Comparison of adjuvant chemotherapy and radiotherapy in patients with cervical adenocarcinoma of the uterus after radical hysterectomy: SGSG/ TGCU Intergroup surveillance

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Summary

Purpose: The authors conducted this retrospective study to evaluate the efficacy of radiotherapy (RT) for high-risk patients with adenocarcinoma (AC) compared with chemotherapy (CT) after radical hysterectomy. *Materials and Methods*: There were 263 patients with AC and 58 with adenosquamous cell carcinoma (ASCC). Of these 321 patients, 151 received adjuvant treatment. Of these 151 patients, 69 received radiotherapy (RT) alone, including concurrent chemoradiotherapy (CCRT) with weekly cisdiamminedichloroplatinum (CDDP), 64 patients received CT alone, and 18 patients received concomitant RT and CT (RT + CT). *Results*: The five-year overall survival (OS) was 70.9% for patients receiving RT, 79.2% for CT, and 66.2% for RT + CT. Adjuvant treatment did not affect the incidence or the pattern of recurrence. The incidence of lymph node involvement was 9.0% in Stage Ib1, 23.9% in Stage Ib2, 30.8% in Stage IIa, and 41.2% in Stage IIb. *Conclusions:* Adjuvant CT may be effective for high-risk patients with cervical adenocarcinoma.

Key words: Adenocarcinoma; Uterine cervix; Radiotherapy; Chemotherapy.

Introduction

The standard treatment for patients with International Federation of Gynecology and Obstetrics (FIGO) Stage Ib to II cervical cancer is radical hysterectomy and/or radiotherapy (RT). National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend RT and radical hysterectomy as useful treatment having an equal effect for patients with Stage Ia2 – IIa cervical cancer having a non-bulky tumor [1]. In Japan, the majority of gynecologic oncologists choose radical hysterectomy for patients with Stage Ib–IIb cervical cancer.

Gynecologic Oncology Group (GOG) showed that adjuvant pelvic RT following radical hysterectomy reduced the number of recurrences in Stage Ib patients with intermediate risk factors [2]. In addition, another GOG study suggested that RT with concurrent cisdiamminedi- chloroplatinum (CDDP) containing chemotherapy (CT) was more useful for Stage Ia2–IIa patients with pelvic lymph node involvement, parametrial extension, or a compromised surgical margin than RT alone after radical hysterectomy [3]. Consequently, patients with pathologic risk factors, such as pelvic lymph node involvement and parametrial extension, should receive adjuvant RT, including concurrent chemoradiotherapy (CCRT) after radical hysterectomy.

Over the past 24 years, the incidence of adenocarcinoma (AC) of the uterine cervix has increased from approximately 12% to 24% of cervical cancers [4]. It is controversial whether the prognosis of patients with cervical cancer depends on the histologic type [5-7]. A GOG study of 813 patients with Stage Ib cervical cancer, 645 with squamous cell carcinomas (SCC), and 168 with AC, including adenosquamous cell carcinoma (ASCC), suggested that no statistically significant differences were seen in the recurrence-free interval among histological types [5]. In contrast, Park reported that the survival difference between AC and SCC was small but significant [6]. The present authors also reported that Stage II patients with AC showed a significantly worse prognosis than those with SCC; however, the survival in Stage Ib patients did not differ between AC and SCC [7]. Although a few studies have assessed specific treatment for AC, NCCN clinical practice guidelines recommend that AC can be effectively treated in a similar manner to SCC [1].

Revised manuscript accepted for publication June 28, 2012

Table 1. — *Patients' characteristics.*

Age	46.2 (18 – 84)
FIGO Stage	
Ib1	211
Ib2	46
IIa	13
IIb	51
Histological type	
Adenocarcinoma	263
Adenosquamous cell carcinoma	58
Adjuvant treatment	
Yes	151
No	170

Table 2. — *The incidence of lymph node involvement.*

FIGO Stage	LN involvement (%)
Ib1	9.5% (20 / 211)
Ib2	23.9% (11 / 46)
IIa	30.8% (4 / 13)
IIb	41.2% (21 / 51)

Radiosensitivity may be important in the treatment of patients with pathologic risk factors after radical hysterectomy. Landoni suggested that RT was less effective for patients with AC than those with SCC [8]. Niibe also reported lower radiosensitivity for AC compared with SCC [9]. Consequently, adjuvant RT might be limited for high-risk patients with AC. The present authors conducted this large retrospective study to evaluate the efficacy of adjuvant RT for high-risk patients with AC compared with adjuvant CT after radical hysterectomy.

Materials and Methods

A total of 321 patients with FIGO Stage Ib to IIb cervical AC, who underwent type III radical hysterectomy in 13 institutes (Hyogo Cancer Center, Kagoshima City Hospital, National Hospital Organization Shikoku Cancer Center, National Hospital Organization Kure Medical Center, Miyagi Cancer Center, Fukushima Medical University, Yamagata University, Akita University, Tohoku University School of Medicine, Hirosaki University School of Medicine, Iwate Medical University, Saitama Medical University International Medical Center and Tottori University Hospital) between April 1997 and March 2003, were enrolled in this study. Data were collected from the patients' medical records. Patients' characteristics are shown in Table 1. There were 263 patients with AC and 58 with ASCC. The study protocol was approved by the institutional review board at each institution.

One hundred seventy patients (53.0%) underwent radical hysterectomy alone. The remaining 151 patients (47%) received adjuvant treatment after radical hysterectomy. Of these 151 patients, 69 patients received RT alone including CCRT with weekly CDDP, 64 patients received CT alone, and 18 patients received concomitant RT + CT. The indications for adjuvant treatment were as follows: pelvic lymph node involvement, parametrial extension, deep stromal invasion, lymphovascular invasion, and a compromised surgical margin, although the indications for adjuvant treatment were not identical among our 13 institutions. External irradiation with a parallel opposing portal technique using Lineac was used for the adjuvant RT. External irradiation consisted of 10-20 Gy whole pelvis and additional parametrial dose with midline block to deliver a total of 45-50 Gy to the pelvic sidewall. Intensity- modulated whole radiation therapy was not used in all 13 institutions at 2003. Most of the adjuvant CT, including 31 subjects for mytomycin C, etoposide and cisplatin combination CT (MEP), 11 for taxane compound and platinum compound combination CT, nine for cyclophosphamide, doxorubicin HCl and cisplatin combination CT (PAF), three for etoposide and cisplatin combination CT (EP), two for doxorubicin HCl and cisplatin combination CT (AP), irinotecan HCl and cisplatin combination CT, was platinum-based CT. The chemotherapeutic regimens and number of cycles were also decided in each institution.

Table 3. — *Pathological risk factors and adjuvant treatment.*

Pathological risk factor	CT	RT	RT + CT
LN involvement	13	27	13
Parametrial extension	12	14	7
Deep stromal invasion	19	17	2
Vessel permeation	26	35	3
Compromised surgical margin	1	7	0
Bulky tumor	26	28	9

Patient survival distribution was calculated using the Kaplan-Meier method. The significance of the survival distribution in each group was tested by the log-rank test. The chi-square test was used to compare any associations of prognostic factors. Additionally, multivariate analysis was performed with Stat View Version J-5.0 to fit the Cox proportional hazards model. A $p < 0.05$ was considered significant.

Results

The five-year progression-free survival (PFS) rate and overall survival (OS) rate were 89.8% and 91.4% in Stage Ib1, 66.2% and 76.2% in Stage Ib2, 46.2% and 61.5% in Stage IIa, and 51.9% and 63.7% in Stage IIb, respectively. No significant difference in the outcome was shown between patients with AC and those with ASCC (five-year OS; 83.7% vs. 82.2%, $p = 0.9725$). The incidences of lymph node involvement and FIGO Stage are shown in Table 2.

The five-year OS for patients with and without adjuvant treatment was 86.5% and 95.6% in Stage Ib1, 78.6% and 66.7% in Stage Ib2, 42.9% and 75.0% in Stage IIa, and 57.3% and 64.8% in Stage IIb, respectively. These differences were significantly different in all FIGO Stages. Of 151 patients receiving adjuvant treatment after radical hysterectomy, there were 70 patients in Stage Ib1, 33 in Stage Ib2, 8 in Stage IIa, and 40 in Stage IIb. Table 3 shows full details of the risk factors and adjuvant treatments after radical hysterectomy. The five-year OS for patients receiving RT was 70.9%, 79.2% for those receiving CT, and 66.2% for those receiving RT + CT (Figure 1). CT showed a superior outcome to RT or RT+CT, but the difference was not statistically significant ($p = 0.3701$).

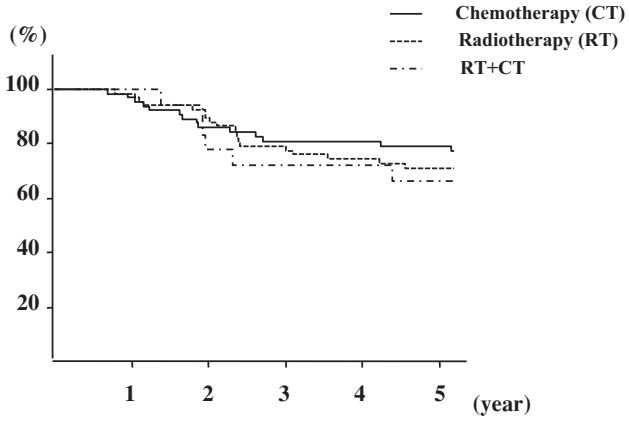

Figure 1. — The five-year overall survival rate and adjuvant treatment for cervical AC patients with pathological risk factors.
The five-year OS rate was 79.2% for patients receiving adjuvant CT, 70.9% for adjuvant RT, and 66.2% for concomitant adjuvant RT + CT, respectively. Adjuvant treatment did not significantly affect the outcome of cervical AC patients with pathological risk factors ($p = 0.3701$).

Table 4. — *Univariate analysis in patients receiving adjuvant treatment.*

Prognostic factor	Number	Five-year OS	*p* value
LN involvement			
Positive	51	32.0%	<0.0001
Negative	100	84.5%	
Parametrial extension			
Positive	30	32.1%	<0.0001
Negative	121	75.5%	
Tumor size			
≥ 4cm	61	50.2%	0.0002
< 4cm	90	78.3%	
Deep stromal invasion			
Positive	37	62.1%	0.0518
Negative	114	81.1%	
Vessel permeation			
Positive	63	64.3%	0.7402
Negative	88	68.5%	
Compromised surgical margin			
Positive	8	50.0%	0.2005
Negative	143	67.7%	

Table 5. — *Multivariate analysis in patients receiving adjuvant treatment*

Prognostic factors	Risk ratio	95% CI	*p* value
Lymph node involvement	6.003	2.954 – 12.198	< 0.0001
Parametrial extension	2.115	1.108 – 4.039	0.0232
Tumor size	1.597	0.844 – 3.024	0.1503

Univariate analysis revealed that pelvic lymph node involvement, parametrial extension, and tumor size affected the outcome of patients with adjuvant treatment, but deep stromal invasion, vessel permeation and a compromised surgical margin did not (Table 4). Adjuvant treatment did not affect the outcome of patients with lymph node involvement (five-year OS; 42.0% for RT, 51.4% for CT, 52.7% for RT + CT, $p = 0.8214$). In patients with parametrial extension, adjuvant treatment also did not affect the outcome (five-year OS; 52.4% for RT, 44.4% for CT, 16.7% for RT + CT, $p = 0.1475$). Multivariate analysis revealed that pelvic lymph node involvement and parametrial extension were independent prognostic factors, but tumor size was not (Table 5).

Eighteen patients recurred of those receiving adjuvant CT, 28 of those with adjuvant RT, and five of those with concomitant RT and CT. The incidence of recurrence was not significantly different among adjuvant treatments (CT: 24.3% (18/74), RT: 40.0% (28/70), RT + CT: 29.4% (5/17), $p = 0.1269$). Adjuvant treatment also did not affect the pattern of recurrence.

Discussion

Many authors have attempted to clarify whether the histological type affected the outcome of Stage I-II cervical cancer [5-7, 10-12]. Shingleton reported that the histological type had no significant effect on survival in patients with Stage Ib cervical cancer [10]. Kasamatsu also reported that FIGO Stage I-II patients with SCC and AC showed similar prognosis in their retrospective analysis [11]. In contrast, Chen reported that the outcome of 277 patients with AC was significantly worse than 2,917 patients with SCC in Stage I-II [12]. Lai also demonstrated that the prognosis of AC and ASC was slightly worse than SCC [13]. The present authors' previous study also revealed that patients with AC showed significantly worse prognosis than those with SCC [7]. It has been controversial whether the prognosis of patients with cervical cancer is dependent on the histologic type.

Lymph node involvement is one of the most important prognostic factors in patients with cervical cancer. It remains unclear whether patients with AC had a higher incidence of lymph node involvement than those with SCC. Nakanishi showed no significant difference in the frequency of lymph node involvement between patients with AC and SCC [14]. Sakuragi also demonstrated that the histological type did not affect the incidence of lymph node involvement in patients with Stage Ib–IIb (20.0% (9/45) vs. 27.0% (44/163)) [15]. In contrast, the largest series of patients with cervical cancer suggested that the incidence of lymph node involvement was more frequent in patients with SCC than in those with AC and ASC (9.5% (51/538) vs. 12.6% (279/2,217), $p = 0.0466$) [10]. To the authors' knowledge, the present data on the incidence of lymph node involvement in each stage are one of the largest series of Stage Ib–II patients with cervical AC. In this series, the incidence of lymph node involvement was 9.0% (19/211) in Stage Ib1, 23.9% (11/46) in Stage Ib2, 30.8% (4/13) in Stage IIa, and 41.2% (21/51) in Stage IIb. The incidence of lymph node involvement gradually rose in proportion to the FIGO Stage.

A randomized study of radical surgery and/or adjuvant RT versus RT for Stage Ib–II cervical cancer showed that RT was less effective than surgery in patients with AC [8], suggesting low radiosensitivity for AC of the uterine cervix. In addition, Eifel reported that AC had a worse prognosis than SCC in 1,767 patients with Stage I cervical cancer receiving initial RT because of the higher incidence of distant metastasis in patients with AC; however, there was no significant difference in the rate of pelvic disease recurrence between patients with AC and SCC [16]. In the present series, adjuvant treatment did not affect the site of recurrence in patients with AC. Furthermore, adjuvant RT might induce a relatively high incidence of serious complications, including small bowel obstruction and leg lymphedema [17, 18]. Consequently, it is suspected that RT including CCRT is the best treatment for high-risk patients with AC.

Adjuvant CT can avoid these serious complications after radical hysterectomy. Furthermore, RT can be selected as a useful strategy for possible pelvic recurrence. In the present retrospective study, adjuvant CT was equally effective for patients with AC as adjuvant RT. Takeshima *et al*. also indicated the potential role of adjuvant CT for patients with cervical cancer because of the equal effect and lower toxicity than with adjuvant RT [19, 20].

Conclusion

CT may be effective adjuvant treatment for high-risk patients with cervical AC. A phase II study is necessary to evaluate the efficacy and safety of adjuvant CT for cervical AC patients with pathological risk factors. Additionally, a randomized phase III trial to compare adjuvant CT and adjuvant RT for high-risk patients with AC is also necessary in the near future.

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