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Survival outcomes of adjuvant radiotherapy and chemotherapy in women with stage I serous papillary and clear cell carcinoma of the endometrium: a Korean multicenter study

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ABSTRACT

Objective: To compare the survival outcomes of adjuvant radiotherapy and chemotherapy in women with uterine-confined endometrial cancer with uterine papillary serous carcinoma (UPSC) or clear cell carcinoma (CCC).


Methods: Medical records of 80 women who underwent surgical staging for endometrial cancer were retrospectively reviewed. Stage I UPSC and CCC were pathologically confirmed after surgery. Survival outcomes were compared between the adjuvant radiotherapy and chemotherapy groups.

Results: Fifty-four (67.5%) and 26 (32.5%) women had UPSC and CCC, respectively. Adjuvant therapy was administered to 59/80 (73.8%) women (25 radiotherapy and 34 chemotherapy). High preoperative serum cancer antigen-125 level (25.1±20.2 vs. 11.5±6.5 IU/mL, $p < 0.001$), open surgery (71.2% vs. 28.6%, $p = 0.001$), myometrial invasion (MI) $\geq 1/2$ (33.9% vs. 0, $p = 0.002$), and lymphovascular space invasion (LVSI; 28.8% vs. 4.8%, $p = 0.023$) were frequent in women who received adjuvant therapy compared to those who did not. However, the histologic type, MI $\geq 1/2$, and LVSI did not differ between women who received adjuvant radiotherapy and those who received chemotherapy. The 5-year progression-free survival (78.9% vs. 80.1%, $p > 0.999$) and overall survival (77.5% vs. 87.8%, $p = 0.373$) rates were similar between the groups. Neither radiotherapy (hazard ratio [HR]=1.810; 95% confidence interval [CI]=0.297–11.027; $p = 0.520$) nor chemotherapy (HR=1.638; 95% CI=0.288–9.321; $p = 0.578$) after surgery was independently associated with disease recurrence.

Conclusion: Our findings showed similar survival outcomes for adjuvant radiotherapy and chemotherapy in stage I UPSC and CCC of the endometrium. Further large study with analysis stratified by MI or LVSI is required.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

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INTRODUCTION

Endometrial cancer is the most common malignancies of the female reproductive tract in the United States, with over 65,050 cases estimated to be diagnosed in 2016; its incidence exceeds those of cervical, ovarian and vaginal cancers combined [1]. Although many cases present with early-stage disease, there are 10,470 total annual deaths in the United States from this disease. Endometrial cancers have been classified into type I and type II cancers based on their risk factors and prognosis. Type I comprises 80% of all endometrial cancers and endometrioid endometrial carcinoma (EEC) accounts for 85% of type I cases. While type I endometrial cancer generally has a favorable prognosis, type II disease, which includes the more aggressive histologies of uterine papillary serous carcinoma (UPSC), and clear cell carcinoma (CCC), portends a poorer prognosis [2-4]. Although UPSC and CCC represent 10% and 3% of endometrial cancer cases, they account for 39% and 8% of disease-related deaths, respectively [5].

Approximately, 10% to 15% of women with endometrial cancer will experience recurrence, even in early-stage disease [6,7]. To reduce the recurrence rate, adjuvant radiotherapy and/or chemotherapy have been applied after surgery; however, a definite standard of care has not yet been established worldwide. Pelvic external beam radiotherapy (EBRT) has been performed as an adjuvant treatment for women with high-risk endometrial cancer for many decades, although there is a paucity of evidence on the improvement of overall survival (OS) [7-9]. Until now, almost all large-scale studies have reported the prognostic impact of adjuvant therapy for all of intermediate-to-high risk endometrial cancers (International Federation of Gynecology and Obstetrics [FIGO] stage IA grade 3 EEC, FIGO stage IB [grade 1-3] EEC, and all stages with non-endometrioid type). Because UPSC and CCC are very rare to study separately even for all stages, there is a lack of evidence for adjuvant therapy in early-stage disease. Therefore, we aimed to evaluate the survival outcomes of adjuvant therapy and radiotherapy or chemotherapy alone in uterine-confined endometrial cancer of UPSC and CCC.

MATERIALS AND METHODS

1. Patients

The study cohort was retrospectively recruited from eight institutions. The study protocol was revised and accepted by each institutional ethics committee. We recruited a total of 80 women diagnosed with FIGO stage I endometrial cancer after primary staging surgery between January 2001 and May 2017. All eligible women were pathologically confirmed as having UPSC or CCC after surgery. No women who had undergone prior systemic chemotherapy or radiotherapy for another malignancy were included in the study population.

The staging surgery included total hysterectomy and bilateral salpingo-oophorectomy; peritoneal washing cytology and omentectomy were left to the surgeon's discretion. Pelvic and para-aortic lymph node dissections were also omitted at the discretion of the surgeon if there was no evidence of lymph node metastasis in preoperative computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography-computed tomography (PET-CT) scans. Lymph nodes with a short diameter ≥ 1.0 cm in imaging were considered

significantly enlarged. Surgical specimens were reviewed by pathologists specializing in gynecologic pathology who were blinded to the patients' outcomes. We obtained the final pathologic results, which included the histologic type and grade, FIGO stage, lymphovascular space invasion (LVSI), and the presence of malignant cells in peritoneal washing cytology.

In accordance with the clinical policies in each participating institution, adjuvant therapy was administered after surgery to patients whose final pathologic results indicated an intermediate or high risk. Of 80 women, 59 (73.8%) received adjuvant therapy after surgery: 25 radiotherapy and 34 chemotherapy. The radiotherapy included concurrent chemoradiation with a radiosensitizing agent. We excluded five women who received sequential chemoradiation, radiotherapy followed by chemotherapy (n=3) or its reverse (n=2) from the analysis.

2. Statistical analysis

Five-year progression-free survival (PFS) and OS rates were compared using the Kaplan-Meier method. Survival time was counted from the date of surgery until recurrence or death and compared between the two adjuvant therapy method groups by log-rank tests. We classified recurrence as local, regional, or distant. Recurrences limited to the vaginal vault were defined as local metastasis; recurrences beyond the vaginal vault but limited to the pelvic region were defined as regional metastasis; and recurrences beyond the pelvis, the extraperitoneal cavity, and outside the abdominal cavity were defined as distant metastasis.

Student's t-test and χ^2 test were used to examine continuous and categorical variables, respectively. For corresponding non-parametric statistics, Mann-Whitney U and Fisher's exact tests were used, respectively. Logistic regression was used to identify the clinicopathological factors associated with disease recurrence. Variables with $p \leq 0.25$ were included in the multivariate analysis, and $p < 0.05$ was considered to be significant. IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

RESULTS

1. Patient characteristics

The median age at diagnosis was 63 years (range, 41–85) and the median follow-up period was 32 months (range, 1–143) in the study population. Comparison of the baseline characteristics between the women who underwent adjuvant therapy after surgery and those who did not are shown in **Table 1**. The mean serum level of cancer antigen (CA)-125 at diagnosis was higher in women with adjuvant therapy than that in those without (25.1 ± 20.2 vs. 11.5 ± 6.5 IU/mL, $p < 0.001$). Lymph node involvement on preoperative CT or MRI scan were suspected in 4 women in total study population, however, it was not different between the women without adjuvant therapy and with adjuvant therapy (1 [4.8%] vs. 3 [5.1%], $p > 0.999$).

The staging surgery by open approach was frequently performed in women with adjuvant therapy (42 [71.2%] vs. 6 [28.6%], $p = 0.001$). However, peritoneal washing cytology (16 [76.2%] vs. 52 [88.1%], $p = 0.188$), omentectomy (8 [38.1%] vs. 33 [55.9%], $p = 0.160$), pelvic (18 [85.7%] vs. 48 [81.4%], $p = 0.652$) and para-aortic lymph node dissection (12 [57.1%] vs. 34 [57.6%], $p = 0.969$) were similarly conducted between women with and without adjuvant therapy.

After surgery, 54 (67.5%) and 26 (32.5%) women were pathologically confirmed as having UPSC and CCC, respectively. The proportions of women with adjuvant therapy did not differ

Table 1. Patient characteristics (n=80)

Parameters	No adjuvant therapy (n=21)	Adjuvant therapy (n=59)	p
Age (yr)	63.3±9.4	63.2±7.5	0.968
Body mass index (kg/m ²)	24.9±3.8	25.0±3.5	0.918
Preoperative evaluation			
Serum CA-125 level (IU/mL)	11.5±6.5	25.1±20.2	<0.001
Endometrial biopsy (n=74)			0.829
Endometrioid	4 (20.0)	10 (18.5)	
Serous papillary	13 (65.0)	31 (57.4)	
Clear cell	0	8 (14.8)	
Other	3 (15.0)	5 (9.3)	
LN involvement on CT or MRI scan			>0.999
No	20 (100.0)	56 (94.9)	
Yes	1 (4.8)	3 (5.1)	
Operation details			
Approach			0.001
Open	6 (28.6)	42 (71.2)	
Laparoscopic	15 (71.4)	17 (28.8)	
WC in pelvic cavity			0.188
No	5 (23.8)	7 (11.9)	
Yes	16 (76.2)	52 (88.1)	
Omentectomy			0.160
No	13 (61.9)	26 (44.1)	
Yes	8 (38.1)	33 (55.9)	
Pelvic LN dissection			0.652
No	3 (14.3)	11 (18.6)	
Yes	18 (85.7)	48 (81.4)	
Retrieved node (No.)	15.3±8.4	17.9±10.4	0.342
Para-aortic LN dissection			0.969
No	9 (42.9)	25 (42.4)	
Yes	12 (57.1)	34 (57.6)	
Retrieved node (No.)	5.3±5.8	7.7±8.4	0.287
Pathological results			
Histology			0.924
Serous papillary	14 (66.7)	40 (67.8)	
Clear cell	7 (33.3)	19 (32.2)	
MI ≥1/2			0.002
No	21 (100.0)	39 (66.1)	
Yes	0	20 (33.9)	
LVSI			0.023
No	20 (95.2)	42 (71.2)	
Yes	1 (4.8)	17 (28.8)	
Malignant cells in WC (n=68)			>0.999
No	16 (100.0)	49 (94.2)	
Yes	0	3 (5.8)	

The values are presented as the median (range) or number (%), unless otherwise indicated.

CA-125, cancer antigen-125; CT, computed tomography; LN, lymph node; LVSI, lymphovascular space invasion; MI, myometrial invasion; MRI, magnetic resonance imaging; WC, washing cytology.

between the women who had UPSC and CCC (40/54 [74.1%] vs. 19/26 [73.1%], $p=0.924$). Instead, myometrial invasion (MI) $\geq 1/2$ (20 [33.9%] vs. 0, $p=0.002$) and LVSI (17 [28.8%] vs. 1 [4.8%], $p=0.023$) were more common in women who underwent adjuvant therapy than in those who did not.

2. Clinical course by adjuvant therapy methods: radiotherapy vs. chemotherapy

The clinical courses after surgery are described in **Table 2**. A total of 25 and 34 women received radiotherapy and chemotherapy after surgery, respectively. The mean age (63.8±8.8 vs. 62.8±6.5, $p=0.6314$), body mass index (24.6±4.2 vs. 25.3±2.9 kg/m², $p=0.495$), and

Table 2. Clinical course by adjuvant therapy methods

Parameters	Radiotherapy (n=25)	Chemotherapy (n=34)	p
Age (yr)	63.8±8.8	62.8±6.5	0.631
Body mass index (kg/m ²)	24.6±4.2	25.3±2.9	0.495
Serum CA-125 level (IU/mL)	27.0±22.6	23.7±18.4	0.543
Postoperative histology			0.085
Serous papillary	20 (80.0)	20 (58.8)	
Clear cell	5 (20.0)	14 (41.2)	
Concordance between preoperative and postoperative histologic results			0.549
No	13 (52.0)	15 (44.1)	
Yes	12 (48.0)	19 (55.9)	
MI ≥1/2			0.160
No	14 (56.0)	25 (73.5)	
Yes	11 (44.0)	9 (26.5)	
LVSI			0.200
No	20 (80.0)	22 (64.7)	
Yes	5 (20.0)	12 (35.3)	
Malignant cells in WC (n=52)			>0.999
No	22 (95.7)	27 (93.1)	
Yes	1 (4.3)	2 (6.9)	
Approach of radiotherapy			-
Brachytherapy	2 (8.0)	-	
EBRT	23 (92.0)	-	
EBRT with brachytherapy	0	-	
Concurrent chemotherapy with cisplatin			-
No	12 (48.0)	-	
Yes	13 (52.0)	-	
Platinum based chemotherapy			-
No	-	1 (2.9)	
Yes	-	33 (97.1)	
Cycles of chemotherapy (cycles)			-
<6	-	17 (50.0)	
≥6	-	17 (50.0)	
Recurrence			0.891
No	21 (84.0)	29 (85.3)	
Yes	4 (16.0)	5 (14.7)	
Regional	0	3	
Distant	4	2	
Mean time to recurrence	18.0±11.2	13.8±3.7	0.518
Death			0.386
No	21 (84.0)	32 (94.1)	
Yes	4 (16.0)	2 (5.9)	
Mean time to death	23.0±12.5	35.6±22.6	0.354

The values are presented as the median (range) or number (%), unless otherwise indicated.

CA-125, cancer antigen-125; EBRT, external beam radiation therapy; LVSI, lymphovascular space invasion; MI, myometrial invasion; WC, washing cytology.

preoperative serum cancer antigen-125 level (27.0±22.6 vs. 23.7±18.4 IU/mL, p=0.543) did not differ significantly between the women who received radiotherapy and those who received chemotherapy. Radiotherapy was mainly performed in women with UPSC, whereas chemotherapy was mainly performed in women with CCC. However, the difference was not statistically significant (p=0.160). In addition, MI ≥1/2 (11 [44.0%] vs. 9 [26.5%], p=0.160), LVSI (5 [20.0%] vs. 12 [35.3%], p=0.200), and malignant cells in washing cytology (1 [4.3%] vs. 2 [6.9%], p>0.999) were also similar between groups.

Almost all women (23/25 [92.0%]) with radiotherapy underwent EBRT, and no one received vaginal brachytherapy combined with EBRT simultaneously. Concurrent chemoradiation

with cisplatin, a radiosensitizing agent, was performed in 13/23 (52.0%) women. Almost all chemotherapy was based on platinum regimens and was applied for at six least cycles in 17/34 (50.0%) women. Recurrence was diagnosed in four (16.0%) and five (14.7%) women with radiotherapy and chemotherapy, respectively ($p=0.891$). There was no recurrence in two women with brachytherapy. There was no significant difference in recurrence rates between the women who received radiotherapy without and with radiosensitizer (3 [25.0%] vs. 1 [7.7%], $p=0.238$). Notably, all recurrence in the four women with radiotherapy was distant metastasis. In contrast, three and two women who received chemotherapy had regional and distant metastasis, respectively, at the diagnosis of recurrence. The mean times to recurrence also did not differ significantly (18.0 ± 11.2 vs. 13.8 ± 3.7 months, $p=0.518$). In addition, disease-related deaths occurred similarly in the two groups (4 [16.0%] vs. 2 [5.9%], $p=0.386$).

Fig. 1 presents the 5-year PFS rates. The rates were significantly inferior in women with MI $\geq 1/2$ (61.8% vs. 89.0%, $p=0.010$) and LVSI (57.4% vs. 90.1%, $p=0.006$). However, there was no significant difference between the women with radiotherapy or chemotherapy after surgery (78.9% vs. 80.1%, $p>0.999$). In contrast, only MI $\geq 1/2$ was associated with a significantly

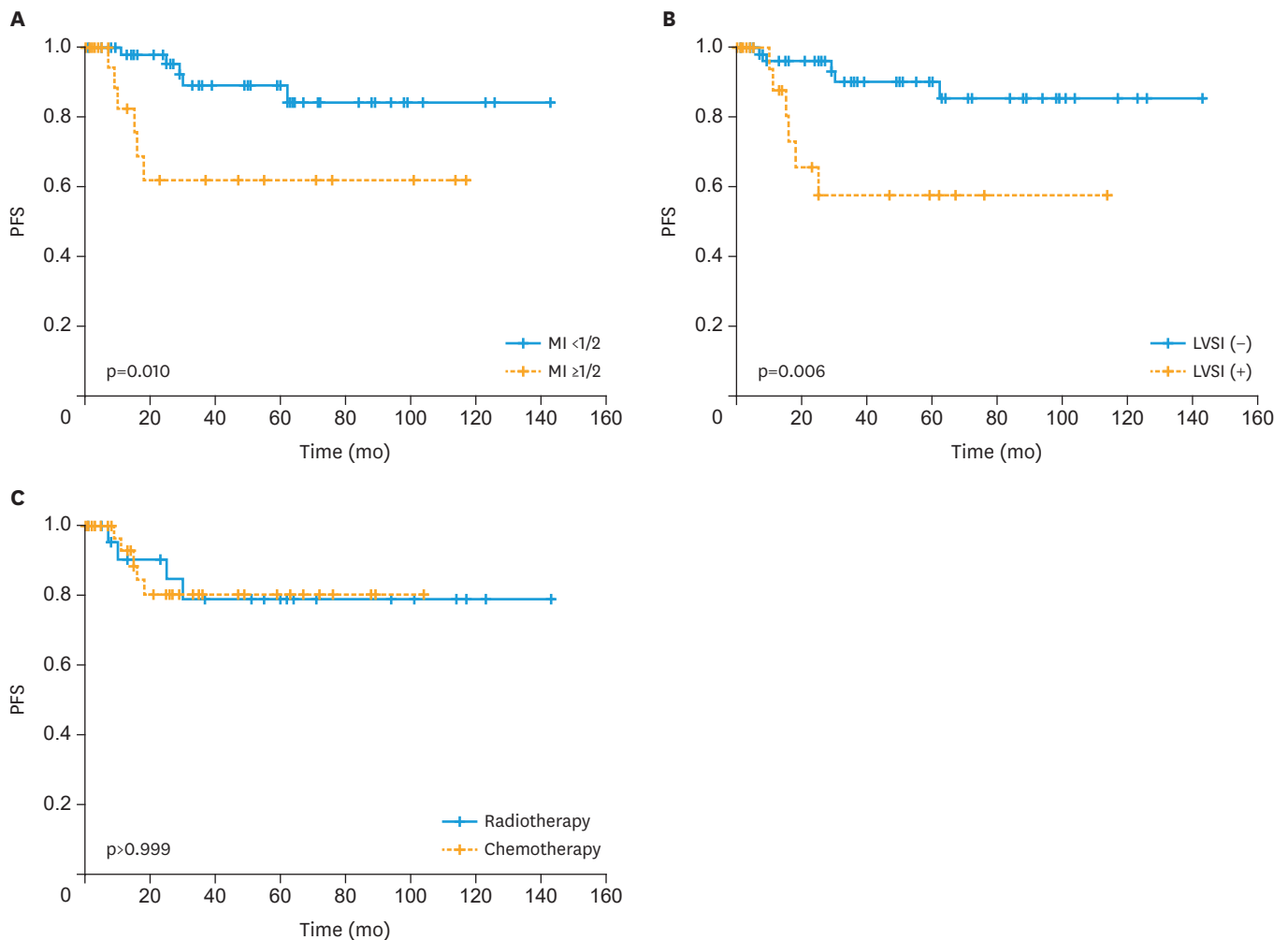


Fig. 1. Kaplan-Meier curves of PFS rates by (A) MI (5-year PFS; 61.8% vs. 89.0%, $p=0.010$), (B) lymphovascular invasion (5-year PFS; 57.4% vs. 90.1%, $p=0.006$), and (C) adjuvant therapy method (5-year PFS; radiotherapy vs. chemotherapy; 78.9% vs. 80.1%, $p>0.999$). LVSI, lymphovascular space invasion; MI, myometrial invasion; PFS, progression-free survival.

Adjuvant therapy in stage I UPSC and CCC

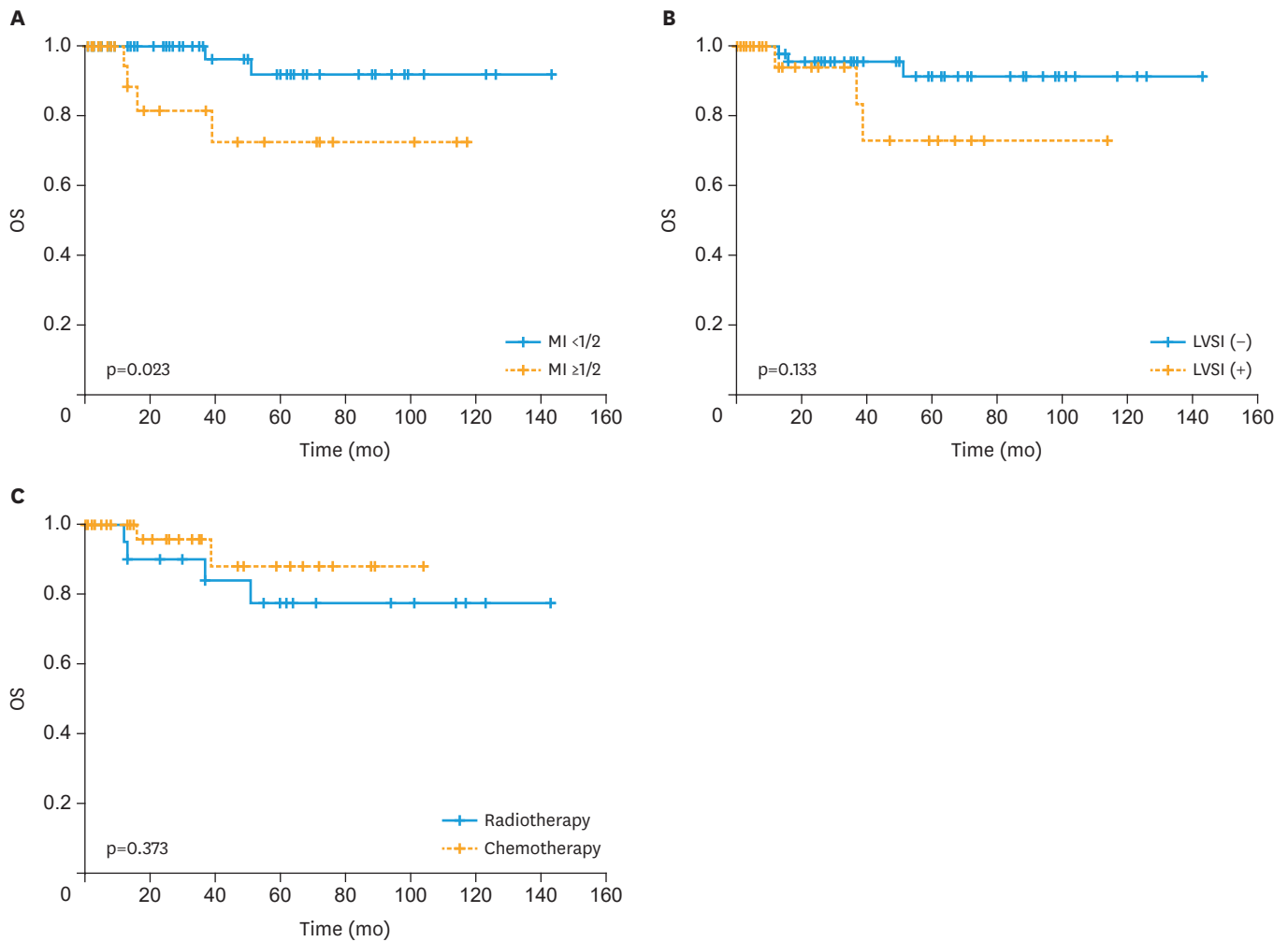


Fig. 2. Kaplan-Meier curves of OS rates by (A) MI (5-year OS; 72.4% vs. 91.8%, $p=0.023$), (B) lymphovascular invasion (5-year OS; 91.3% vs. 72.9%, $p=0.133$), and (C) adjuvant therapy method (5-year OS; radiotherapy vs. chemotherapy; 77.5% vs. 87.8%, $p=0.373$). LVSI, lymphovascular space invasion; MI, myometrial invasion; OS, overall survival.

inferior 5-year OS rate (72.4% vs. 91.8%, $p=0.023$) (**Fig. 2**). LVSI (91.3% vs. 72.9%, $p=0.133$) and adjuvant therapy methods (77.5% vs. 87.8%, $p=0.373$) did not affect the 5-year OS rates. In addition, survival curves in women with radiotherapy and chemotherapy are presented in stratified groups by LVSI or MI (**Supplementary Figs. 1 and 2**). There is no difference in PFS and OS according to the adjuvant therapy.

3. Clinicopathologic factors associated with recurrence

Table 3 shows the results of univariate and multivariate analyses of the risk factors for recurrence. In univariate analysis, MI $\ge 1/2$ (hazard ratio [HR]=1.714; 95% confidence interval [CI]=1.254–17.717; $p=0.022$) and LVSI (HR=5.700; 95% CI=1.492–21.772; $p=0.011$) were significantly associated with recurrence. However, neither radiotherapy (HR=1.810; 95% CI=0.297–11.027; $p=0.520$) nor chemotherapy (HR=1.638; 95% CI=0.288–9.321; $p=0.578$) was related to recurrence. Multivariate analysis revealed no independent risk factor for predicting recurrence.

Table 3. Univariate and multivariate analysis for predicting the recurrence in the study population

Characteristics	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Age >59 yr	1.333 (0.323–5.506)	0.691	-	-
Serum CA-125 level >35 IU/mL	1.350 (0.318–5.726)	0.684	-	-
Clear cell histology	0.417 (0.083–2.085)	0.287	-	-
Lymphadenectomy	2.321 (0.272–19.777)	0.441	-	-
MI \geq 1/2	1.714 (1.254–17.717)	0.022	3.179 (0.770–13.119)	0.110
LVSI	5.700 (1.492–21.772)	0.011	4.073 (0.985–16.842)	0.052
Malignant cells in WC	3.562 (0.289–43.921)	0.322	-	-
No adjuvant therapy			-	-
Radiotherapy	1.810 (0.297–11.027)	0.520		
Chemotherapy	1.638 (0.288–9.321)	0.578		

CA-125, cancer antigen-125; CI, confidence interval; LVSI, lymphovascular space invasion; MI, myometrial invasion; HR, hazard ratio; WC, washing cytology.

DISCUSSION

Presently, adjuvant radiotherapy is generally considered standard care after staging surgery for intermediate-to-high risk endometrial cancer. The Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 trial showed that adjuvant radiotherapy reduces locoregional recurrence in women with early-stage endometrial cancer, including grade 1 with MI \geq 1/2, grade 2 with any invasion, or grade 3 with MI <1/2 [7]. The 5-year locoregional recurrence rate was significantly lower in women with adjuvant radiotherapy than that in women without adjuvant therapy (4% vs. 14%, $p < 0.001$) but there was no difference in OS rates (81% vs. 85%, $p = 0.031$). The Gynecologic Oncology Group (GOG)-99 study also showed that adjuvant radiotherapy decreases the 2-year cumulative recurrence rate in early-stage intermediate risk endometrial cancer (3% vs. 12%, $p = 0.007$) [9]. However, these two fundamental randomized trials mainly included women with endometrial cancer women with endometrioid cell type and did not show stratified results by histologic type. Of 714 women with endometrial cancer in the PORTEC-1 trial, only one and four women were diagnosed with UPSC and CCC, respectively. There was no confirmed UPSC and CCC in the GOG-99 study.

While recurrence in early-stage EEC generally occurs in the vagina or pelvis, the majority of UPSC and CCC patients relapse in multiple sites beyond the pelvis [10]. Furthermore, UPSC and CCC have a worse prognosis resulting from the different histologic patterns compared to that of EEC. Hendrickson et al. [11] showed early that stage 1 UPSC has a poor PFS compared to those of non-papillary pathologic grade 2 or 3 stage I disease ($p < 0.001$). Similarly, Hamilton et al. [5] reported poorer 5-year PFS rates of 55% and 68% in women with UPSC and CCC, respectively, compared to 77% in women with grade 3 EEC. Regarding its aggressive behavior, frequent *p53* gene mutations and *HER-2/neu* gene amplification have been demonstrated as characteristic molecular genetic profiles of UPSC and CCC [12,13]. Psammoma bodies with a prominent papillary architecture in uterine specimens resemble serous papillary ovarian carcinoma; therefore, it may be related to the clinical features of UPSC [11]. CCC of the endometrium is a rare, but also aggressive variant [14,15]. However, there are conflicting studies on the prognosis of UPSC and CCC [3,16-18]. Fader et al. [19] suggested that an increased UPSC percentage in uterine specimens is not relevant to high recurrence rates and poor survival outcomes; therefore, adjuvant therapy may not provide any additional benefit to women with UPSC. Creasman et al. [17] also reported 5-year UPSC and CCC survival rates of 72% and 81%, respectively, which were not inferior to the 76% rate for

grade 3 EEC. They suggested that radiotherapy after surgery for stage I UPSC and CCC may not significantly improve survival.

Because the pattern and frequency of recurrence in women with UPSC and CCC differ from those of EEC, authors have suggested that adjuvant therapy have to be more systemically applied, even in early-stage disease. Until now, few studies have assessed the prognostic impact of adjuvant chemotherapy in women with early-stage UPSC and CCC. Dietrich et al. [20] showed that paclitaxel/carboplatin chemotherapy after surgery is effective in reducing recurrence in stage I UPSC. Among 21 women with stage I UPSC treated with a combination of carboplatin (AUC 6 [n=16], AUC 5 [n=5]), and paclitaxel (135 mg/m² [n=2], 150 mg/m² [n=1], and 175 mg/m² [n=18]), only one patient was diagnosed vaginal recurrence at 4 months after adjuvant chemotherapy of three cycles during the follow-up period (mean 41 months). In women with stage II UPSC, Fader et al. [21] reported recurrence rates of 50% (5/10), 50% (13/26), and 10.5% (2/19) in women who received no adjuvant therapy, radiotherapy, and chemotherapy ± radiotherapy, respectively. However, these 2 retrospective studies are based on small populations and the survival outcomes were not directly compared between women who received chemotherapy and those who received radiotherapy. Meanwhile, in a national cancer data-based study by Xu et al. [22], neither radiotherapy (HR=1.02; 95% CI=0.70–1.48; p=0.936) nor chemotherapy (HR=1.15; 95% CI=0.60–2.18; p=0.678) improved the survival outcomes compared to that of observation in 1,672 women with stage I–II CCC. Therefore, they suggested that radiotherapy and chemotherapy should be combined to minimize both locoregional and distant metastasis. Hong et al. [23] also reported a national cancer data-based study in recent. In 5,432 women with stage I UPSC, brachytherapy (HR=0.71; 95% CI=0.59–0.86; p<0.001) and chemotherapy (HR=0.92; 95% CI=0.80–1.07; p=0.26) were associated with increased survival, however, not in CCC. It is still unclear that additional chemotherapy with radiotherapy improves the survival outcomes in early-stage UPSC or CCC, contrary to their effects in advanced disease [24,25].

This study evaluated the survival outcomes in women diagnosed with stage I UPSC and CCC. The 5-year PFS (78.9% vs. 80.1%, p>0.999) and OS (77.5% vs. 87.8%, p=0.373) did not differ between the groups who received radiotherapy or chemotherapy alone. However, this study has some limitations due to its retrospective nature. Firstly, although we showed the stratified results of sub-analysis by LVSI or deep MI or LVSI (**Supplementary Figs. 1 and 2**), its statistical power is weak because of the small population size. While it appears that any adjuvant therapy was ineffective in improving survival outcomes in this study population (**Table 3**), there is a strong possibility of a selection bias. Women who received any adjuvant therapy, radiotherapy or chemotherapy, more often had MI ≥1/2 (33.9% vs. 0%, p=0.002) and LVSI (28.8% vs. 4.8%, p=0.023) and these two factors were significantly associated with recurrence (**Table 3**). Secondly, the therapeutic protocols of radiotherapy or chemotherapy were not homogenized across the eight institutions. Only a half of the women who received radiotherapy received concurrent cisplatin. Similarly, women who received chemotherapy underwent various treatment cycles.

Our findings showed that the survival outcomes between women who received radiotherapy or chemotherapy after staging surgery were similar in stage I UPSC and CCC of endometrial cancer. In addition, chemotherapy did not significantly decrease regional or distant metastases, as expected. Significant findings might be revealed in stratified analysis of women with deep MI or LVSI; therefore, further studies with larger populations are required.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1

Kaplan-Meier curves of PFS rates by adjuvant therapy in stratified groups by LVSI and MI.

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Supplementary Fig. 2

Kaplan-Meier curves of OS rates by adjuvant therapy in stratified groups by LVSI and MI.

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