis Software, Cary, NC, USA). Prognostic factors were analyzed by chi-square test, and survival curves were calculated by the Kaplan–Meier method [11]. A log-rank test [12] was used to test for survival differences. A multivariate analysis using the Cox proportion hazards model [13] was performed to assess the hazard ratio of the prognostic factors for PFS and OS. All reported *P*-values are based on two-sided tests with $P<0.05$ taken as significant.

Results

As shown in the trial profile (Fig. 1), the initial enrollment was 475 patients, 41 of whom were ineligible due to myometrial invasion of less than 50%, histological diagnosis of sarcoma, or rapid progression of disease after enrollment. An additional 49 patients with non-endometrioid histology were excluded. As a result, 385 patients were eligible for this trial. Seven patients in the PRT group did not receive PRT and 4 patients in the CAP group did not receive CAP.

As shown in Table 1, the study groups were well balanced for patient characteristics including age, postmenopausal status, co-morbidity, type of hysterectomy, postoperative stage, tumor grade, myometrial invasion, lymphovascular space invasion, cervical involvement, parametrial invasion, peritoneal cytology, adnexal metastasis, pelvic lymph node metastasis, and paraaortic lymph node metastasis. None of these characteristics was significantly different between groups in univariate analysis. The distribution of postoperative stages was 61.0% IC, 13.8% II, 13.0% IIIA, and 11.9% IIIC. Pelvic lymphadenectomy was performed in 96.1% of the patients, and paraaortic lymphadenectomy was performed in 28.6% of the patients.

The analysis was performed using data finalized on April 14, 2005. The median follow-up periods in the PRT and CAP groups were 59.5 (2.2–60.8) months and 60.8 (5.0–60.8) months, respectively.

Protocol compliance

Treatment was completed in 98.9% (184/186) and 97.3% (183/188) of the patients in the PRT and CAP groups, respectively. We regarded pelvic radiation as being completed when the total radiation dose reached 40 Gy and regarded chemotherapy as being completed when the number of CAP courses reached three. The median total doses were 50 Gy of pelvic irradiation and 1309 mg/m^2 cyclophosphamide, 120 mg/m^2 doxorubicin, and 180 mg/m^2 cisplatin. The median number of CAP courses was 3, ranging from 1 to 7. The median duration of treatment was 5.1 weeks and 11.4 weeks in the PRT and CAP groups, respectively.

Table 3
Sites of initial recurrence

Recurrence sites*	PRT	CAP
	$n=193$	$n=192$
Pelvis	11	5
Vagina only	2	9
Intrapelvic recurrence	13 (6.7%)	14 (7.3%)
Peritoneal cavity	2	2
Liver	3	1
Lung	11	15
Paraaortic lymph node	3	10
Others	7	3
Extrapelvic recurrence	26 (13.5%)	31 (16.1%)
Total recurrent cases	30 (15.5%)	33 (17.2%)

*Including multiple recurrence.
CAP: cyclophosphamide, doxorubicin, and cisplatin.
PRT: pelvic radiation treatment.

Adverse effects

G3 and G4 toxicities were experienced in 1.6% (3/193) of the PRT and 4.7% (9/192) of the CAP groups. Bowel obstructions were the main complication in the PRT group, and myelosuppression was detected in the CAP group. No treatment-related deaths occurred in either group.

Prognostic factors

We performed univariate analyses to detect prognostic factors in all eligible patients. The statistically significant prognostic factors predicting worse PFS were age (≧60 years vs. <60 years), co-morbidity, clinical staging (IIIA vs. II vs. IB vs. IA), tumor grade (G2/3 vs. G1), myometrial invasion (beyond serosa vs. serosa vs. ≧2/3 to < serosa vs. ≧1/2 to <2/3), pelvic lymph node metastasis, adnexal involvement, cervical involvement, peritoneal cytology, and surgical staging (IIIC vs. IIIA vs. IIB vs. IIA vs. IC). For OS, the statistically significant prognostic factors were age, co-morbidity, clinical staging, tumor grade, myometrial invasion, pelvic lymph node metastasis, lymphovascular space invasion, and surgical staging.

Table 2
Multivariate analysis of prognostic factors

Prognostic factors	PFS				OS			
	Hazard ratio	95% confidence interval		*P*-value	Hazard ratio	95% confidence interval		*P*-value
		Lower	Upper			Lower	Upper	
Treatment (CAP vs. PRT)	1.07	0.651	1.762	0.788	0.72	0.399	1.290	0.268
Age (≧60 vs. <60)	1.92	1.142	3.210	0.014	3.30	1.634	6.646	0.001
Co-morbidity	1.61	0.974	2.647	0.063	2.24	1.226	4.109	0.009
Tumor grade	1.55	1.125	2.137	0.007	1.64	1.115	2.418	0.012
Cervical involvement	2.28	1.352	3.829	0.002	n.d.	n.d.	n.d.	n.d.
Peritoneal cytology	2.07	1.091	3.920	0.026	n.d.	n.d.	n.d.	n.d.
Pelvic lymph node metastasis	n.d.	n.d.	n.d.	n.d.	4.25	2.235	8.072	<0.001

CAP: cyclophosphamide, doxorubicin, and cisplatin.
PRT: pelvic radiation treatment.
n.d.: not done.

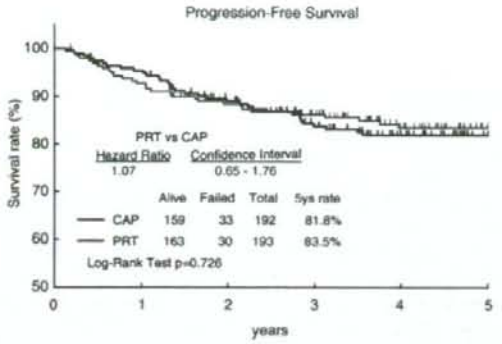

Fig. 2. Progression-free survival rates of all patients in the PRT (pelvic radiation treatment) group and CAP (cyclophosphamide, doxorubicin, and cisplatin) group. Kaplan–Meier analysis. Data for both groups nearly overlap, with no statistical difference.

The significant prognostic factors were used to perform a multivariate analysis with a Cox regression model (Table 2). The multivariate analysis showed that age (≧60 years) and tumor grade (G2/3) were the most important poor prognostic factors for both PFS and OS in this trial.

Recurrence sites

Table 3 presents data on sites of initial recurrence. Thirty recurrences (15.5%) occurred in the PRT group, and 33 recurrences (17.2%) occurred in the CAP group. The patterns of recurrence were similar in both treatment groups. Specifically, the incidence of intrapelvic recurrence sites, such as the pelvis or vagina, was 6.7% (13/193) in the PRT group and 7.3% (14/192) in the CAP group, while the incidence of extrapelvic recurrence sites, such as the peritoneal cavity, liver, lung, paraaortic lymph nodes, and others, was 13.5% (26/193) and 16.1% (31/192) respectively.

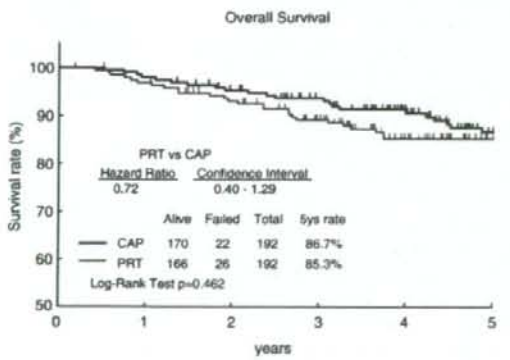

Fig. 3. Overall survival rates in the PRT (pelvic radiation treatment) group and CAP (cyclophosphamide, doxorubicin, and cisplatin) group. Kaplan–Meier analysis. Overall survival rates in both groups were also similar, with no statistical difference.

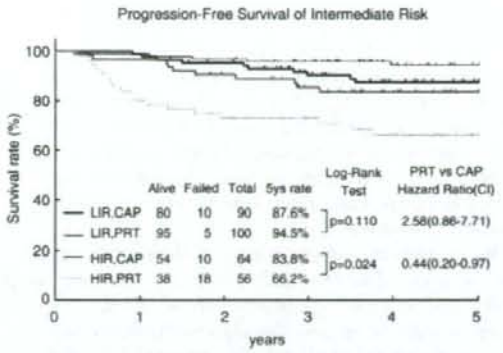

Fig. 4. Progression survival rates of intermediate risk in the PRT (pelvic radiation treatment) group and CAP (cyclophosphamide, doxorubicin, and cisplatin) group. Low–intermediate risk (LIR) was defined as stage IC patients under 70 years of age and with G1/2 endometrioid adenocarcinoma. High–intermediate risk (HIR) was defined as (1) stage IC patients over age 70 years or having G3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology) patients with deeper than 50% myometrial invasion in the corpus. Among LIR patients, PFS rates at 5 years in the PRT and CAP groups were not statistically different. However, among HIR patients, the CAP group had significantly higher PFS rate.

Outcome

Fig. 2 presents the PFS rates of all patients in both randomized treatment groups. Data for the two groups nearly overlap. PFS rate at 5 years was 83.5% in the PRT group and 81.8% in the CAP group. The hazard ratio was 1.07 (95% CI, 0.65–1.76; $P=0.726$).

Fig. 3 shows that the OS rates in both groups were also similar, with no statistical difference. The OS rate at 5 years was

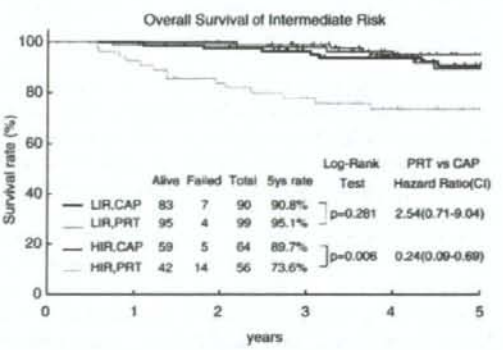

Fig. 5. Overall survival rates of intermediate risk in the PRT (pelvic radiation treatment) group and CAP (cyclophosphamide, doxorubicin, and cisplatin) group. Low–intermediate risk (LIR) was defined as stage IC patients under 70 years of age and with G1/2 endometrioid adenocarcinoma. High–intermediate risk (HIR) was defined as (1) stage IC patients over age 70 years or having G3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology) patients with deeper than 50% myometrial invasion in the corpus. Among LIR patients, OS rates at 5 years in the PRT and CAP groups were not statistically different. However, among HIR patients, the CAP group had significantly higher OS rate.

85.3% in the PRT group and 86.7% in the CAP group (log-rank test $P=0.462$). The hazard ratio was 0.72 (95% CI, 0.40–1.29; Cox proportion hazards model $P=0.268$).

Overall, 48 patients died, of whom 26 had been assigned to the PRT group and 22 to the CAP group. In the PRT group, 21 deaths were related to endometrial cancer, 1 death to another cancer, and 2 deaths to other diseases. In the CAP group, 13 deaths were related to endometrial cancer, 4 deaths to other cancers, and 4 deaths to other diseases.

We performed a subgroup analysis, defining the criteria for low- to intermediate-risk (LIR) and high- to intermediate-risk (HIR) subgroups. When LIR was defined as stage IC patients under 70 years of age and with G1/2 endometrioid adenocarcinoma, among 190 LIR patients, PFS rates at 5 years in the PRT and CAP groups were 94.5% and 87.6% respectively ($P=0.110$) (Fig. 4), and OS rates at 5 years in the PRT and CAP groups were 95.1% and 90.8% respectively ($P=0.281$) (Fig. 5). The HIR subgroup was defined as (1) stage IC patients over age 70 years or having G3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology) patients with deeper than 50% myometrial invasion in the corpus. Among these 120 patients, the CAP group had significantly higher PFS rate (83.8%) (hazard ratio 0.44, 95% CI, 0.20–0.97; $P=0.024$) (Fig. 4) and OS rate (89.7%) (hazard ratio 0.24, 95% CI, 0.09–0.69; $P=0.006$) (Fig. 5) versus the PRT group (66.2% and 73.6%, respectively).

We performed another analysis for high-risk group. For 75 cases in high-risk group, OS rates and PFS rates were not statistically different between PRT group and CAP group. The OS rate at 5 years was 75.8% in the PRT group and 71.1% in the CAP group (log-rank test $P=0.667$). The hazard ratio was 1.123 (95% CI, 0.42–3.04; $P=0.819$). The PFS rate at 5 years was 78.6% in the PRT group and 64.4% in the CAP group (log-rank test $P=0.169$). The hazard ratio was 1.847 (95% CI, 0.73–4.65; $P=0.193$).

Discussion

This study by the Japan Gynecologic Oncology Group is the first report of a randomized controlled study comparing adjuvant pelvic RT with chemotherapy for early-stage endometrial cancer with deeper than 50% myometrial invasion. We observed no statistically significant differences in survivals in the two regimens. We also found that adverse effects were not significantly increased in a platinum-based combined chemotherapy group, and we showed that chemotherapy significantly improved PFS and OS in HIR patients, versus pelvic radiation.

The eligibility criteria for this study were FIGO stage IC–IIIC endometrial carcinoma with deeper than 50% myometrial invasion. The majority (77.4%) of registered patients had stage IC or II lesions, and only 11.9% had stage IIIC lesions. We therefore believe that the efficacy of pelvic radiation and chemotherapy as adjuvant treatments for early-stage endometrial cancer was compared appropriately.

All patients had undergone a hysterectomy and bilateral adnexectomy, and pelvic lymphadenectomy and paraaortic lymphadenectomy were performed in 96.1% and 28.6% of patients respectively. Paraaortic lymphadenectomy was not performed when no paraaortic lymph nodes were palpable and no enlarged paraaortic lymph nodes were detected preoperatively by computed tomography. We therefore regard our surgical staging as appropriate. However, our eligibility criteria were somewhat heterogeneous for the inclusion of post-surgical stage IC, IIA, IIB, IIIA, IIIB, and IIIC lesions.

To verify the efficacy of chemotherapy in intermediate- and high-risk groups, a subgroup analysis is potentially important. Generally, prognostic risk factors have been classified as low, intermediate, or high risks using different criteria [2,3,6,8,14,15]. In these previous reports, stage IC was definitely classified as intermediate risk. Stage III and IV were usually classified as high-risk, locally advanced. The GOG defined stage IC and II, without inclusion of IIIA (positive cytology) as intermediate risk. GOG Study 99 [8] defined HIR as (1) G2/3 tumors with lymphovascular space invasion and outer-third myometrial invasion, (2) age of 50 years or greater in addition to any two factors listed above, or (3) age of at 70 years or greater with any risk factor listed above. FIGO stages IB, IC, and II (occult disease) were defined as LIR.

In our subgroup analysis an LIR group comprised stage IC patients under 70 years of age with G1/2 endometrioid adenocarcinoma. Our HIR group comprised (1) stage IC patients who were over 70 years of age or had G3 endometrioid adenocarcinoma and (2) stage II or IIIA (positive cytology) patients with deeper than 50% myometrial invasion in the corpus. Our high-risk group comprised other stage IIIA patients with factors other than a positive peritoneal cytology and stage IIIB and IIIC patients.

PFS and OS rates for the PRT and CAP groups were the same in the LIR subgroup. In the HIR subgroup, however, we found significantly higher PFS and OS rates in the CAP group versus the PRT group. Since patients with FIGO stage IIIA endometrial cancer only with positive washing cytology have a better prognosis [5,16], we included patients with positive washing cytology in the HIR group, along with stage II disease patients. However, we recognize that the validity of this subset analysis is limited. Demonstration of a true advantage of chemotherapy requires a large-scale randomized controlled trial with stratification for risk factors including age and tumor grade prior to randomization.

In the early 1990s, the CAP regimen was used as the standard chemotherapy for endometrial cancer and ovarian cancer in Japan. Most Japanese gynecologists adopted CAP as the standard adjuvant chemotherapy rather than AP. In our trial, the dosage of doxorubicin was lower than in other trials using AP, such as GOG study 107/122/177 (60 mg/m^2) and GOG study 184 (45 mg/m^2) [17–19]. Due to this relatively low dose, G3 and G4 adverse effects were rare (4.7%), and protocol compliance was very high (95.3%) in the CAP group. The number of CAP courses was relatively small (median: 3 courses). Thus, cisplatin-based chemotherapy may be a feasible alternative to adjuvant pelvic radiation therapy for patients with intermediate-risk endometrial cancers. However, validation of a true efficacy of adjuvant chemotherapy for early-stage endometrial cancer, especially for LIR patients, requires a randomized controlled trial of no-treatment versus chemotherapy.

In HIR patients, chemotherapy was superior to radiation therapy. In patients with low-risk and LIR endometrial cancer, most recurrence sites are vaginal or intrapelvic, making pelvic

radiation or vaginal vault brachytherapy effective for reducing the loco-regional recurrence rate [7,20,21]. The reason for the superiority of chemotherapy in HIR patients is partly that extrapelvic recurrence cannot be prevented by pelvic radiation, as reported by Creutzberg et al. [7,14] and other investigators [6,8,20–22]. In this study, the incidence of recurrences at vaginal wall was lower in PRT group compared with CAP group, however, there was no significant difference in the incidences of extrapelvic recurrence between the PRT and CAP groups. In Japan, different types of hysterectomy, such as simple hysterectomy, extended hysterectomy (type II modified radical hysterectomy), and radical hysterectomy (type III), were performed in each institution. However, radical hysterectomy is selected only for those patients with macroscopically apparent cervical involvement in most of JGOG institutions. In addition, in this study, we included simple hysterectomy with a small amount of removal of vaginal cuff into extended hysterectomy. For this reason, the percentage of radical hysterectomy and modified radical hysterectomy is not thought to be high, and the influence of surgical procedure over the incidence of vaginal recurrence may be limited in our study.

In our study, we performed pelvic lymphadenectomy in 96% cases. Local recurrence rate was 2.6% in the cases of LIR and HIR with pelvic radiation treatment. Local recurrence rate in the radiotherapy group was 3.9% in PORTEC study [2,7] with no pelvic lymphadenectomy and 1.6% at 2 years in GOG study 99 [8] with selective pelvic and paraaortic lymphadenectomy. It seems that there is a tendency of low local recurrence rate in the intermediate-risk patients with pelvic lymphadenectomy in pelvic radiation treatment, however, we cannot simply compare those data as there are differences in the definition of intermediate risk.

The superiority of chemotherapy in HIR patients must also be considered in relation to the conclusions of GOG study 122 on advanced-stage endometrial cancer [4]. In stage III/IV endometrial cancer, AP chemotherapy was superior to whole-abdominal radiation as a therapeutic modality. Further investigation of the use of chemotherapeutic agents in patients with HIR endometrial cancer or high-risk endometrial cancer is needed. The JGOG has just finished accruing for a comparative phase II trial comparing three combined chemotherapy regimens (paclitaxel and carboplatin vs. docetaxel and cisplatin vs. docetaxel and carboplatin). These results are forthcoming.

In patients with early-stage endometrial cancer and deeper than 50% myometrial invasion, adjuvant platinum-based combined chemotherapy and pelvic radiation therapy each led to a good prognosis. In patients with HIR endometrial cancers, the aforementioned chemotherapy improved the prognosis significantly compared to pelvic radiation. Additional phase III randomized controlled trials are required to establish a standard adjuvant chemotherapy regimen including anthracyclin, taxane or platinum for intermediate-risk or high-risk endometrial cancer.

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The participating institutions for all studies described in this report are listed in Appendix A.

Appendix A

The following member institutions participated in this study: Akita City Hospital, Aomori Prefectural Central Hospital, Asahi General Hospital, Asahikawa Medical College, Asahikawa Red Cross Hospital, Chiba Kaihin General Hospital, Chiba Social Insurance Hospital, Chiba University, Daiyukai General Hospital, Dokkyo University School of Medicine, Fujita Health University, Gifu Prefectural Tajimi Hospital, Gifu University, Hakodate Goryokaku Hospital, Hamamatsu Medical Center, Himeji Red Cross Hospital, Hiroshima University, Hyogo Medical Center for Adults, Hyogo Prefectural Awaji Hospital, Hyogo Prefectural Tsukaguchi Hospital, Iwate Medical University, Iwate Prefectural Kuji Hospital, JA Kochi Hospital, Japanese Red Cross Akita Hospital, Jiaikai Imamura Hospital, Juntendo University Urayasu Hospital, Kagawa University, Kanazawa Medical University, Kanazawa University, Kanebo Memorial Hospital, Kansai Medical University, Kanto Central Hospital of the Mutual Aid Association of Public School Teachers, Kawasaki Medical School, Keio University, Keiyu Hospital, Kinki University, Kitasato University, Kobe University, Kokura Memorial Hospital, Kumamoto City Hospital, Kumamoto University, Kurashiki Central Hospital, Kurume University, Kyosai Tachikawa Hospital, Kyoto Prefectural University of Medicine, Kyoto Second Red Cross Hospital, Kyoundo Hospital, Kyushu University (Medical Institute of Bioregulation), Miyazaki Prefectural Nichinan Hospital, Nagaoka Red Cross Hospital, Nagasaki University, Nagoya Daini Red Cross Hospital, Nantan General Hospital, Nara Medical University, Nara Prefectural Hospital, National Hospital Organization Hokkaido Cancer Center, National Hospital Organization Iwakuni Clinical Center, National Hospital Organization Matsumoto National Hospital, National Hospital Organization Saitama National Hospital, National Hospital Organization Sendai Medical Center, National Hospital Organization Tokyo Medical Center, Ogaki Municipal Hospital, Ohta General Hospital (Nishinouchi Hospital), Oita University, Okayama Red Cross General Hospital, Okayama Saiseikai General Hospital, Osaka City General Hospital, Osaka General Medical Center, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Medical College, Osaka Police Hospital, Saga University, Saiseikai Central Hospital, Saiseikai Utsunomiya Hospital, Saitama Shakai-Hoken Hospital, Sapporo Medical University, Sapporo-Kosei General Hospital, Sasebo City General Hospital, Seirei Yokohama Hospital, Senboku Kumiai General Hospital, Shimane Prefectural Central Hospital, Shimane University, Shizuoka General Hospital, Shonai Hospital, Showa University, Showa University Fujigaoka Hospital, Social Insurance Tagawa Hospital, St. Marianna University School of Medicine, St. Marianna University School of Medicine Yokohama City Seibu Hospital, Takamatsu Red Cross Hospital, Teikyo University Ichihara Hospital, Tohoku University, Tokyo Medical and Dental University, Tokyo Medical University, Tokyo Women's Medical University, Tosei General Hospital, Tottori

Municipal Hospital, Tottori University, Toyama Medical and Pharmaceutical University, Toyama Prefectural Central Hospital, University of Tokushima, Yamagata University, Yamaguchi Grand Medical Center.

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