



A retrospective comparison of outcome in IB2 and IIA cervical cancer patients treated with primary concurrent chemoradiation versus radical hysterectomy with or without tailored adjuvant therapy

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Objective

The aim of our study is to compare the overall survival (OS), progression-free survival (PFS), and treatment-related morbidities between primary concurrent chemoradiation therapy (CCRT) vs. radical hysterectomy (RH) with or without tailored adjuvant therapy in patients with stages IB2 and IIA cervical cancer.

Methods

This was a retrospective study of 113 patients with IB2 or IIA cervical cancer treated with either primary CCRT (n=49) or RH (n=64) with or without tailored adjuvant therapy between 2002 and 2011 at Keimyung University Dongsan Medical Center. Patients in RH group was divided into those undergoing surgery alone (n=26) and those undergoing surgery with adjuvant therapy (n=38).

Results

The median follow up period was 66 months. The 5-year OS by treatment modality was 88.7% for the 64 patients in the RH group and 72.8% for 49 patients in the CCRT group ($P=0.044$). The 5-year PFS was 82.3% and 65.6% after RH group and CCRT group ($P=0.048$), respectively. Grade 3–4 complication was less frequent after RH alone (7.7%) than RH with adjuvant therapy (34.2%) or CCRT group (28.6%) ($P=0.047$).

Conclusion

The RH group seems to be superior to the CCRT group in oncologic outcomes. However, considering the selection bias including tumor size, lymph node meta, and parametrial invasion in pretreatment magnetic resonance imaging, both treatment modalities are reasonable and feasible in cervical cancer IB2 and IIA. It is important to choose the appropriate treatment modality considering the age and general condition of the patient. Randomized controlled study is needed to confirm the result of our study and determine the optimal treatment.

Keywords: Cervical cancer; Concurrent chemoradiotherapy; Hysterectomy

Introduction

Cervical cancer is the most common gynecologic cancer in Korea, with an estimated 9.7 new cases per 100,000 females every year and it is the second leading cause of death in gynecologic cancer in Korea, with estimated 2.0 deaths per 100,000 females every year [1]. Although the incidence and survival rate for cervical cancer has been improving in recent years due to vaccination and regular cervical screening, it is

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still considered to be a major female health problem worldwide including in Korea [2-4]. For the cervical cancer, treatment strategy is relatively well established for most stages; however, for locally bulky early stage cervical cancer (IB2–IIA), there are no optimal treatment guideline in these patients. Although either primary concurrent chemoradiation therapy (CCRT) or radical hysterectomy (RH) with or without tailored adjuvant therapy is considered to be feasible in IB2 and IIA cervical cancer, primary treatment remains controversial because both RH and CCRT have been reported to be similarly effective even though both group show different morbidity [5-10]. Adjuvant therapy has been applied to patients with high risk pathological factor (positive lymph nodes [LNs], positive surgical margins, invasion to parametrium). More recently, a randomized trial by the Gynecologic Oncology Group (GOG) 92 found patients with intermediate risk factor (larger than 4 cm in tumor size, lympho-vascular space involvement, deep stromal involvement) also appear to derive a benefit from adjuvant therapy to reduce the recurrence rate [10,11]. Due to this theoretical background, tailored adjuvant therapy has been required to the more patients who underwent RH. However, as the percentage of patients from RH followed by tailored adjuvant therapy increases, risk of the morbidity including complication related to the dual-treatment also has been increased. Concerns about overlapping treatment modality have made to doubt the requirement for treatment using both RH and CCRT.

In the point view of uncertain current treatment option for patients with stage IB2 and IIA cervical cancer, the aims of this retrospective study were to evaluate the comparison of oncologic outcomes (overall survival [OS], progression-free survival [PFS]) and treatment-related morbidities between primary CCRT and RH with or without tailored adjuvant therapy in IB2 and IIA cervical cancer patients.

Materials and methods

1. Patients and study design

We reviewed retrospectively the medical records of patients in IB2 and IIA cervical cancer who were managed at Keimyung University Dongsan Medical Center between 2002 and 2011. According to the International Federation of Obstetrics Gynecology (FIGO) staging system revised in 2009 [12], patients histologically confirmed cervical cancer of stages IB2 or

IIA were selected. Among the selected patients in IB2 and IIA cervical cancer, patients were excluded by the following conditions: 1) biopsy confirmed by histologically neuroendocrine carcinoma due to their high possibility of metastasis and poor prognosis; 2) patients who managed by the neoadjuvant chemotherapy as a primary modality; 3) patients who diagnosed as having occult cervical cancer after a simple hysterectomy; 4) patients who did not receive appropriate treatment after RH in intermediate risk group and high risk group. The reason why we excluded last No. 4 is to increase the risk of recurrence if patients in intermediate risk group and high risk group did not manage the adjuvant radiation therapy (RT)/CCRT [13].

Approval to conduct this retrospective study was received independently from an institutional review board (No. 2016-09-008). All patients underwent clinical staging and radiologic imaging with computed tomography (CT) and magnetic resonance imaging (MRI). Treatment method as primary modality was decided at the discussion of the weekly gynecology oncology tumor board review. Those patients had been decided suitable for surgical treatment were noticed that they might require adjuvant RT/CCRT according to the postoperative biopsy results. They also were noticed of morbidities associated with each modality (RH, RT, and CCRT) before treatment. We obtained the basic information including patient's demographic and clinical data, primary and adjuvant treatment modalities, response to treatment, morbidities associated with treatment modalities and postoperative pathological risk factors (intermediate and high risk) at the medical records of patients.

OS was defined as the time from the beginning date of primary treatment (RH or CCRT) to the date of death or for living state. PFS was defined as the time from beginning date of primary treatment (RH or CCRT) to the date of first recurrence reported by our medical team or no recurrence state. Morbidities associated with treatment modalities were classified according to the Radiation Therapy Oncology Group (RTOG) toxicity scores [14]. All of grade 3–4 toxicities occurred after beginning date of primary treatment (RH or CCRT) were documented in our study.

2. RH and adjuvant therapy (RT/CCRT)

All radical hysterectomies were performed through an abdominal approach until 2004, but after that, the procedure was shifted to a laparoscopic surgery. All patients underwent

Korean Gynecologic Oncologic Group classification of hysterectomy type C with lymphadenectomy level 2 or 3 [15]. Para-aortic node dissection was not routine procedure for patients undergoing primary RH and was surgeon's decision if the para-aortic nodes metastasis was doubtful at pre-operative imaging or intraoperatively. According to GOG protocol 92 [10,11], patients in the high risk group as well as those in the intermediate risk group received the adjuvant RT/CCRT.

The postoperative radiotherapy was composed of external beam radiotherapy at a dose ranged from 4,500 to 5,400 cGy in 22 to 25 fractions given 5 days (from Monday to Friday) per week for 30 days. Those patients received adjuvant RT/CCRT and did not receive intracavitary brachytherapy. Until 2007, Chemotherapy regimen in patients who received

CCRT was paclitaxel/carboplatin or cisplatin/carboplatin or 5-fluorouracil/cisplatin. Since 2008, all patients managing either primary or adjuvant CCRT received chemotherapy with cisplatin 40 mg/m² weekly during each of the 6 weeks of external beam radiotherapy.

3. Primary CCRT

Primary CCRT group received external pelvic RT at a dose ranged from 4,500 to 5,400 cGy and then intracavitary brachytherapy at a dose ranged from 3,000 to 3,500 cGy. As above mentioned, all patients received CCRT during external beam RT consisted of 3 cycle paclitaxel (body surface area×135)/carboplatin (area under curve=5) every 3 weeks or 3 cycle of paclitaxel (body surface area×135)/cisplatin (body

Table 1. Basic characteristics of patients (n=113)

Characteristics	RH group	CCRT group	P-value
No.	64 (56.6)	49 (43.4)	-
Adjuvant therapy ^{a)}	38 (59.4)	3 (6.1)	-
Age at diagnosis (yr)	46.1±11.0	54.8±11.6	<0.001
Comorbid medical disease ^{b)}			0.066
Yes	6 (9.3)	11 (22.4)	
No	58 (90.7)	38 (77.6)	
FIGO staging			0.019
IB2	45 (70.3)	23 (46.9)	
IIA	19 (29.7)	26 (53.1)	
Histologic classification			0.595
Squamous cell carcinoma	49 (76.6)	41 (83.7)	
Adenocarcinoma	10 (15.6)	6 (12.2)	
Adenosquamous cell carcinoma	5 (7.8)	2 (5.2)	
Maximum tumor diameter in MRI (mm)	32.1±2.0	39.6±2.6	0.020
<40	38 (59.4)	20 (40.8)	0.004
40–60	26 (40.6)	23 (46.9)	-
>60	0 (0.0)	6 (12.2)	-
Lymph nodal status in MRI			<0.001
Positive	11 (17.2)	27 (55.1)	
Negative	53 (82.8)	22 (44.9)	
Parametrial invasion status in MRI			0.013
Positive	9 (14.1)	17 (34.7)	
Negative	55 (85.9)	32 (65.3)	

Data are presented as number (%) or mean±standard deviation.

RH, radical hysterectomy; CCRT, concurrent chemoradiation therapy; FIGO, International Federation of Obstetrics Gynecology; MRI, magnetic resonance imaging; RT, radiation therapy.

^{a)}Adjuvant therapy: RT or CCRT in RH group/type I hysterectomy in CCRT group; ^{b)}Comorbid medical disease: hypertension, diabetes mellitus, medical thyroid disease, stroke, myocardial infarction, chronic liver disease.

surface area×60) every 3 weeks or 2 cycle of 5-fluorouracil (body surface area×1,000)/cisplatin (body surface area×60) every 4 weeks until 2007, after which there were a move toward weekly 6 cycle cisplatin (body surface area×40).

4. Statistical analysis

The main outcomes of our study were to compare the OS, PFS, and complication by treatment modality (RH vs. CCRT). The 5-year OS and PFS were calculated using the Kaplan-Meier method and compared using log rank test. The means of 2 or 3 groups were compared using the Student's t-test for documented data and Frequency distributions were compared using the χ^2 test for categorical variables. *P*-value <0.05 was considered as statistical significance. All statistical analyses were performed using SPSS ver. 19.0 (SPSS Inc., Chicago, IL, USA).

Results

1. Basic characteristic of patients

A total of 133 patients with stage IB2 or IIA cervical cancer were identified. 20 of the 133 patients with stage IB2 and IIA cervical cancer were excluded in our study due to exclusion criteria. Among those who were excluded, 8 patients underwent RT alone as primary modality, 4 patients underwent neoadjuvant therapy as primary modality, 3 patients were diagnosed with occult cervical cancer detected after a simple hysterectomy, 3 patients did not manage RT or CCRT after RH in intermediate risk and high risk group and 2 patients were diagnosed with histologically neuroendocrine carcinoma.

Basic characteristic of patients by the treatment groups are summarized in Table 1. Sixty-four (56.6%) of the 113 patients underwent primary RH; and of these, 38 (59.4%) patients required to have adjuvant RT or CCRT. Forty-nine (43.4%) of the 113 patients had primary CCRT; and of these, 3 (6.1%) patients underwent additional management with type I hysterectomy. The mean age was statistically lower in the RH group (46.1 vs. 54.8 years, *P*<0.001). At FIGO staging, IB2 patients was significantly higher in the RH group (70.3% vs. 46.9%, *P*=0.019), on the other hand, IIA patients was significantly higher in the CCRT group (29.7% vs. 53.1%, *P*=0.019). According to maximum tumor diameter in MRI, the mean tumor size is smaller in the RH group (32.1 vs. 39.6 mm, *P*=0.020) and based on 40 mm, the proportion of patients with tumor size lesser than 40 mm significantly was higher in the RH group as primary modality (59.4% vs. 40.8%, *P*=0.004). In particularly, at bulky tumor which tumor size is larger than 60 mm, all patients underwent CCRT as primary modality (0% vs. 12.2%, *P*=0.004). According to LN and parametrial invasion status in MRI, the proportion of patients who is negative finding in MRI significantly was higher in the RH group (82.8% vs. 44.9%; LN invasion, *P*<0.001, 85.9% vs. 65.3%; parametrial invasion, *P*=0.013). However, there was no difference by the treatment group in histologic classification and status of comorbid medical disease.

2. Oncologic outcomes

The median follow up period was 66 months (range, 5–122 months) for all patients. Table 2 shows the patterns of recurrence and survival rate by the treatment groups. Eleven (17.2%) patients had recurrence in the RH group and 14

Table 2. Patterns of recurrence and survival rates (n=113)

Recurrence and death	RH group (n=64)	CCRT group (n=49)	<i>P</i> -value
No recurrence	53 (82.8)	35 (71.4)	0.147
Recurrence	11 (17.2)	14 (28.6)	-
Local	6 (9.3)	4 (8.1)	
LN	3 (4.7)	2 (4.1)	
Distant	2 (3.2)	7 (12.2)	
Alive	55 (85.9)	38 (77.6)	0.312
Death	9 (14.1)	11 (22.4)	-
Due to disease	8 (12.5)	11 (22.4)	
Related to disease	1 (1.6)	0 (0.0)	

Data are presented as number (%).

RH, radical hysterectomy; CCRT, concurrent chemoradiation therapy; LN, lymph node.

(28.6%) patients had recurrence in the CCRT group ($P=0.147$). In the RH group, 6 of 11 recurred patients showed the pattern of local recurrence. However, in the CCRT group, 7 of 14 recurred patients showed the pattern of distant recurrence. Nine (14.1%) patients died of disease in the RH group and of these, 1 patient died due to septic shock related to bowel perforation at postoperative 3 months. 11 (22.4%) patients died of disease in CCRT group ($P=0.312$).

The 5-year PFS and OS rates were schematized by Fig. 1. The 5-year PFS and OS rates of the RH group were significantly better than CCRT group.

The 5-year PFS rates was 82.3% in the RH group and 65.6% in the CCRT group ($P=0.048$) (Fig. 1A). The 5-year OS rates were 88.7% in the RH group and 72.8% in the CCRT group ($P=0.044$) (Fig. 1B). When RH group was subdivided into a group with RH alone and a group with followed by adjuvant therapy (RT/CCRT), the 5-year PFS and OS rates were compared by 3 treatment group; those who underwent RH alone ($n=26$), those who underwent RH followed by adjuvant therapy ($n=38$), and those who managed primary CCRT ($n=49$). The 5-year PFS

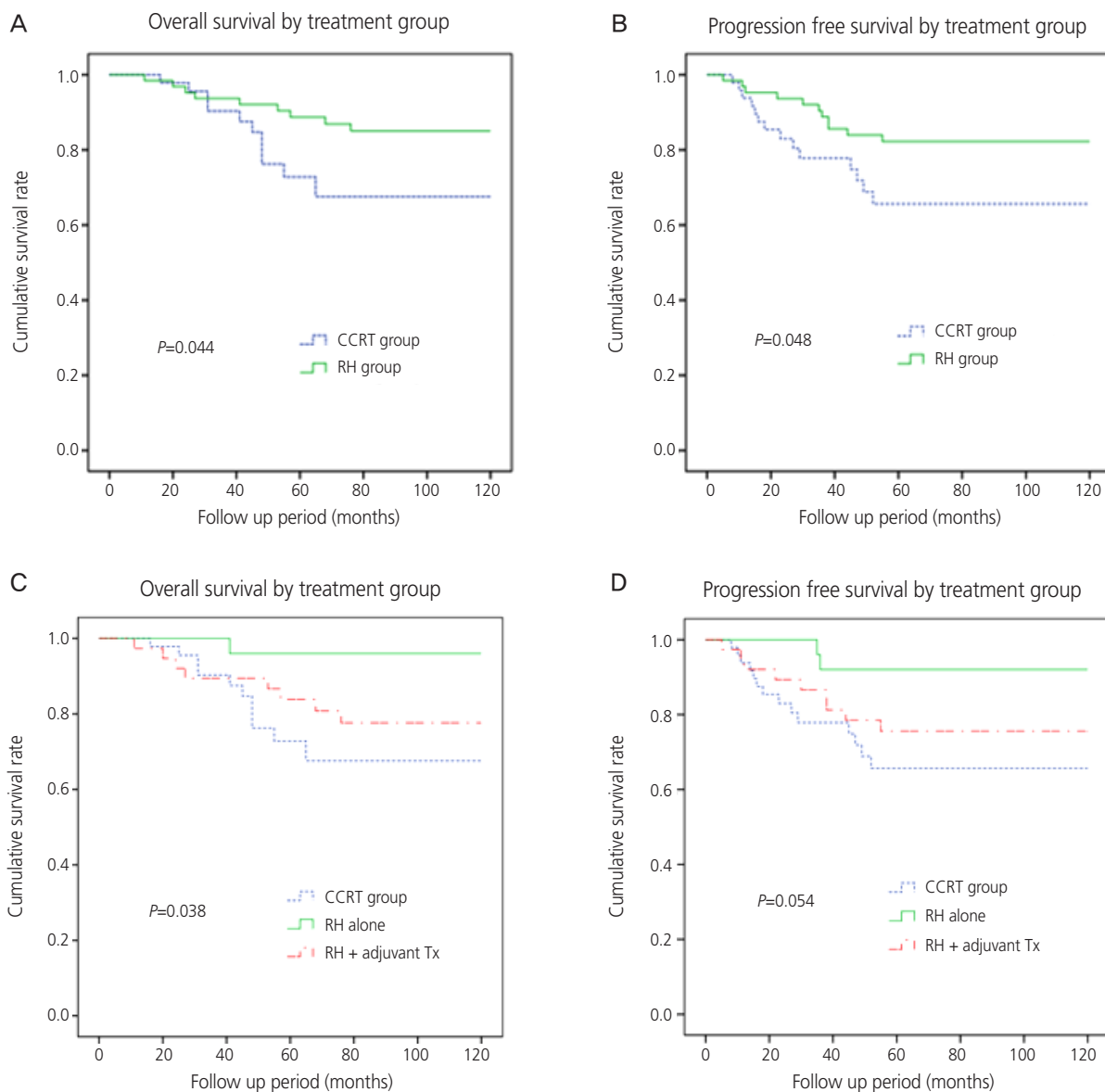


Fig. 1. (A, B) Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) by treatment group. Concurrent chemoradiation (CCRT) vs. radical hysterectomy (RH). (C, D) Kaplan-Meier curves of PFS and OS by treatment group. CCRT vs. RH alone vs. RH followed by tailored therapy.

Table 3. Complication by treatment group (n=113)

Complication	RH alone (n=26)	RH+adjuvant Tx (n=38)	CCRT group (n=49)	P-value
Grade 3–4 complication	2 (7.7)	13 (34.2)	14 (28.6)	0.047
Hematological abnormality ^{a)}	0 (0.0)	0 (0.0)	2 (4.1)	0.348
Gastro-intestinal abnormality ^{b)}	0 (0.0)	2 (5.3)	3 (6.1)	0.534
Lymph edema	1 (3.8)	5 (13.2)	7 (14.3)	0.477
Urinary tract injury	1 (3.8)	1 (2.6)	0 (0.0)	0.504
Intestinal perforation	0 (0.0)	1 (2.6)	0 (0.0)	0.566
Sepsis	0 (0.0)	1 (2.6)	1 (2.0)	1.000
Thrombosis	0 (0.0)	2 (5.3)	0 (0.0)	0.162
Fistula	0 (0.0)	1 (2.6)	1 (2.0)	1.000

Data are presented as number (%).

RH, radical hysterectomy; CCRT, concurrent chemoradiation therapy.

^{a)}Neutropenia, anemia, thrombocytopenia; ^{b)}Nausea, vomiting, diarrhea.

for patients undergoing RH alone (92%) was better than for RH patients followed by adjuvant therapy (75.6%) or patients managed by primary CCRT (65.6%) ($P=0.054$) (Fig. 1C). The 5-year OS rates for patients undergoing RH alone (96%) was statistically better than each 2 group (83.9% and 72.8%, $P=0.038$) (Fig. 1D). Only 2 (7.7%) of 26 patients had recurrence in the RH alone group and of these, 1 patient died of disease. To sum up, 24 patients were treated by surgery alone without adjuvant therapy.

3. Complication

Grade 3–4 complication was identified by dividing into 3 groups (Table 3). Grade 3–4 complication was observed in 2 (7.7%), 13 (34.2%), and 14 (28.6%) patients of the RH alone group, RH followed by adjuvant therapy group and CCRT group ($P=0.047$). Grade 3–4 hematologic complication was observed in only the CCRT group (2 patients, 4.1%). Among non-hematologic grade 3–4 complications, lymphedema of the lower extremities was most commonly identified at each treatment group. Lymphedema was observed in 1 (3.8%), 5 (13.2%), and 7 (14.3%) patients of these groups ($P=0.477$).

Discussion

This study is a retrospective analysis of 113 patients in FIGO stages IB2 to IIA cervical cancer treated with either primary CCRT (n=49) or primary RH with or without tailored adjuvant therapy (n=64). Reviewing our retrospective study, it seems

that RH group has better OS and PFS than primary CCRT group in current result. However, it is difficult to conclude which is superior between the 2 groups. Park et al. [16] reported comparison of outcomes between RH followed by tailored adjuvant therapy vs. primary CCRT in IB2 and IIA2 cervical cancer at 2 institutions. This retrospective study reported about 29% of patients was treated by RH alone and these patients showed the best survival outcomes with the lowest morbidity rates. However, our research needs to consider selection bias including tumor size, LN metastasis, and parametrial invasion. These differences could be attributed to the fact that patients with the higher possibility of pelvic LN metastasis and parametrial invasion and larger tumor size (>6 cm in diameter) at preoperative pelvic examination or imaging work up tends to receive a primary CCRT to prevent the dual treatment modality due to necessity of the adjuvant therapy. As pelvic LN metastasis and parametrial invasion at preoperative MRI imaging is strongly suspected, the results which more patients received the primary CCRT were confirmed in our study. Thereby, RH alone group had a lower risk for recurrence at evaluation of postoperative biopsy.

In our study, the 5-year OS and PFS were more superior to the RH group and difference showed over 15% points (OS: 88.7% vs. 72.8%, PFS: 82.3% vs. 65.6%). Although selection bias would be present, A difference of more than 15% may be significantly important and exhibits primary surgical approach has distinct advantages over primary CCRT. First, uncertainty or errors of imagery interpretation could be occurred in the evaluation of lymph nodal status or parametrial inva-

sion. Imaging work up with CT or MRI scan has a low sensitivity for evaluating LN metastasis and parametrial invasion [17]. By contrast, application of positron emission tomography-computed tomography (PET-CT) has been shown to better detection rate about evaluation of LN metastasis compared to conventional imaging (CT or MRI), although detection rates are controversial for early-stage cervical cancer [18]. In spite of introduction of the several preoperative methods, surgery can permit confidently the status of the LNs and parametrial invasion, the most dependent factor associated with OS. Accurate histologic staging can be performed by only surgical approach and then adequate adjuvant therapy can be decided according to the postoperative biopsy results of individual patient. Primary surgical approach can make the patients prevent unnecessary RT or CCRT in patients who show the ambiguous imaging findings. Second, many cervical malignancies occur in young, premenopausal women and ovarian function is strongly associated with life of quality in these patients. Primary RT or CCRT can lead to RT-induced ovarian failure and patients can complain various postmenopausal symptoms. Primary surgery can provide patients with chance to preserve the ovarian function and take better sexual function when compared with RT or CCRT [19]. Even if adjuvant RT or CCRT is required at each patient, surgeon can perform procedure named transposition of ovary during the surgery and save the ovarian function. Its effect is that external pelvic radiation does not have an influence on both ovaries. Last, as the result was shown in our study associated with morbidity, compared to morbidity of RH followed by adjuvant therapy and primary CCRT group, morbidity of RH alone group was significantly low rates (RH alone: 7.7% vs. RH followed by adjuvant therapy: 34.2% vs. primary CCRT: 28.6%). It is reasonable that RH alone group was lower complication than other 2 treatment group, because most complications were related to level of RT therapy. An amount of RH followed by adjuvant RT or CCRT irradiates only external pelvic RT, at doses ranged from 4,500–5,400 cGy, whereas primary CCRT patients irradiates composed of external pelvic RT followed by intracavitary brachytherapy, at doses of about 3,000 cGy. It seems reasonable that rate of RT-induced complication should be higher at primary CCRT group compared to the adjuvant RT group. However, the morbidity related to dual treatment (RH followed by adjuvant RT or CCRT) was slight higher than primary CCRT in our study. A several studies have reported that use of RH followed by adjuvant therapy was associated

with higher morbidity rates compared to RH alone group and primary CCRT group [5,20]. On the other hand, a recent study reported by Gruen et al. [21] have found that the rates of grade 3–4 complication were lower (7%) at RH followed by adjuvant therapy and were not different compared to RH alone and primary CCRT group and Havrilesky et al. [9] also reported the similar results associated with the lower morbidity at RH followed by adjuvant therapy. Although the contrary results associated with the morbidity were reported, it is clear that RH alone group has the lowest morbidity compared to the other 2 groups who received the RT.

What should be noted here is a high morbidity due to increasing adjuvant therapy. Since the conclusions of GOG 92 proved that adjuvant RT reduced rate of cancer recurrences in patients with intermediate risk factor, many postoperative patients have received the adjuvant RT or CCRT to decrease the rate of cancer recurrence. In this study, more than half patients of RH group (59.4%) required the adjuvant therapy. Other studies also reported that rate of cervical cancer patients who underwent RH followed by adjuvant therapy was about 40%–60% [5,22]. As the rates of adjuvant RT or CCRT due to postoperative risk factor increase, RT-induced morbidities also increase compared to the RH alone. Therefore, when we decide to select the treatment options of cervical cancer IB2 to IIA as primary modality, we must consider not only OS and PFS, but also various conditions including age, medical comorbidities, quality of life, and patient preference of treatment options at each patient. For postmenopausal patients with medical problem, primary surgery should not be considered as the first treatment option. There are no reasons to save the ovarian function and to accept the surgical risk.

There are some limitations of our study. As this study was performed retrospectively in a single institution, the number of patients was relatively small. And we have evaluated each patient data during the long period followed up. There were meaningful changes in 2 treatment modalities during the long-term follow-up period, including criteria for adjuvant therapy, surgical method for RH group and chemotherapy agent for primary CCRT group or RH followed by adjuvant therapy group. Thereby it was difficult to obtain the consistent, well designed data from the patient medical records. In addition, selection bias also must be considered at our study. As mentioned above, when tumor size was large (>6 cm) and LN and parametrial metastasis were suspected in MRI, there was a tendency to perform CCRT rather than primary RH.

Although the intention was to avoid the dual treatment, oncologic outcome was significantly better in the RH group than in the CCRT, which is a somewhat biased outcome.

Despite several limitations in our study, the results of current study can suggest that both treatment modalities are reasonable and feasible in patients with cervical cancer IB2 and IIA. Although primary surgical approach has several distinct advantages over CCRT, it is important to choose the appropriate treatment modality considering the age and general condition of the patient. A large scaled randomized controlled study between the 2 treatment modalities is required.

Conflict of interest

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

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