

## Original Article



# Comparison of treatment outcomes of surgery and radiotherapy, including concurrent chemoradiotherapy for stage Ib2-IIb cervical adenocarcinoma patients: a retrospective study

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## ABSTRACT

**Objective:** The study compared the treatment outcomes of surgery versus radiotherapy, including concurrent chemoradiotherapy, in stage Ib2–IIb cervical adenocarcinoma patients in Japan.


**Methods:** Of 57,470 patients diagnosed with stage I–IV cervical cancer from January 2001–December 2011, 1,932 patients with stage Ib2–IIb cervical adenocarcinoma were initially treated by surgery or radiotherapy. The primary endpoint was 5-year overall survival (OS) in all and 614 propensity score-matched (PSM) patients (307 per group). We compared OS and prognosis factors based on age, primary stage, and treatment arm.

**Results:** In Japan, >80% (n=1,573) of stage Ib2–IIb cervical adenocarcinoma patients underwent surgery. The 5-year OS of surgery vs. radiotherapy groups were 82.1% (n=704) vs. 79.7% (n=59) (hazard ratio [HR]=1.494; 95% confidence interval [CI]=0.826–2.702; p=0.181) for stage Ib2, 76.6% (n=239) vs. 66.7% (n=54) (HR=1.679; 95% CI=0.986–2.858; p=0.053) for stage IIa, and 71.1% (n=630) vs. 58.9% (n=246) (HR=1.711; 95% CI=1.341–2.184; p<0.001) for stage IIb. In 614 PSM patients balanced for age and carcinoma stage Ib2–IIb, the 5-year OS of surgery vs. radiation groups was 73.0% (n=307) vs. 65.5% (n=307) (HR=1.394; 95% CI=1.044–1.860; p=0.023). In multivariable analysis, age (HR=1.293; 95% CI=1.045–1.601; p=0.018), treatment arm, radiotherapy (HR=1.556; 95% CI=1.253–1.933; p<0.001), and stage IIb (HR=1.783; 95% CI=1.443–2.203; p=0.018) were independent prognosis factors for 5-year OS in stage Ib2–IIb adenocarcinoma patients.

**Conclusion:** Age (>65 years), treatment arm (radiotherapy), and stage IIb significantly affect OS in cervical adenocarcinoma patients. Surgery may be considered for <65-year-old patients with stage IIb adenocarcinoma.

**Keywords:** Adenocarcinoma; Cervical Cancer; Radiotherapy; Survival Rate; Treatment Outcome

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### Conflict of Interest

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

### Author Contributions

Conceptualization: K.E., T.T.; Data curation: K.E.; Formal analysis: K.E., Y.K.; Investigation: K.E., N.S., M.H., M.M.; Methodology: K.M.; Project administration: M.M.; Resources: K.E.; Software: K.E.; Supervision: M.M.; Validation: K.E.; Visualization: K.E.; Writing - original draft: K.E.; Writing - review & editing: K.E., Y.K., T.T., K.Y., Y.W., E.Y., K.M., N.S., M.H., M.M.

### Synopsis

Beginning with 1,932 patients, propensity score matching results in 614 cases (307 per group), the 5-year overall survival of the surgery group vs the radiation group were 73.0% (n=307) vs. 65.5% (n=307) (hazard ratio=1.394; 95% confidence interval=1.044–1.860; p=0.023).

## INTRODUCTION

Cervical cancer is one of the most common gynecological malignancies in women with an estimated number of 604,127 new cases and 341,831 deaths reported worldwide, in 2020 [1]. Patients with early-stage cervical adenocarcinoma (AC) tend to undergo surgical treatment instead of radiotherapy, including concurrent chemoradiotherapy (CCRT), because these patients have low radiosensitivity and have a poor prognosis compared to patients with cervical squamous cell carcinoma (SCC) [2-5].

In the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines, there is no classification of treatment strategies by histology of cervical cancer [6,7]. Moreover, the United States and European countries recommend CCRT instead of surgery for IIB disease. Two important clinical trials of neoadjuvant chemotherapy (NAC) before surgery have recently been reported for stages Ib2 to IIB [8,9]. Both the trials did not find any benefit with NAC followed by surgery compared with chemoradiation. The trials highlighted the use of chemoradiation as the standard of care [8,9].

Surgical treatment is more often selected for a patient with AC than for a patient with SCC. In Japan, surgical treatment is preferred to treat patients with stage Ia1 to IIB AC, which is similar to that reported in several previous studies [10]. Even in stage IIB disease that represents 25% of cervical cancer cases, primary surgical treatment is performed in 30%–50% of patients [11,12].

The modest guidelines of cervical cancer in Japan recommend surgery for stage IIB disease. However, it remains unclear whether surgical treatment or CCRT is better for stage Ib2–IIB AC patients.

The purpose of this study was to compare the treatment outcomes of surgery versus radiotherapy, including CCRT, for stage Ib2–IIB cervical AC using the gynecologic cancer registry of the Japan Society of Obstetrics and Gynecology (JSOG).

## MATERIALS AND METHODS

This is a retrospective observational study focused on the Gynecologic Tumor Registry database of the JSOG. The institutional review board approval was obtained from the JSOG's Clinical Research Committee (2018-36-67) and the hosting institution, the Tokai University School of Medicine (17R-100).

The records of all patients with stages I to IV cervical cancer (FIGO 1994) who were treated consecutively from January 2001 to December 2011 were reviewed from the Gynecologic

Cancer Registry of JSOG. The FIGO stage was determined by examination by a physician and MRI imaging in this study. A total of 57,470 cervical cancer patients with stage I to IV cancer and all histology reports intact were found. Among 2,590 patients with stage Ib2, IIa, and IIb cervical AC, 658 patients with incomplete medical records or follow-up information were excluded. Finally, 1,932 patients (763 patients classified as stage Ib2, 293 as stage IIa, and 876 as stage IIb), treated by surgical treatment or radiotherapy as the initial treatment, were enrolled in this study. Surgery was performed only by laparotomy, type III radical hysterectomy, and pelvic lymphadenectomy. The choice of surgery or radiation therapy depended on the criteria established by each institution. Patients who underwent NAC were excluded from the statistics. AC was defined as mucinous AC, endocervical type, intestinal type, endometrioid AC, clear cell carcinoma, serous AC, and mesonephric AC. Adenosquamous carcinoma (ASC) and other scarce histology were excluded from AC.

The primary endpoint was the 5-year overall survival (OS) of AC patients after surgery or radiotherapy. Of the 1,932 patients, the propensity scores matched in 614 cases (307 per group) when balanced for age and FIGO stage. We compared the 5-year OS and prognosis factors using the following criteria: histology, age, primary stage, and treatment arm.

Clinicopathological factors were analyzed by chi-square test and Mann–Whitney U test. The baseline characteristics between patients in the surgery and radiotherapy groups were compared with the median test. The survival rate was determined using the Kaplan–Meier method, Cox regression analysis, and examined using the log-rank test. All analyses were performed using SPSS (version 24.0; IBM Corp., Armonk, NY, USA), and  $p < 0.05$  was considered to be statistically significant.

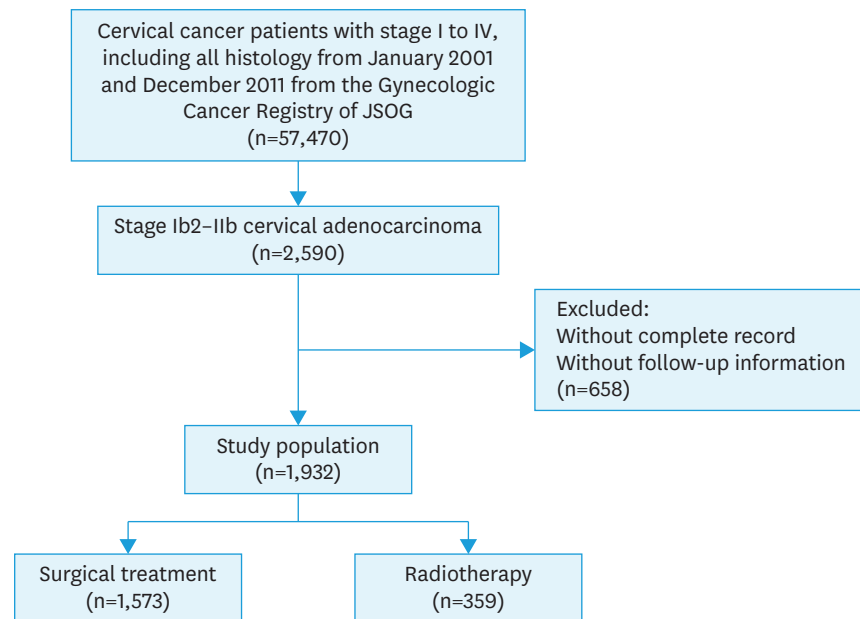
Univariate analysis and multivariate analysis were performed with a Cox-proportional hazard regression model. Factors analyzed in the multivariable analysis included histology, age, primary stage, and treatment arm. This study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

## RESULTS

The overall flowchart is shown in **Fig. 1**. In this study, the 5-year OS of patients with AC, classified as per FIGO 1994, were as follows: Stage Ia,  $n=823$  (98.7%); Ib1,  $n=3,709$  (94.6%); Ib2,  $n=955$  (81.6%); IIa,  $n=370$  (74.6%); IIb,  $n=1,265$  (68.2%); IIIa,  $n=52$  (59.6%); IIIb,  $n=616$  (51.1%); IVa,  $n=158$  (43.7%); and IVb,  $n=505$  (34.7%), respectively.

The background characteristics of the surgery and radiation groups are shown in **Table 1**.

Among the 1,932 patients, 1,573 patients (81.4%, median age 49 years [range 18–86]) underwent surgical treatment and 359 patients (18.6%, median age 63 years [range 28–98]) received radiotherapy as the initial treatment. Of 1,573 patients in the surgery group, 695 (44%) patients received adjuvant chemotherapy, 283 (18%) patients received CCRT, and 202 (14%) patients received radiotherapy after surgery. Adjuvant therapy was performed in 66%, 71%, and 75% of patients with stage Ib2, IIa, and IIb AC. In the 2007 and 2011 JSOG guidelines on the treatment of uterine cervical cancer following primary hysterectomy, the presence of one or more pathologic risk factors may warrant the use of adjuvant therapy. Of



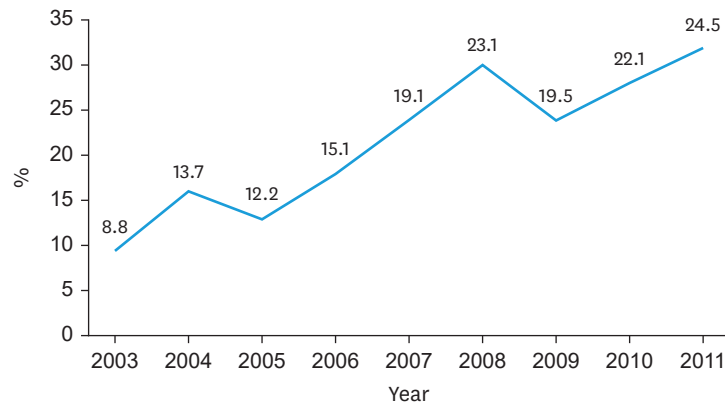
**Fig. 1.** The overall flowchart. JSOG, Japan Society of Obstetrics and Gynecology.

**Table 1.** The background characteristics of stage Ib2, IIa, and IIb cervical AC patients treated by surgery and radiotherapy

Variables	Level	Surgery group	Radiation group	p-value
No.		1,573	359	
			(radiation only 162)	
Age (median [IQR])		49.0 (18–86)	63.0 (28–98)	<0.001
Stage (%)	Ib2	704 (44.7)	59 (16.0)	<0.001
	IIa	239 (15.2)	54 (15.0)	
	IIb	630 (13.5)	246 (69.0)	
The number of <65-year-old patients (%)	Ib2	639 (91%)	33 (56%)	
	IIa	201 (84%)	23 (33.3%)	
	IIb	507 (80.5%)	124 (54.5%)	
Adjuvant therapy post-operative	Chemotherapy	695 (44.1)		
	Radiation	202 (12.8)		
	CCRT	283 (17.9)		
	None	393 (24.9)		
Year at diagnosis (%)	2001/2002	132 (83)	27 (17)	
	2003	114 (91.2)	11 (8.8)	
	2004	120 (86.3)	19 (13.7)	
	2005	139 (87.8)	18 (12.2)	
	2006	169 (84.9)	30 (15.1)	
	2007	170 (80.9)	40 (19.1)	
	2008	164 (76.9)	49 (23.1)	
	2009	190 (80.5)	46 (19.5)	
	2010	180 (77.9)	51 (22.1)	
	2011	210 (75.5)	68 (24.5)	

AC, adenocarcinoma; CCRT, concurrent chemoradiotherapy; IQR, interquartile range.

359 patients in the radiation group, 196 patients underwent CCRT, majorly with cisplatin (40 mg/m<sup>2</sup>, weekly), and 163 patients underwent radiation therapy alone. The rate of choosing radiotherapy as the initial therapy showed a significantly increasing trend from 2003 to 2011 in **Fig. 2**. The median age of patients in the surgery group was less than that in the radiation group (p<0.01). The rate of patients with an advanced stage of cancer at the time of initial treatment between the two groups was significantly different (p<0.05). The median follow-up



**Fig. 2.** The number of patients choosing radiotherapy as the initial therapy significantly increased from 2001 to 2011.

period of patients was 45 (0–103) months. The 5-year OS for the surgery group (n=1,573) vs. the radiation group (n=359) was 76.9% vs. 63.5%, respectively (hazard ratio [HR]=1.419; 95% confidence interval [CI]=1.084–1.858; log-rank p=0.011). Assessed by stage, the 5-year OS of the surgery group vs the radiation group were 82.1% (n=704) vs. 79.7% (n=59) (HR=1.494; 95% CI=0.826–2.702; p=0.181) for stage Ib2, 76.6% (n=239) vs. 66.7% (n=54) (HR=1.679; 95% CI=0.986–2.858; p=0.053) for stage IIa, and 71.1% (n=630) vs. 58.9% (n=246) (HR=1.711; 95% CI=1.341–2.184; p<0.001) for stage IIb.

Of 1,932 patients, the propensity scores matched in 614 cases (307 per group) when balanced for age and FIGO stage (**Table 2**). The 5-year OS of the surgery group vs. the radiation group was 73.0% (n=307) vs. 65.5% (n=307) (HR=1.394; 95% CI=1.044–1.860; p=0.023) (**Fig. 3**). Furthermore, we analyzed patients treated with radiation alone (n=118) and with CCRT (n=189). After propensity score-matched, the 5-year OS was 66.9% in the radiation alone group (n=118) and 64.7% in the CCRT group (n=189) (HR=1.084; 95% CI=0.720–1.609; p=0.688) (**Fig. 4**).

Furthermore, the 5-year OS of patients under and over 65 years in each group were compared.

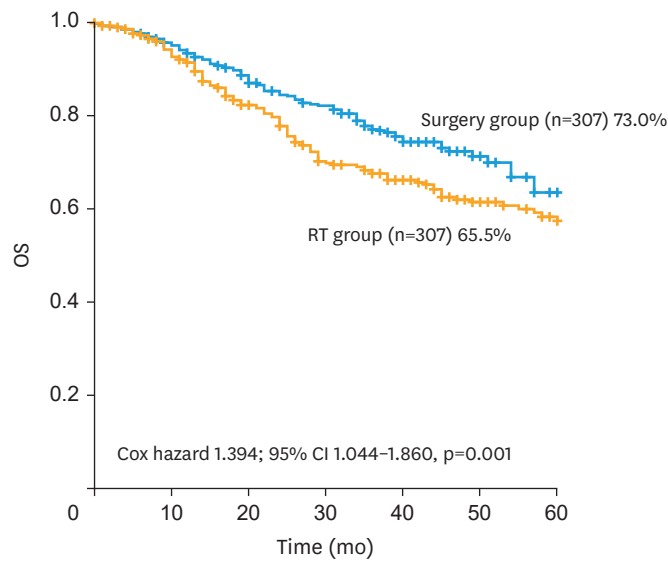
In patients under and over 65 years of age with stage Ib2, and over 65 years of age with stage IIa and IIb cervical AC, the 5-year OS of the surgery group vs. the radiation group were 83.9% vs. 78.8% (HR=1.401; 95% CI=0.592–3.314; p=0.443), 80.8% vs. 64.6% (HR=0.435; 95% CI=0.145–1.306; p=0.138), 73.7% vs. 72.2% (HR=1.077; 95% CI=0.386–3.005; p=0.887), and 69.1% vs. 58.9% (HR=1.559; 95% CI=0.912–2.666; p=0.105), respectively. There was no statistically significant difference in each group (**Fig. S1A, D, E, and F**).

**Table 2.** Propensity score matching of 614 cases (307 per group), balanced for age and FIGO stage

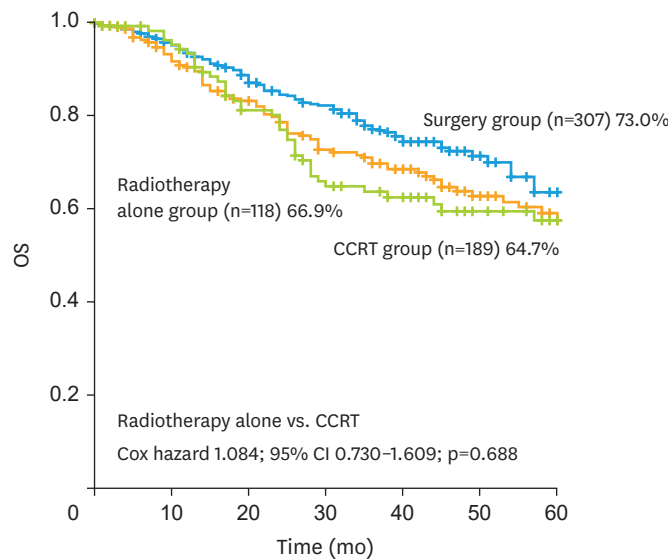
Variables	Level	Surgery group	Radiation group	p-value
Number		307	307	
Age (median [IQR])		60.0 (28–86)	60.0 (28–98)	0.965
Stage	Ib2	61 (19.8)	59 (19.2)	
	IIa	52 (16.9)	54 (17.5)	
	IIb	194 (63.1)	194 (63.1)	
Adjuvant therapy post-operative	Chemotherapy	129 (42.0)		
	Radiation	43 (14.0)		
	CCRT	63 (20.5)		
	None	72 (23.4)		

Values are presented as number (%) unless indicated otherwise.

CCRT, concurrent chemoradiotherapy; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range.



**Fig. 3.** Kaplan–Meier curve for OS in propensity-matched patients (surgery vs. radiotherapy). CI, confidence interval, OS, overall survival.



**Fig. 4.** Kaplan–Meier curve for overall survival in propensity-matched patients (surgery vs. radiotherapy alone vs. CCRT). CCRT, concurrent chemoradiotherapy; CI, confidence interval.

In patients under 65 years of age with stage IIa and IIb cervical AC, the 5-year OS of the surgery group vs. the radiation group was statistically significant (77.1% vs. 55.6% (HR=2.696; 95% CI=1.005–7.227; p=0.049) and 71.6% vs. 59.0% (HR=1.183–2.604; 95% CI=1.183–2.604; p=0.005; **Fig. S1B and C**).

We performed univariate and multivariate analysis and found that the Cox-proportional hazards model identified independent-prognosis factors for 5-year OS in AC patients with Ib2, IIa, and IIb. Factors entered in the multivariate analysis included age, treatment arm, and stage. In the univariate analysis, age (HR=1.655; 95% CI=1.355–2.020; p<0.001), treatment arm (HR=1.981; 95% CI=1.622–2.420; p<0.001), and stages IIa (HR=1.454; 95%

CI=1.096–1.928;  $p=0.009$ ) IIb (HR=2.047; 95% CI=1.670–2.510;  $p<0.001$ ) were identified as independent prognosis factors for 5-year OS in patients with AC.

In the multivariate analysis, age (HR=1.293; 95% CI=1.045–1.601;  $p=0.018$ ), treatment arm (HR=1.556; 95% CI=1.253–1.933;  $p<0.01$ ), and stage IIb (HR=1.783; 95% CI=1.443–2.203;  $p=0.018$ ) were identified as independent prognosis factors for 5-year OS in patients with AC.

## DISCUSSION

In the NCCN and ESMO guidelines, there is no classification of treatment strategies by histology of cervical cancer. However, surgical treatment is more often selected for patients with AC than for those with SCC [10]. According to our data, we found that more than 80% ( $n=1,573$ ) of stage Ib2–IIb cervical AC underwent surgical treatment between January 2001 and December 2011. A previous report found that the surgery group had significantly better 5-year cause-specific survival and OS than the no surgery group [13]. It has been reported that the 3-year OS of patients with AC is poorer than patients with SCC [2]. However, a few studies have also reported that the prognosis of early-stage cervical cancer patients with AC and SCC are similar [14–16]. The Cochrane Database of Systematic Reviews recommends surgery for early-stage AC of the uterine cervix in carefully staged patients [17].

For stage Ib2 or selected IIa AC patients with smaller lesions, surgery is typically reserved for early-stage disease. The primary treatment of for patients with, stage Ib2 or IIa cervical cancer is either surgery or radiotherapy. The NCCN guidelines recommend definitive pelvic external beam radiation therapy plus concurrent platinum-containing chemotherapy for stage Ib2 and IIa cervical cancer. Two important clinical trials of NAC before surgery for stages Ib2 to IIb cancer have been reported recently. Both the trials did not find any benefit in NAC followed by surgery compared with chemoradiation. The trials highlighted the use of chemoradiation as the standard of care [8,9].

In this study, propensity score matching resulted in 614 cases (307 per group), when balanced for age and FIGO stage. The 5-year OS of the surgery group vs the radiation group was 73.0% ( $n=307$ ) vs. 65.5% ( $n=307$ ) (HR=1.394; 95% CI=1.044–1.860;  $p=0.023$ ). Surprisingly, there was no significant difference in prognosis between the radiation alone and CCRT groups. Recent studies have reported that the 5-year OS rate was 10%–20% lower in non-SCC than in SCC cases [18,19]. Indeed, AC cases presented lower local control and OS rates than SCC cases, even when CCRT with three-dimensional- image guided brachytherapy were used.

Furthermore, Nishio et al. [20,21] have reported that 95 (28.9%) of 328 patients with stage I or II endocervical ACs, who were examined between 2000 and 2009 in Japan, were re-classified as having gastric-type mucinous carcinoma. The disease-free survival ( $p<0.0001$ ) and OS ( $p<0.0001$ ) rates were lower in patients with gastric-type mucinous carcinoma than in those with mucinous AC, it was suggested that gastric-type mucinous carcinoma may be resistant to platinum-based chemotherapy [20,21]. The reason for the lack of difference in prognosis between CCRT and RT remains unknown; platinum resistance in AC may be one of the reasons why the addition of chemotherapy to radiation therapy is ineffective. The prognosis of the surgery group was better than that of the CCRT group in this study. The reason for this was that almost 75% of patients (235/307) underwent adjuvant therapy (chemotherapy, radiation, or CCRT) in the surgical group. The

recommendation in JSOG 2007 and 2011 guidelines for the treatment of uterine cervical cancer is as follows: CQ11 (JSOG 2007) and CQ16 (JSOG 2011). Is postoperative adjuvant therapy necessary? Recommendations: (3) Whole-pelvis irradiation is considered to be a postoperative adjuvant therapy, and CCRT should also be considered for patients with positive lymph node metastasis (grade C) [22], (1) CCRT is recommended for patients at high risk of recurrence (grade B) [23]. The rate of radiation therapy after radical hysterectomy was considered to be influenced by these two guidelines. In brief, the majority of patients received multidisciplinary treatment. The limitations of this study were the adverse events, and the long-term complications after surgical treatment and radiotherapy were unknown. Furthermore, the disease-free survival was unknown. So, we cannot know the patient's quality of life.

In Japan, surgery is the most common primary treatment of choice for cervical cancer, such as stage Ib2 or IIa and stage IIb, which represents 25% of cervical cancer cases; primary surgical treatment is performed in 30%–50% [11,12]. The recommendation in JSOG 2007 and 2011 guidelines for the treatment of uterine cervical cancer is as follows: CQ29. What primary treatments are recommended for invasive AC? Recommendations: In principle, surgery is recommended for stage I and II disease (grade B) [22]. CQ15. Recommendations: In principle, surgery should be considered for stage IB and II disease (grade C1) [23]. Therefore, we analyzed the data between January 2001 and December 2011 in our study. The rate of surgery for AC was considered to be influenced by these two guidelines. However, the most recent guideline published in 2017 states the following: Recommendations: surgical treatment and CCRT can be considered. Radiation therapy technology has advanced rapidly in recent years, and clinical trials of cisplatin used alone and in combination are in progress [24,25]. Accumulation of evidence in Japan is necessary for the future as a proposal for future directions [26].

For the survival rates for stage Ib2 disease between the surgery and radiation groups, no statistically significant difference was observed (**Fig. S1A and D**). This data is similar to the results of previous reports [27,28]. Furthermore, patients aged 60 years or older had poor survival than younger women with no significant difference for stage I-II a [27].

Zhou et al. [29] reported that AC and ASC subtypes are independent prognostic factors for cervical cancer patients treated with definitive radiotherapy.

Our analysis revealed that age (<65 vs. >65;  $p=0.018$ ), treatment arm in radiotherapy ( $p<0.01$ ), and stage IIb ( $p=0.018$ ) were independent prognosis factors for 5-year OS in the multivariable analysis. In this study, surgical treatment had a significantly better prognosis than radiotherapy for patients <65 years and with stage IIa and IIb cancer. On the other hand, for patients >65 years with stage Ib2, IIa, and IIb, radiotherapy may be equivalent to surgical treatment. This study is unique because surgical treatment was performed for stage IIb patients with cervical AC, and radiotherapy was performed for all stage IIb patients with cervical cancer nationwide. In other countries, all advanced stage IIb cervical cancer cases were treated by radiation therapy; therefore, we consider our study to contribute valuable data. This study confers several benefits, including a large sample size. However, the study has several limitations, such as the presence of an inherent selection bias for those choosing surgical treatment versus radiotherapy. Furthermore, the indications for adjuvant chemotherapy, radiotherapy, and CCRT were unknown. Further prospective studies are required to examine whether surgical treatment or radiotherapy is better for patients with AC.



In conclusion, our findings revealed that of 1,932 patients, the propensity scores of 614 cases (307 per group) matched when balanced for age and FIGO stages Ib2, IIa, and IIb cervical AC. The 5-year OS of the surgery group vs. the radiation group was 73.0% (n=307) vs. 65.5% (n=307) (HR=1.394; 95% CI=1.044–1.860; p=0.023). Surgical treatment might be considered in patients <65 years with stage IIa or IIb cervical AC.

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## SUPPLEMENTARY MATERIAL

### Fig. S1

Kaplan–Meier curves for overall survival in (A) <65 years old in stage Ib2, (B) <65 years old in stage IIa, (C) <65 years old in stage IIb; (D) >65 years in stage Ib2, (E) >65 years in stage IIa, (F) >65 years in stage IIb.

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