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CLINICAL ARTICLE

Gynecology

Prognosis of bulky pTIIB cervical cancer treated by radical hysterectomy comparing adenocarcinoma with squamous cell carcinoma using propensity score matching

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Abstract

Objective: To investigate whether radical hysterectomy (RAH) can effectively treat true Stage IIB (pTIIB) cervical adenocarcinoma (AC) because FIGO (clinical) Stage IIB cervical cancer is rarely treated with RAH and radiotherapy has unfavorable effects on AC.

Methods: We retrospectively analyzed data for 82 patients with Stage pTIIB cervical cancer who underwent RAH at our institution between January 1997 and December 2017. The end points were disease-free survival (DFS) and overall survival (OS) among squamous cell carcinoma (SCC) (n = 60) and AC (n = 22) patients. Kaplan–Meier survival analysis with and without propensity score matching was conducted to identify the impact of RAH.

Results: Para-aortic lymph node metastasis and tumor diameter were significant factors for recurrence, and adjuvant chemotherapy prevented recurrence on multivariate analysis. After propensity score matching, there was no significant difference in DFS and OS between the groups. Five-year DFS and OS of the SCC group were 0.505 (95% confidence interval [CI] 0.268–0.702) and 0.619 (95% CI 0.351–0.803), respectively, and those of the AC group were 0.444 (95% CI 0.232–0.638) and 0.602 (95% CI 0.351–0.782), respectively.

Conclusion: Bulky Stage pTIIB cervical cancer is hard to cure, but RAH plus adjuvant therapy might be an option for radio-resistant pTIIB cervical AC.

KEYWORDS

Adenocarcinoma, Cervical cancer, Concurrent chemoradiotherapy, Propensity score matching, Radical hysterectomy, Squamous cell carcinoma

1 | INTRODUCTION

Most women with Stage IIB cervical cancer are treated with primary concurrent chemoradiotherapy (CCRT). Radical abdominal hysterectomy (RAH) for this disease is not performed in most countries because the late complication rate of surgery for grade 3/4 cervical cancer is greater than that for primary CCRT.[1] There are different opinions regarding the treatment response of the histological

types of cervical cancer to radiotherapy (RT).[2-5] However, a large study of 64 531 patients with squamous cell carcinoma (SCC) and 7265 with adenocarcinoma (AC) of the uterine cervix revealed that patients with AC were more likely to die than those with SCC, both before and after the era in which concurrent chemotherapy was added to primary RT.[6]

In Japan, class III RAH including lymphadenectomy remains the standard treatment for Stage IB1 to IIB cervical cancer, regardless of the histology.[7-9] RT of cervical AC seems to have a less favorable effect than that for SCC,[4-6] and Japanese women with cervical AC tend to undergo RAH. The National Comprehensive Cancer Network guidelines recommend primary CCRT to treat Stage IIB cervical cancer, regardless of the histology.[10] However, there is little information regarding the survival of patients with Stage IIB AC after primary RT/CCRT. Recently, a study on the treatment options for cervical AC reported that curative surgery improved survival in cervical AC at FIGO (the International Federation of Gynecology and Obstetrics) clinical Stage IIB when curative surgery and curative definitive CCRT were compared.[11] It seems significant to investigate whether RAH is useful to treat Stage IIB cervical AC. In the present study, we used propensity score matching to compare the survival of patients with bulky Stage pTIIB cervical AC or SCC treated with RAH. We focused on surgical cases with true Stage IIB (Stage pTIIB) cancer because FIGO clinical Stage IIB disease included cases without parametrial involvement.

2 | MATERIALS AND METHODS

All procedures in the current study were conducted in accordance with the ethical standards of the Institutional Research Committee of the National Hospital Organization (NHO) Kyushu Cancer Center, the ethical guidelines of the Ministry of Health, Labor, and Welfare of Japan, and the 1964 Helsinki Declaration and its later amendments. We analyzed only the data and medical or radiological images for which the participants gave permission at their first consultation at our hospital. No patient-identifiable data were reported, and no direct interaction with patients was necessary.

This was a retrospective cohort study of patients with Stage pTIIB cervical cancer who underwent RAH at the Gynecology Service of the NHO Kyushu Cancer Center between January 1997 and December 2017. Clinical staging was classified according to the FIGO 2008 cervical cancer staging system and histology by the World Health Organization 2003 histological classification system. We reviewed the databases of cervical cancer treatment performed by our service and identified 82 women with Stage pTIIB cervical cancer who had undergone class III RAH including two who received class II RAH[12] during the study period (Figure 1). For patients who underwent RAH, we reviewed their medical records from the NHO Kyushu Cancer Center. The records included treatment summaries, surgical records, pathological reports with/without images of resected uteruses, records of latest consultation, and outpatient summaries, if available, to obtain the patients' background characteristics, laboratory data, radiological images, and complications. Tumor size and depth of stromal invasion were obtained from surgical records/pathological reports and imaging data.

Indications for postoperative RT other than Stage pTIIB disease included full-thickness cancer invasion of the cervix and pelvic lymph node metastasis. Intravaginal brachytherapy was used when the cancer invasion was <1 cm from the vaginal margin. The range of intravaginal brachytherapy was 9 Gy/3 Fr to 30 Gy/10 Fr and each fraction was administered once weekly. Regarding the dose of conventional postoperative pelvic external RT, we used radiation doses of 40 Gy/25 Fr for the whole pelvis from 1997 to 2002, 45 Gy/25 Fr from 2002 to March 2010, and 50.4 Gy/28 Fr from April 2010 onwards. Postoperative intensity-modulated RT at 50.4 Gy/28 Fr was begun around August 2012. When the para-aortic lymph nodes (PALNs) were involved, the field of pelvic external RT was extended to these lymph nodes. The total dose of RT was 45 Gy/25 Fr in these cases. Every fraction of pelvic external RT was administered 5 days a week. Cisplatin was used in CCRT at a dose of 30 or 40 mg/m^2 per week for up to 6 weeks.

The reasons for adjuvant chemotherapy treatment instead of postoperative CCRT included postoperative ileus, temporary vesicovaginal fistula, ureteral injury, and pretreatment colitis episodes. The reasons for adjuvant chemotherapy being added to postoperative CCRT included AC with PALN involvement, tumors with poorly differentiated components with plural lymph node involvement, and tumors of 6 cm or larger with pelvic lymph node involvement. The patients underwent additional adjuvant chemotherapy after CCRT. Adjuvant chemotherapy regimens were as follows: paclitaxel + carboplatin, docetaxel + carboplatin, and peplomycin + ifosfamide + carboplatin. Fifteen patients with AC received paclitaxel + carboplatin, two of whom also received docetaxel + carboplatin. Eight patients with SCC received paclitaxel + carboplatin and four received peplomycin + ifosfamide + carboplatin.

We also studied the rate of complications for each histological cancer type as well as that of the total population.

Background characteristics were determined using descriptive statistics or contingency tables. The normality of numerical factors was tested using the Shapiro–Wilk normality test. Comparisons of numerical factors between SCC and AC were tested using the Mann-Whitney *U* test. Risk factors for recurrence were assessed using logistic regression analysis. All *p* values were two-sided and $p < 0.05$ was considered to indicate statistical significance. Cumulative distributions of disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan–Meier method. The log-rank test was used to compare differences between survival curves. A propensity score matching method with a 1:1 ratio was applied to reduce selection bias and the potential baseline differences between the SCC and AC groups. All statistical analyses were performed using EZR version 1.30 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

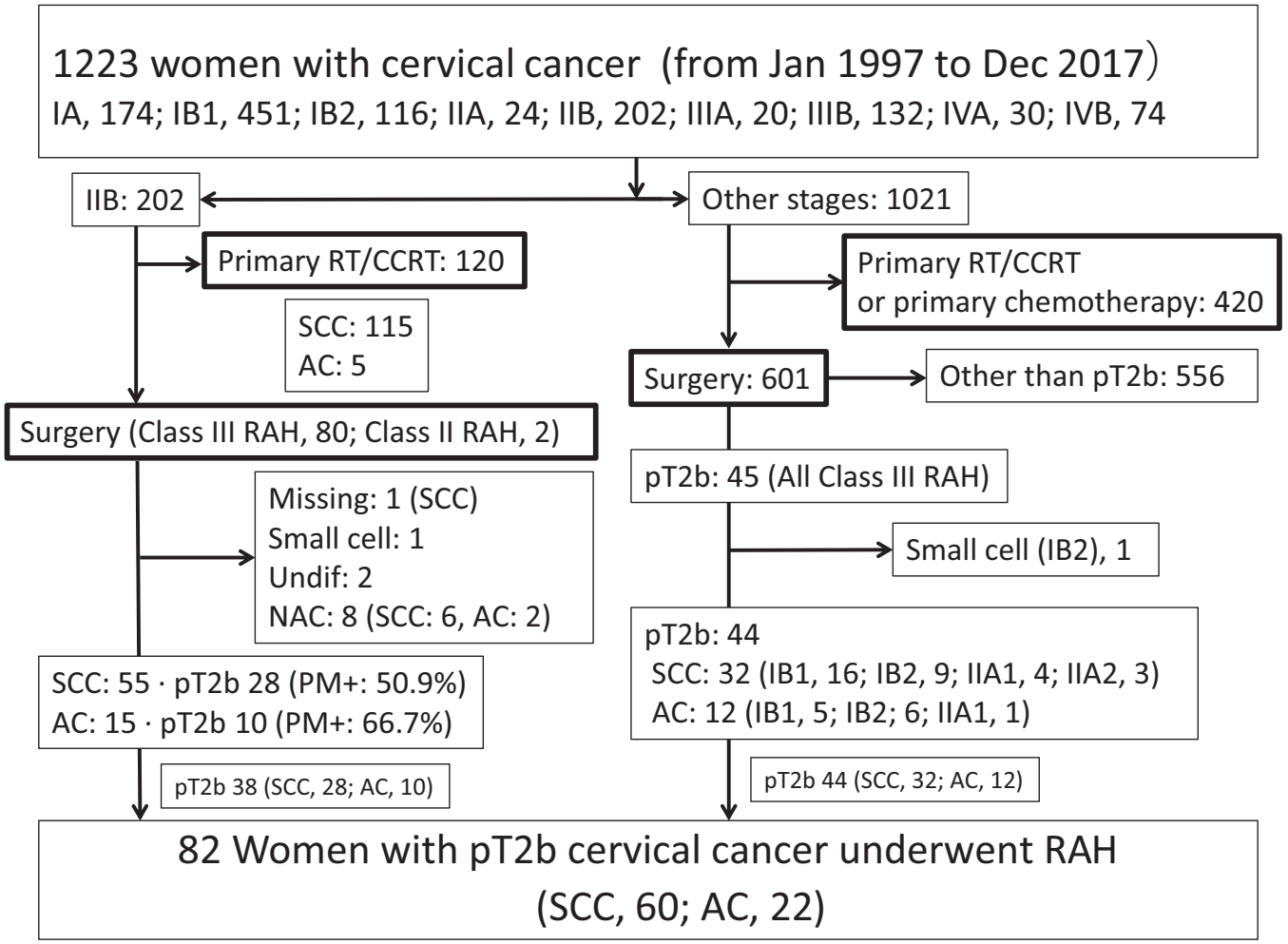

FIGURE 1 Enrollment of patients with Stage pTIIB cervical cancer who underwent radical hysterectomy. AC, adenocarcinoma; NAC, neoadjuvant chemotherapy; PM, parametrial involvement; RAH, radical hysterectomy; SCC, squamous cell carcinoma; Small cell, small cell carcinoma; Undif, undifferentiated carcinoma.

3 | RESULTS

A schematic illustration of the patient enrollment for RAH is presented in Figure 1. Between January 1997 and December 2017, 1223 women with cervical cancer were treated by our service (Fig. 1). The number of patients with each stage is also indicated. In total, 82 patients with Stage pTIIB cervical cancer were analyzed. Sixty of the 82 patients had SCC and 22 had AC. The patients with AC included one case each of serous carcinoma, endometrioid carcinoma, and adenosquamous carcinoma; the remainder were endocervical type according to the World Health Organization 2003 histological classification (Fig. 1). Two of the AC group underwent class II RAH and the remainder underwent class III RAH.

Patients' background characteristics are shown in Table 1. The Shapiro–Wilk normality test indicated a lack of normal distribution in the follow-up period tested in Table 1; for this reason, the Mann-Whitney *U* test was adopted to compare the follow-up periods between the SCC and AC groups. Other nominal factors were analyzed using Fisher's exact test.

When the whole data set was analyzed, the median follow-up period of the AC group was significantly shorter than that of the SCC group ($p = 0.02$). The number of dissected PALNs of the SCC group was almost significantly higher than that of the AC group ($p = 0.07$; Table 1). Patients with AC had a significantly higher rate of adjuvant chemotherapy than patients with SCC ($p < 0.01$; Table 1) and a significantly larger tumor size, 6 cm or more, than SCC patients ($p = 0.02$; Table 1). Of 82 patients, 29 (35.4%) had cancer recurrence. The recurrence rate of AC was significantly higher than that of SCC ($p = 0.04$). Of the 82 patients, 20 (24.4%) died, and the death rate of the AC group was significantly higher than that of the SCC group ($p = 0.05$, Table 1).

Univariate analysis indicated that histological type, PALN metastases, pelvic lymph node metastases, and tumor diameter were significantly associated with recurrence (Table 2). Adjuvant chemotherapy and cisplatin dose were close to significance for recurrence using univariate analysis (Table 2). We selected a tumor diameter of 6 cm or more from the results shown in Table 1.

All factors examined by univariate analysis were also evaluated using multivariate analysis. Multivariate analysis demonstrated that

TABLE 1 Background characteristics of whole population and SCC and AC groups before and after propensity score matching.[a]

	Background characteristics before propensity score matching			Background characteristics after propensity score matching		
	SCC (n = 60)	AC (n = 22)	*p* value	SCC (n = 22)	AC (n = 22)	*p* value
Follow-up period, mo	69.0 (33.3–122.3)	42.0 (28.8–61.5)	0.02*	36.5 (27.3–75.0)	42.0 (28.8–61.5)	0.89
	SCC (n = 55)[c]	AC (n = 16)[c]	*p* value	SCC (n = 22)	AC (n = 22)	*p* value
Hb≥12 g/dL[b]	12 (21.8)	5 (31.2)	0.51	6 (35.3)	5 (31.2)	1
	SCC (n = 60)	AC (n = 22)	*p* value	SCC (n = 22)	AC (n = 22)	*p* value
Age ≥60 y	11 (18.3)	6 (27.3)	0.37	6 (27.3)	6 (27.3)	1
Blood loss ≥1000 g	10 (16.7)	4 (18.2)	1	3 (13.6)	4 (18.2)	1
No. of dissected PALNs ≥6	41 (68.3)	10 (45.5)	0.07	11 (50.0)	9 (40.9)	0.76
No. of dissected PLNs ≥30	37 (61.7)	11 (50.0)	0.45	11 (50.0)	11 (50.0)	1
	SCC (n = 58)[d]	AC (n = 22)	*p* value	SCC (n = 21)[d]	AC (n = 22)	*p* value
Stromal invasion ≥2/3	55 (94.8)	21 (95.5)	1	20 (95.2)	21 (95.5)	1
	SCC (n = 60)	AC (n = 22)	*p* value	SCC (n = 22)	AC (n = 22)	*p* value
Charlson comorbidity Score ≥1	6 (10)	2 (9.1)	1	1 (4.5)	2 (9.1)	1
Year of surgery			0.08			0.74
Feb 1997 to Jul 2007	34 (56.7)	7 (31.8)		5 (22.7)	7 (31.8)	
Aug 2007 to Aug 2017	26 (43.3)	15 (68.2)		17 (77.3)	15 (68.2)	
Adjuvant chemotherapy+	12 (20)	15 (66.7)	0.0001*	6 (27.3)	15 (68.2)	0.01*
Pelvic ERT dose ≥45 Gy/25 Fr	47 (78.3)	13 (59.1)	0.10	16 (72.7)	13 (59.1)	0.53
Cisplatin total dose ≥120 mg/m^2	41 (68.3)	10 (45.5)	0.07	12 (54.5)	10 (45.5)	0.76
ICRT (vaginal vault)+	16 (26.7)	4 (18.2)	0.57	5 (22.7)	4 (18.2)	1
IMRT+	9 (15)	7 (31.8)	0.11	6 (27.3)	7 (31.8)	1
PALN ERT+	11 (18.3)	5 (22.7)	0.76	5 (22.7)	5 (22.7)	1
Tumor size and extent						
≥4 cm	43 (71.7)	20 (90.9)	0.08	19 (86.4)	20 (90.9)	1
≥6 cm	10 (16.7)	10 (45.5)	0.02*	9 (49.9)	10 (45.5)	1
Vaginal involvement+	36 (60.0)	12 (54.5)	0.80	10 (45.5)	12 (54.5)	0.76
Vessel permeation+	55 (91.7)	17 (77.3)	0.12	20 (90.9)	17 (77.3)	0.41
PLN metastases+	35 (58.3)	12 (54.5)	0.81	16 (72.7)	12 (54.5)	0.35
PALN metastases+	5 (8.3)	5 (22.7)	0.12	4 (18.2)	5 (22.7)	1
Prognosis						
Recurrence	17 (28.3)	12 (54.5)	0.04*	11 (50.0)	12 (54.5)	1
Local recurrence	6 (10)	5 (22.7)	0.16	4 (18.2)	5 (22.7)	1
Local and distant recurrence	0 (0)	2 (9.1)	0.07	0 (0)	2 (9.1)	0.49
Distant recurrence	11 (18.3)	5 (22.7)	0.76	7 (31.8)	5 (22.7)	0.74
Death	11 (18.3)	9 (40.9)	0.05*	7 (31.8)	9 (40.9)	0.76

Note: The follow-up period was analyzed by Mann-Whitney *U* test and the other (nominal) variables were analyzed by Fisher's exact test.

Abbreviations: AC, adenocarcinoma; CI, confidence interval; ERT, external radiotherapy; Hb, hemoglobin; ICRT, intracavitary radiotherapy; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; PALN, para-aortic lymph node; PLN, pelvic lymph node; SCC, squamous cell carcinoma.

[a]Values are given as median (interquartile range) or as number (percentage).

[b]Hemoglobin level at start of radiotherapy.

[c]Eleven women did not undergo radiotherapy and the total number was 71.

[d]Two women did not have data about stromal invasion and the SCC number was 58, and one woman did not have data about stromal invasion after propensity score matching.

*Significant according to the Mann-Whitney U test and Fisher's exact test.

TABLE 2 Univariate and multivariate analyses of recurrence using logistic regression.

			Recurrence	Univariate analysis		Multivariate analysis	*p* value
Factor			***n/N* (%)**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	
Adjuvant chemotherapy	−	Reference	16/55 (29.1)	2.26 (0.87–5.87)	0.093	0.15 (0.02–0.99)	0.049*
	+		13/27 (48.1)				
Cisplatin ≥120 mg/m^2	−	Reference	15/31 (48.4)	0.40 (0.16–1.03)	0.057	0.38 (0.09–1.64)	0.195
	+		14/51 (27.5)				
Pelvic ERT dose							
<45 Gy/25 Fr		Reference	10/22 (45.5)	0.56 (0.21–1.51)	0.250	0.87 (0.18–4.28)	0.860
≥45 Gy/25 Fr			19/60 (31.7)				
Histological type							
SCC		Reference	17/60 (28.3)	3.04 (1.11–8.33)	0.031*	2.52 (0.62–10.30)	0.198
AC			10/22 (54.5)				
PALN metastases	−	Reference	21/72 (29.2)	9.71 (1.90–49.60)	0.006*	35.80 (3.11–413.00)	0.004*
	+		8/10 (80.0)				
PLN metastases	−	Reference	8/35 (22.9)	2.73 (1.03–7.24)	0.044*	1.47 (0.40–5.43)	0.567
	+		21/47 (44.7)				
Tumor diameter ≥6 cm	−	Reference	15/62 (24.2)	7.31 (2.39–22.40)	0.001*	19.80 (3.47–113.00)	0.001*
	+		14/20 (70.0)				

Abbreviations: AC, adenocarcinoma; CI, confidence interval; ERT, external radiotherapy; OR, odds ratio; PALN, para-aortic lymph node; PLN, pelvic lymph node; SCC, squamous cell carcinoma.

*Significant according to logistic regression analysis on univariate and multivariate analyses.

recurrence was associated with PALN metastases and tumor diameter of at least 6 cm (Table 2). Multivariate analysis also revealed that adjuvant chemotherapy had an inhibitory effect on recurrence (Table 2). The results in the univariate and multivariate analyses were not of a time-to-event design and we used logistic regression analyses with odds ratios instead of Cox proportional hazards regression analyses with hazard ratios (Table 2).

Kaplan–Meier plots using the whole data set are shown in Figure 2A (DFS) and Figure 2B (OS). The differences in DFS and OS between the SCC and AC groups were significant ($p = 0.01$ and $p = 0.03$, respectively).

Kaplan–Meier plots using propensity score matching are shown in Figure 2C (DFS) and Figure 2D (OS). The objective variable was the histological type of carcinoma. We chose PALN metastasis, tumor size, and cisplatin dose as the explanatory variables because these three variables were unbalanced between the SCC group and the AC group, and they were also clinically important from the result of the univariate analysis (Tables 1 and 2). Background characteristics after propensity score matching are also demonstrated in Table 1. Most of the imbalances of each factor before propensity score matching were corrected. However, the difference in the rate of adjuvant chemotherapy between the SCC and AC groups remained significant (Table 1). The differences in DFS and OS between the SCC and AC groups were not significant ($p = 0.65$ and $p = 0.63$, respectively).

The prognosis of the patients with recurrent disease after propensity score matching is shown in Figure 3. The survival difference between the SCC and AC groups was not significant ($p = 0.54$). The median survival with 95% confidence interval (CI) of the SCC and AC groups was 16.0 (95% CI 11.0–not applicable) months and 12.5 (95% CI 7.0–not available) months, respectively. There were 11 patients with recurrent disease among the SCC group (Table 1). Two of them underwent RT and chemotherapy, five underwent chemotherapy only, one underwent CCRT, and one underwent RT only. Two patients underwent no recurrent treatment. There were 12 patients with recurrent disease among the AC group (Table 1). Four of them underwent RT and chemotherapy, two underwent chemotherapy only, one underwent vaginal brachytherapy, and one underwent CCRT. Three patients underwent no recurrent treatment. The patient with the longest survival was a woman with cervical SCC who underwent RT for recurrent disease in the supraclavicular lymph nodes. There was no evidence of disease for 53 months after treatment of the recurrence.

Complications requiring long-term treatment or surgical treatment are indicated in Table 3. Thirty-five (42.7%) patients had troublesome complications and 21 (25.7%) required hospital admission and/or surgery (grade II or higher complications by the Clavien–Dindo classification[13]; Table 3).

4 | DISCUSSION

In Asian countries including Japan, RAH might be a feasible alternative for clinical FIGO Stage IIB cervical cancer.[14-16] One of the reasons is that preoperative and postoperative occurrence of

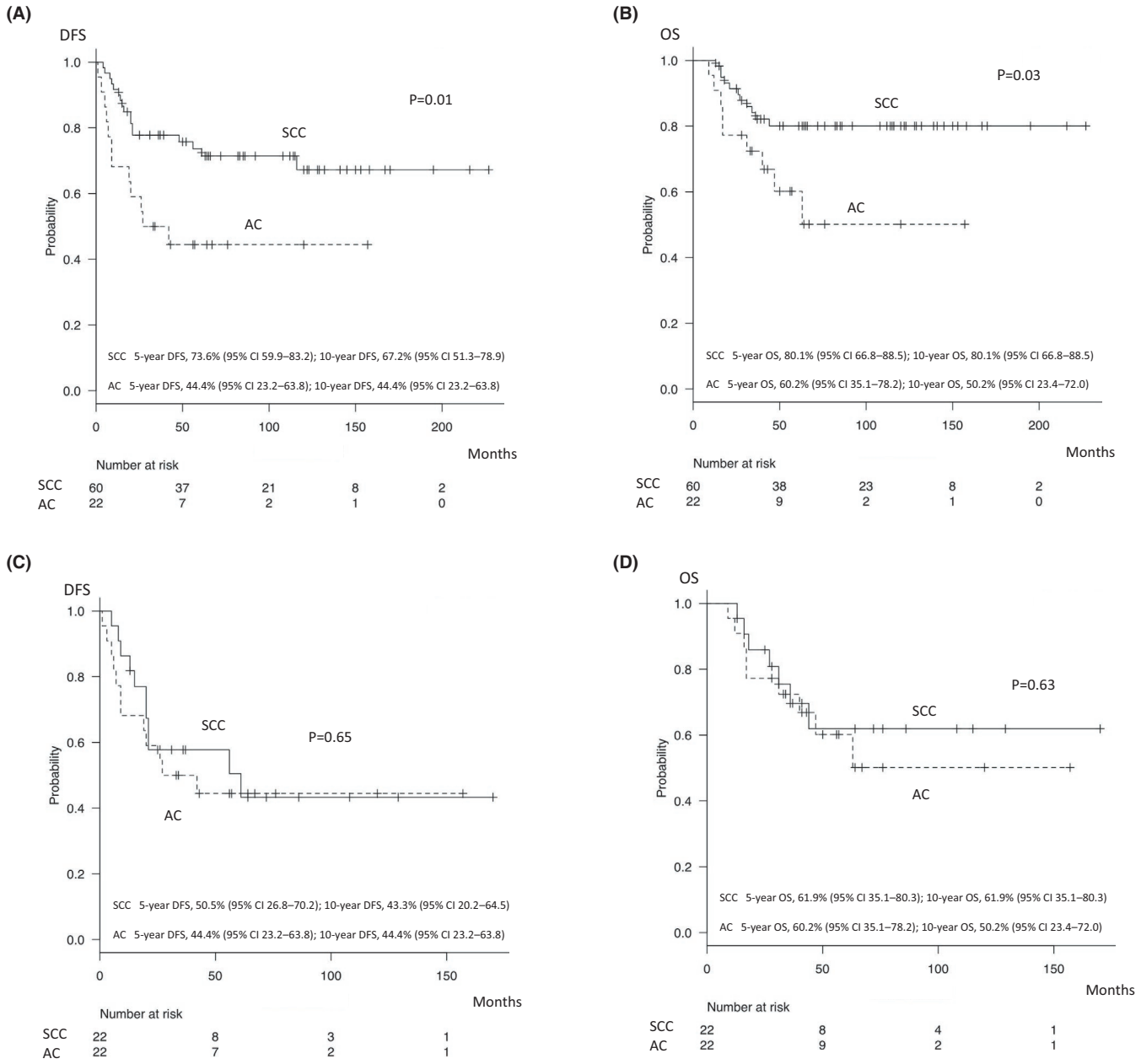

FIGURE 2 Cumulative survival curves of SCC and AC. (A) Kaplan–Meier analysis of DFS using the whole data set. (B) Kaplan–Meier analysis of OS using the whole data set. (C) Kaplan–Meier analysis of DFS after propensity score matching. (D) Kaplan–Meier analysis of OS after propensity score matching. AC, adenocarcinoma; CI, confidence interval; DFS, disease-free survival; OS, overall survival; SCC, squamous cell carcinoma.

parametrial involvement is relatively low.[14] Consequently, we had the opportunity to investigate Stage pTIIB AC as well as SCC. Five-year DFS and 5-year OS (0.736, 95% CI 0.599–0.832, and 0.801, 95% CI 0.668–0.885, respectively) of patients with Stage pTIIB SCC among the whole population in the present study seemed comparable with previous results (0.767, 95% CI 0.716–0.818, and 0.747, 95% CI 0.694–0.800, respectively) obtained with primary CCRT for clinical FIGO Stage IB2 to IIB cervical SCC.[17] In this previous study, the results of the neoadjuvant chemotherapy (NAC) plus RAH group were inferior to those of the primary CCRT group.[17] In a Japanese prospective study of cervical SCC with one AC case that included FIGO Stage IIB disease, OS in the NAC plus RAH group was inferior to that in the primary RAH group.[18] Some populations did not respond to chemotherapy in NAC studies, and NAC could cause treatment delay in non-responders.

In the present study, the proportion of patients who underwent adjuvant chemotherapy in the AC group was significantly higher than that in the SCC group, even after propensity score matching, because one of the indications of adjuvant chemotherapy was AC with PALN involvement. A previous study including 46 patients with clinical FIGO Stage IIB cervical AC concluded that postoperative RT/CCRT might not suffice as adjuvant treatment for patients with

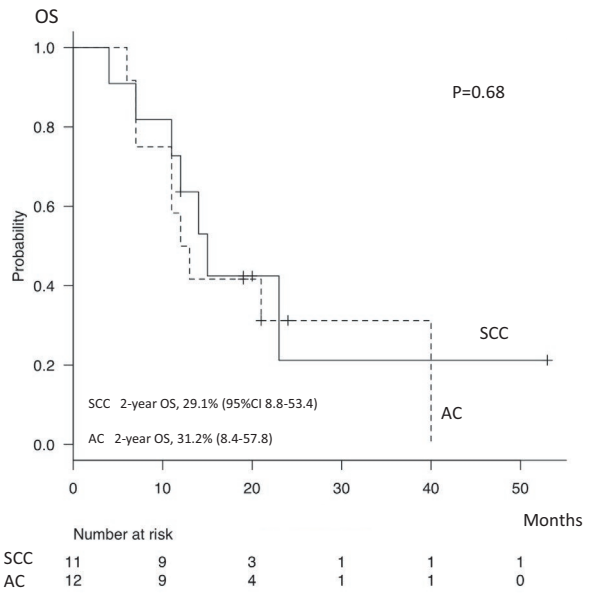

FIGURE 3 Cumulative OS curves of SCC and AC after recurrence. AC, adenocarcinoma; CI, confidence interval; OS, overall survival; SCC, squamous cell carcinoma.

Stage IB1 to IIB cervical AC compared with patients with SCC, and suggested the potential role of adjuvant chemotherapy for women with cervical cancer, particularly those with AC.[19]

The strengths of this study include its focus on patients who underwent RAH for bulky Stage pTIIB cervical cancer and its comparison of Stage pTIIB AC with Stage pTIIB SCC. However, there were some limitations to this study, including its retrospective nature and the small size of the AC group. There were 60 cases in the SCC group but only 22 in the AC group. More AC cases might need to be collated in the future.

Unfortunately, there have been no prospective studies comparing RAH plus adjuvant therapy with primary CCRT for clinical FIGO Stage IIB AC with parametrial involvement evaluated using pretreatment magnetic resonance imaging (MRI). There have also been few reports on primary RT/CCRT for bulky clinical FIGO Stage IIB cervical AC. For example, in a study of primary RT for AC in 15 patients with clinical FIGO Stage II cervical cancer, FIGO Stage IIA cases and FIGO Stage IIB cases were not distinguished.[20] Other studies on clinical FIGO Stage IIB cervical cancer included only one AC patient and three AC patients, respectively, in the CCRT group.[16,21]

Recently, a study investigating the prognosis of cervical SCC and cervical AC reported that the overall mortality of clinical FIGO Stage IIB cervical AC was 2.46 of the adjusted hazard ratio (95% CI 1.34–4.53) in 55 patients who received curative definitive CCRT compared with 66 patients who received curative surgery.[11] In our study after propensity score matching, more than 40% of the patients had tumors with diameters of 6 cm or more. It is difficult to cure such large Stage pTIIB cervical tumors regardless of whether the tumor is SCC or AC. However, the controlling ability of RAH for Stage pTIIB cervical AC seemed to be comparable with that for

TABLE 3 Complications requiring long-term treatment or surgery graded by the Clavien-Dindo classification.

	Total	SCC	AC
	n = 82	n = 60	n = 22
Total	35 (42.7)[a]	28 (46.7)[a]	7 (31.8)[a]
Urological complication	6 (7.3)	3 (5.0)	3 (13.6)
Long-lasting CIC (grade I-d)[b]	6 (7.3)	3 (5.0)	3 (13.6)
Intestinal complication requiring hospitalization	14 (17.1)	13 (21.7)	1 (4.5)
Intestinal complication without surgery (grade II)	9 (11.0)[b]	9 (15.0)	0 (0)
Intestinal complication requiring surgery (grade IIIb)	5 (6.1)[b]	4 (6.7)	1 (4.5)
Lymphedema complication	15 (18.3)	12 (20.0)	3 (13.6)
Lymphedema requiring long-term elastic stockings (grade I-d)	8 (9.8)	5 (8.3)	3 (13.6)
Recurrent lymphedema infection and lymph abscess requiring hospitalization with antibiotic therapy (grade II-d)	3 (3.7)[b]	3 (5.0)	0 (0)
Lymphedema requiring surgery (grade IIIb–d)	4 (4.9)[b]	4 (6.7)	0 (0)
Complication requiring hospitalization (grade II to IIIb)	21 (25.7)	20 (33.3)	1 (4.5)

Abbreviations: AC, adenocarcinoma; CIC, continuous intermittent catheterization; SCC, squamous cell carcinoma.

[a]Among women with plural complications, the representative or most important complication is indicated.

[b]The suffix "d" indicates that a follow up is required to comprehensively evaluate the outcome and related long-term quality of life.

Stage pTIIB cervical SCC, and RAH plus adjuvant therapy could be used to treat clinical FIGO Stage IIB AC with parametrial involvement in countries in which RAH is performed on FIGO Stage IIB cervical cancer. Now that we can evaluate parametrial involvement by MRI before treatment, we await studies investigating the OS of patients with FIGO Stage IIB cervical AC with parametrial invasion when they are treated with primary RT/CCRT. Recently, a study reported that 5-year OS was approximately 75% in 12 patients with clinical FIGO Stage IIB cervical AC who were treated with chemo-carbon-ion RT.[22] However, we await the long-term results and information on the toxicities of this potentially promising treatment modality.

In conclusion, Stage pTIIB cervical SCC in the whole population was well controlled by RAH plus adjuvant therapy. Bulky Stage pTIIB cervical AC had a similar 5-year DFS and OS to Stage pTIIB cervical SCC after propensity score matching when patients underwent RAH plus adjuvant therapy. Bulky Stage pTIIB cervical cancer is hard to cure. However, considering that there are few reports of conventional primary RT/CCRT for bulky clinical FIGO Stage IIB cervical AC

with parametrial invasion indicated by MRI, RAH could be an alternative treatment option for Stage pTIIB cervical AC because AC disease control by RAH was comparable with that of SCC.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

MO conceived and designed the study, analyzed the data, and drafted the manuscript. RN collected the data. MS supervised the statistical analysis. Ke So, Ku Sh, and TS made critical comments on the manuscript. All authors contributed to the revision of the article and approved the final version of the manuscript.

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