Journal of Radiation Research, Vol. 57, No. 6, 2016, pp. 684–690
doi: 10.1093/jrr/rrw070
Advance Access Publication: 15 July 2016

Carbon-ion radiotherapy for locally advanced cervical cancer with bladder invasion

Shintaro Shiba[1,2], Masaru Wakatsuki[2,3*], Shingo Kato[4], Tatsuya Ohno[1], Noriyuki Okonogi[2], Kumiko Karasawa[5], Hiroki Kiyohara[1], Hirohiko Tsujii[2], Takashi Nakano[1], Tadashi Kamada[2], Makio Shozu[6] and The Working Group of the Gynecological Tumor

[1]Department of Radiation Oncology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan
[2]National Institutes for Quantum and Radiological Science and Technology, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba-city, Chiba 263-8555, Japan
[3]Department of Radiology, Jichi Medical University, 3311-1, Yakushiji, Simotsuke-city, Tochigi 329-0498, Japan
[4]Department of Radiation Oncology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan
[5]Department of Radiation Oncology, Tokyo Women's Medical University, School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
[6]Department of Reproductive Medicine, Graduate School of Medicine, Chiba University, 1-8-1 Inohara Chuo-ku, Chiba 260-8670, Japan
*Corresponding author. Department of Radiology, Jichi Medical University, 3311-1, Yakushiji, Simotsuke-city, Tochigi 329-0498, Japan.
Tel: +81-285-58-7161; Fax: +81-285-44-4296; Email: wakkun100@yahoo.co.jp
Received January 7, 2016; Revised February 28, 2016; Accepted May 18, 2016

ABSTRACT

The purpose of this study was to evaluate the efficacy and toxicities of carbon-ion radiotherapy (C-ion RT) for locally advanced cervical cancer with bladder invasion by a subset analysis of pooled data from eight prospective clinical trials at the National Institute of Radiological Sciences. Between June 1995 and January 2014, 29 patients with locally advanced cervical cancer with bladder invasion were identified. The median age was 56 years old (range 31–79 years old). The median tumor size at diagnosis on magnetic resonance imaging was 6.7 cm (range 3.5–11.0 cm). Histologically, 20 patients had squamous cell carcinoma and 9 had adenocarcinoma. C-ion RT was performed as a dose-escalation study in the initial trials. All patients received prophylactic whole-pelvic or extended-field irradiation and local boost. The total dose to the cervical tumor was 52.8–74.4 Gy (relative biological effectiveness) in 20 or 24 fractions. Weekly cisplatin (40 mg/m^2/week, five cycles) was concurrently given to four patients. The median follow-up of all patients was 28.6 months (range 8.8–238.6 months). Grade 2 or higher late complications in the bladder were observed in eight patients, with seven developing vesicovaginal fistula. Six patients had Grade 2 or higher complications in the rectosigmoid colon. The 3-year overall survival rate was 47%, the 3-year local control rate was 66%, and the 3-year disease-free survival rate was 28%. In this study, C-ion RT showed favorable local control with reasonable toxicities, but the results were still unsatisfactory. We have the expectation of improvement of therapeutic effects by using C-ion RT with concurrent chemotherapy.

KEYWORDS: carbon-ion radiotherapy, cervical cancer, Stage IVA, bladder invasion, vesicovaginal fistula

INTRODUCTION

Stage IVA cervical cancer is defined by the International Federation of Gynecology and Obstetrics (FIGO) and the Union for International Cancer Control as a disease directly invading the mucosa of the bladder and/or rectum but not metastasizing to distant sites.

Cervical cancer is the second-most common cause of cancer-related death among women worldwide, with 500 000 newly diagnosed annually. Stage IVA cervical cancer is rare, accounting for only 3% of all cervical cancer patients [1, 2], and there are only a small number of reports on the clinical results of Stage IVA cervical cancer [3–5].

In radiotherapy for cervical cancer, the combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is considered one of the standard treatments, and ICBT plays an important role in local tumor control [2, 6]. However, conventional ICBT with a tandem and ovoid system might not deliver a sufficient dose in the case of bulky tumors or bladder invasion. In the FIGO 2006 Annual Report, 326 patients with Stage IVA cervical cancer were reported and the 3-year overall survival rate (3yOS) was 28% [2]. Rose *et al.* reported the clinical outcome of patients with Stage IVA cervical cancer treated with radiotherapy, and the 3yOS was 32% [4]. Clearly, the clinical outcome for Stage IVA cervical cancer is far from satisfactory.

In 1994, carbon-ion radiotherapy (C-ion RT) was started at the National Institute of Radiological Sciences (NIRS) [7]. Carbon-ion beams have improved the dose localization properties because their Bragg peak results in distal tail-off and a sharp penumbra. This property of carbon-ion beams provides a highly conformal dose distribution, and thus a high dose can be delivered to tumors while minimizing normal tissue damage. Moreover, they possess biological advantages due to their high relative biological effectiveness (RBE) in the Bragg Peak [7–10]. A number of Phase I/II or Phase II clinical trials by C-ion RT have been conducted for several malignant tumors at NIRS [11–14]. Our group has conducted eight prospective clinical trials for cervical cancer, and we have reported five clinical trials of C-ion RT for locally advanced cervical cancer [15–20]. These reports describe C-ion RT as showing favorable clinical outcomes with reasonable toxicities, suggesting that C-ion RT is one of the most effective treatments. However, they include few Stage IVA cervical cancer cases individually. Thus, the current study especially analyzed clinical outcomes of C-ion RT for locally advanced cervical cancer with bladder invasion, and it has been presented as a subset analysis of eight clinical trials.

MATERIALS AND METHODS

Patients

This subset analysis was performed using the medical records of patients treated with C-ion RT for pathologically proven primary invasive cervical cancer at NIRS. All patients were diagnosed with clinical Stage IVA cervical cancer with bladder invasion but no rectal invasion by cystoscopy or/and proctoscopy. Pretreatment evaluation was performed, including medical history, physical and bimanual pelvic examinations by gynecologists and radiation oncologists, cervical biopsy, routine blood cell counts, blood chemistry, urine analysis, chest X-ray, computed tomography (CT) scans of the pelvis and abdomen, and magnetic resonance imaging (MRI) of the pelvis. When indicated, proctoscopy was performed. All patients were staged according to the FIGO staging system. Patients were excluded from this study if they had para-aortic lymph node ≥1 cm in minimum diameter on CT images, although patients with enlarged pelvic lymph nodes only were included. Cervical tumor size was assessed by both pelvic examination and MRI, and the dimensions were determined according to T2-weighted MRI images. In eight clinical trials, 229 patients were registered, and a total of 29 patients (12.7%) were entered into this subset analysis.

The treatment protocol for the current study was reviewed and approved by the National Institute of Radiological Sciences Ethics Committee of Human Clinical Research, and all patients signed an informed consent form before the initiation of therapy.

Carbon-ion radiotherapy

The treatment method for C-ion RT has been described previously [15–19]. In brief, patients received C-ion RT once daily, 4 days per week (Tuesday to Friday). At every treatment session, the patient was positioned on the treatment couch with the immobilization devices, and the patient's position was verified by a computer-aided, on-line positioning system. Digital orthogonal X-ray images were taken and transferred to the positioning computer. The positioning images were compared with reference images that were digitally reconstructed from CT scans. If the difference in positioning was >2 mm, the treatment couch was moved until an acceptable position was attained. To minimize internal motion of the uterine cervix, 100–150 ml of normal saline was infused into the bladder and vaginal packing was done tightly at each treatment session. In addition, the cotton for vaginal packing was soaked in a contrast medium and the surface of the uterine cervix could be visualized by X-ray images at the treatment session for the last seven or eight fractions of secondary and last local boost treatment. The internal position of the uterine cervix could be identified by checking the position of the vaginal packing [18]. The radiation dose was calculated for the target volume and surrounding normal structures and was expressed in Gray (relative biologic effectiveness; RBE); it was defined as the physical dose multiplied by the RBE of the carbon ions [21].

The treatment consisted of prophylactic whole-pelvic or extended-field irradiation and local boost. In the patients who registered after June 1998, their planning CT scan was basically performed three times during the treatment course. On the basis of previous clinical trials, the clinical target volume (CTV) for local boost was reduced twice with tumor shrinkage, and gastrointestinal tracts were completely excluded at the last local boost plan for cervical tumor to reduce gastrointestinal tract complications [15]. The CTV for the whole-pelvic irradiation included all areas of gross and potentially microscopic disease, and consisted of the primary site (gross tumor volume: GTV), uterus, ovaries, parametrium, at least the upper half of the vagina, and the pelvic lymph nodes (common iliac, internal iliac, external iliac, obturator and presacral lymph nodes) (= CTV-1). The CTV for the extended-field irradiation consisted of the whole pelvic irradiation area and the para-aortic lymph node area. After completing CTV-1 irradiation, the first reduction of the CTV included the GTV and uterus, parametrium, upper half of the vagina, ovaries and enlarged lymph nodes (= CTV-2). Finally, the CTV was shrunk to the GTV only (= CTV-3). This GTV was determined on the third CT as compared with that on the MRI. MRI was performed one day before or on the same day as the third CT. Figure 1 shows a typical dose distribution.

C-ion RT was performed as a dose-escalation study from the start, and one clinical trial included prophylactic extended-field irradiation for para-aortic lymph node regions. The total dose to the GTV was 52.8–74.4 Gy (RBE) in 20 or 24 fractions. The patient

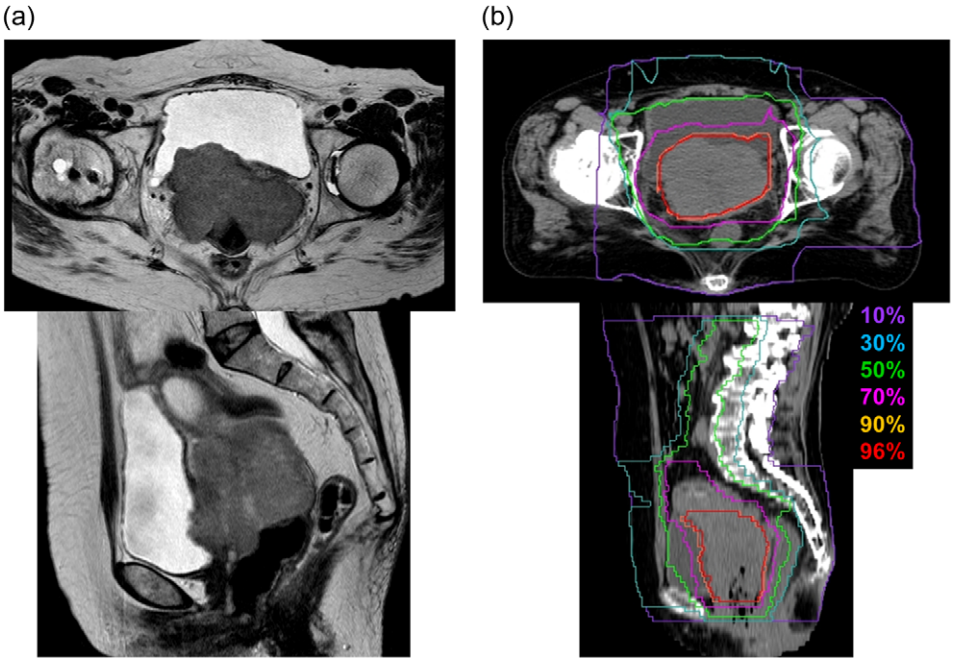

Fig. 1. A case of cT4N1M0 cervical cancer treated with C-ion RT. (a) MRI on axial and sagittal images before the treatment. (b) Dose distribution on axial and sagittal CT images. The primary CTV included the whole pelvic irradiation area with or without the prophylactic para-aortic lymph node irradiation area as about the 50% line of dose distribution. The secondary plan included the GTV and uterus, parametrium, upper half of the vagina, ovaries and enlarged lymph nodes as the 70% line of dose distribution. The last boost plan included the GTV only as 96% of the dose distribution. Figure 1 shows the extended-field irradiation plan.

and disease characteristics are shown in Table 1. Patients were divided into groups according to total dose of <60 Gy (RBE), 60–70 Gy (RBE) and ≥70 Gy (RBE) were 2 patients, 14 patients and 13 patients, respectively.

Chemotherapy

The clinical trials of C-ion RT with concurrent chemotherapy of weekly cisplatin (40 mg/m^2/week) for locally advanced cervical cancer were begun in 2010. C-ion RT with concurrent chemotherapy was not performed in patients with insufficient renal function or age over 70 years, so only 4 of the 29 patients received C-ion RT with concurrent chemotherapy.

Follow-up

After completion of C-ion RT, patients were followed up monthly for 1 year, every 2 months during the second year, and every 3 or 6 months thereafter. The examination consisted of physical and bimanual pelvic examinations, routine blood cell counts, blood chemistry, CT scans of the pelvis and abdomen, and MRI of the pelvis. The CT scan and MRI were performed every 3 months during the first 6 months, then every 6 months for 2 years, and every 6 months or 1 year thereafter. Suspected persistent or recurrent disease was confirmed by biopsy whenever possible in order to evaluate the disease status and late complications. Treatment failures were classified as local failure, pelvic lymph node recurrence or distant metastases. Local failure was defined as recurrent disease in the uterus, vagina or parametrium. Late radiation complications were graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) late radiation morbidity scoring scheme [22].

Statistical analysis

Survival was measured from the date of initiation of treatment to the date of death or the most recent follow-up. Probabilities of overall survival (OS), local control (LC) and disease-free survival (DFS) rates were calculated using the Kaplan–Meier method.

Prognostic values for LC and OS were investigated by log-rank test. Age (≤55 or ≥56), tumor size (<7 cm or ≥7 cm), histological type (squamous cell carcinoma or adenocarcinoma), pelvic lymph node swelling (yes or no), total dose (<70 Gy (RBE) or ≥70 Gy (RBE)) were considered binary variables. Statistical significance was defined as a P value of <0.05. All statistical analyses were performed using SPSS Statistics version 22 (SAS Institute, Tokyo, Japan).

RESULTS

Outcomes

Between June 1995 and January 2014, 29 patients with Stage IVA cervical cancer with bladder invasion were enrolled and received C-ion RT in eight clinical trials. This study was analyzed in May 2016. The patient characteristics are shown in Table 1. The median age was 56 years old (range, 31–79 years old). The median follow-

Table 1. Patient and disease characteristics ($n = 29$)

Characteristics	No.
Age, y, median (range)	56 (31–79)
Histology	
Squamous cell carcinoma	20 (69%)
Adenocarcinoma	9 (31%)
Pelvic lymph node swelling	
Yes	19 (66%)
No	10 (34%)
Tumor size	
≤7 cm	15 (52%)
>7 cm	14 (48%)
Treatment	
C-ion RT alone (consisting of whole-pelvic irradiation)	25 (86%)
C-ion RT with weekly cisplatin	4 (14%)
RT field	
Whole-pelvis	27 (93%)
Extended-field	2 (7%)
Total dose	
<60 Gy (RBE)	2 (7%)
≥60 and <70 Gy (RBE)	14 (48%)
≥70 Gy (RBE)	13 (45%)

Gy (RBE) = Gray (relative biologic effectiveness), y = year.

up for all patients and surviving patients was 28.6 months (range, 8.8–238.6 months) and 65.8 months (range, 25.5–238.6 months), respectively. Histologically, 20 patients had squamous cell carcinoma and 9 had adenocarcinoma. Nineteen of the patients had enlarged pelvic lymph nodes. The tumor size was 3.5–11.0 cm in maximum diameter, with a median size of 6.7 cm.

The OS, LC and DFS curves of all patients are shown in Fig. 2. The 3yOS, 3-year LC (3yLC) and 3-year DFS (3yDFS) rates were 47%, 66% and 28%, respectively. At the end of the current study, 5 patients were alive and disease free, 4 patients were alive with disease, 17 patients had died of disease, and 3 patients had died of intercurrent disease. By univariate analysis, no factor showed a statistically significant impact on 3yLC or 3yOS without 3yOS of LN swelling status (Table 2).

Five patients had regional lymph node metastasis. Seventeen patients had distant metastasis. Nine of 17 had para-aortic lymph node metastasis, and these nine patients did not receive prophylactic extended-field radiation therapy.

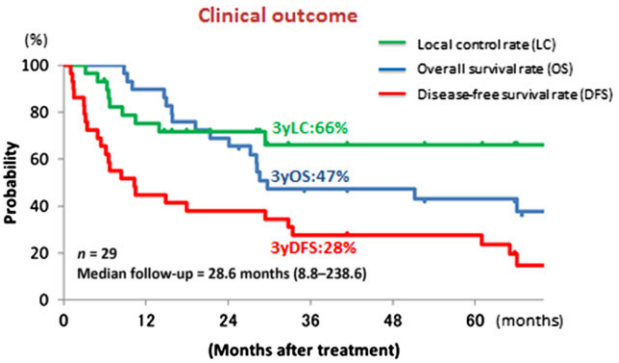

Fig. 2. The overall survival, local control, and disease-free survival curves; overall survival (blue line), local control (green line), disease-free survival (red line) are shown for all patients treated with carbon-ion radiotherapy.

Table 2. Risk factors for recurrence and death (calculated by univariate analysis)

Risk factor	No.	3-y LC (%)	*P* value	3-y OS (%)	*P* value
Age, y					
≤55	14	51	0.295	43	0.957
≥56	15	79		51	
Histology					
Squamous cell carcinoma	20	63	0.680	45	0.526
Adenocarcinoma	9	76		53	
Pelvic lymph node swelling					
Yes	19	62	0.132	29	0.046*
No	10	79		80	
Tumor size					
<7 cm	15	57	0.914	45	0.667
≥7 cm	14	71		50	
RT field					
Whole-pelvis	27	68	0.542	51	0.055
Extended-field	2	50		50	
Total dose					
<70 Gy (RBE)	16	66	0.577	50	0.481
≥70 Gy (RBE)	13	67		45	

*Significance at $P < 0.05$. y = year.

Table 3. Late complications by RTOG/EORTC scoring scheme

Organs involved	Total no.	G0	G1	G2	G3	G4
Rectum/Sigmoid	29	9	14	2	0	4
Bladder	29	17	3	1	8[a]	0
Skin	29	21	7	1	0	0

[a]Includes developing vesicovaginal fistula ($n = 7$). RTOG/EORTC = Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.

Late complications

All of the observed late complications are listed in Table 3. Eleven patients developed late complications of the bladder, and 20 of the rectosigmoid colon. Six patients had Grade 2 or higher complications in the rectosigmoid colon. Grade 4 late complications in the rectosigmoid colon has already been discussed in a previous report [15]. In all cases of Grade 4 late rectosigmoid colon complication, the maximum dose to the rectosigmoid colon was 60 Gy (RBE) or over. On the other hand, <60 Gy (RBE) irradiation for rectosigmoid colon cases did not lead to development of Grade 4 late rectosigmoid colon complication. Therefore, a dose limitation of 60 Gy (RBE) for the rectosigmoid colon has been followed since 1998 [15]. Eight of the 29 patients developed vesicovaginal fistula. In one of these patients, the fistula was diagnosed before treatment. The vesicovaginal fistula formation rate was 28%, and the median time of fistula diagnosis was 13.8 months (range 0–19 months). Four of the eight patients with vesicovaginal fistula had a urostomy.

DISCUSSION

This is the first report of the clinical outcome from C-ion RT for locally advanced cervical cancer with bladder invasion. It was shown that C-ion RT resulted in favorable OS and LC rates regardless of histological type or tumor size, compared with the conventional treatment.

The standard treatment for Stage IVA cervical cancer is concurrent chemoradiotherapy (CCRT). Several researchers reported the outcome for Stage IVA patients treated with RT alone or CCRT. Those reports showed that survival rates for Stage IVA disease were between 10% and 42%, and LC rates were between 18% and 61% [3, 23–26]. In the present study of C-ion RT, 3yOS and 3yLC for Stage IVA patients were 47% and 66%, respectively. Although the number of patients in this study was small, C-ion RT for locally advanced cervical cancer with bladder invasion showed favorable OS and LC rates, compared with earlier reports for the standard treatment.

C-ion RT for cervical cancer was performed as a dose-escalation study; the total dose to the GTV was 52.8–74.4 Gy (RBE) in 20 or 24 fractions in these studies. When this was calculated as the biologically equivalent dose in 2-Gy fractions (EQD2) using the linear–quadratic model for incomplete sublethal damage repair [27], the total dose to the cervical tumor was 56.9–86.4 Gy (RBE) (EQD2). In the European and American standard radiotherapy for cervical cancer, the prescribed dose of combination with EBRT and ICBT was 80–85 Gy (EQD2) [28, 29]. This result showed what a dose-escalation study achieved with a relatively similar dose to the European and American standard treatment. In addition, C-ion RT had a shorter overall treatment time than standard radiotherapy for cervical cancer. This might have contributed to the treatment effect of C-ion RT. In this analysis, 3yOS and 3yLC rates of patients with squamous cell carcinoma were 45% and 63%, and those with adenocarcinoma were 53% and 76%, respectively. The prognosis for patients of cervical adenocarcinoma receiving radiotherapy is thought to be poorer than that of squamous cell carcinoma because adenocarcinoma of the uterine cervix is more radioresistant than squamous cell carcinoma. Therefore, C-ion RT for locally advanced adenocarcinoma of the uterine cervix is expected to improve the clinical outcome because this radiation methodology has a highly conformal dose distribution and biological advantages. In previous reports, Wakatsuki *et al.* reported that clinical outcomes of C-ion RT for locally advanced adenocarcinoma of the uterine cervix were relatively better than those of conventional treatments [19]. Focused on clinical outcomes for Stage III or IVA of adenocarcinoma with conventional treatments, Nakano *et al.* reported a 9% survival rate with Stage IVA adenocarcinoma of the uterine cervix, and a 32% survival rate with Stage III adenocarcinoma of the uterine cervix [30]. Eifel *et al.* reported a 31% survival rate with Stage III/IV adenocarcinoma of the uterine cervix [31]. In the present report, 3yOS rates of patients with adenocarcinoma were 53%, so the clinical outcomes for adenocarcinoma with Stage IVA disease appear to be favorable compared with those of conventional treatment, although the number of patients was small. In this analysis, the 3yLC rate of patients with adenocarcinoma was 76%, which is similar to that for squamous cell carcinoma. Considering adenocarcinoma of the uterine cervix is more radioresistant than squamous cell carcinoma, LC might be favorable compared with conventional treatment. Thus, it is considered that the improvement in LC is one of the factors leading to a better overall survival.

The 3yOS and 3yLC rates of patients with a larger tumor appeared to be similar to those with a smaller tumor, and there was no correlation between tumor size and OS or LC rates in the present study. Tumor size is a well-known prognostic factor. Nakano *et al.* and Kodaira *et al.* reported the correlation between tumor size and treatment outcome for cervical cancer with radiotherapy [6, 30, 32]. One reason for this is that bulky tumor has a larger hypoxic component, which is known to be radioresistant [33]. Palcic and Skarsgard reported that hypoxic cell survival rates were poorer than those of aerated cells in Chinese hamster. The dose-dependent oxygen enhancement ratio (OER) was a true radiological phenomenon in photon irradiation in an in vitro study [34]. In a clinical study, Suzuki *et al.* reported that hypoxic tumors were related to worse LC rates in radiotherapy for cervical cancer [35]. Even though Kizaka-Kondoh *et al.* reported that a small tumor with a volume of more than 2 cm^3 has an extremely hypoxic lesion [36], as the tumor increase in size, the proportion of hypoxic lesion might also become increased. On the other hand, Hirayama *et al.* reported that OER values of C-ion RT with squamous cell carcinoma cells (SCCVII) were small in comparison to those of X-ray *in vitro* [37]. Nakano *et al.* reported similar LC rates after C-ion RT between hypoxic and oxygenated tumors for cervical cancer in a clinical study [38]. Thus,

the therapeutic effect for bulky tumor means that C-ion RT may have an advantage for the hypoxic component.

Vesicovaginal fistula formation is one of the important radiation-induced complications for locally advanced cervical cancer with bladder invasion. Biewenga *et al.* reported that 22% of treated patients developed vesicovaginal fistula at a median time of 9 months [23], and Moore *et al.* reported that 48% developed vesicovaginal fistula at a median time of 2.9 months [25]. In this study, 8 of the 29 patients developed vesicovaginal fistula. In one of these patients, the fistula was diagnosed before treatment. The vesicovaginal fistula formation rates were 28%, and median time of fistula diagnosis was 13.8 months (range 0–19 months). These results were close to those of several reports. Even though there is a risk of vesicovaginal fistula formation, intensive therapy, such as C-ion RT with chemotherapy, should be considered essential for Stage IVA disease.

In conclusion, C-ion RT showed a favorable OS and LC rate regardless of histological type or tumor size, compared with conventional treatment, but the results were still unsatisfactory. In the present study, the number of patients receiving C-ion RT with chemotherapy was small, and there was no noted effect of C-ion RT in combination with chemotherapy. Thus, investigations should be continued, with the expectation of improvement of therapeutic effects from the use of C-ion RT with concurrent chemotherapy.

FUNDING

This work was supported by the Research Project with Heavy Ions at the National Institute of Radiological Sciences, and Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan for programs for Leading Graduate Schools, Cultivating Global Leaders in Heavy Ion Therapeutics and Engineering.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Yang BH, Bray FI, Parkin DM, et al. Cervical cancer as a priority for prevention in different world regions: an evaluation using years of life lost. *Int J Cancer* 2004;109:418–24.
2. Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecology and obstetrics: the official organ of the International Federation of Gynaecol Obstet* 2006;95 Suppl 1:S43–103.
3. Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the Cervix Uteri. *Int J Gynecol Obstet* 2006;95:S43–103.
4. Rose PG, Ali S, Whitney CW, et al. Outcome of stage IVA cervical cancer patients with disease limited to the pelvis in the era of chemoradiation: a Gynecologic Oncology Group study. *Gynecol Oncol* 2011;121:542–5.
5. Wakatsuki M, Kato S, Kiyohara H, et al. The prognostic value of rectal invasion for stage IVA uterine cervical cancer treated with radiation therapy. *BMC Cancer* 2016;16:244.
6. Nakano T, Kato S, Ohno T, et al. Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. *Cancer* 2005;103:92–101.
7. Tsujii H, Kamada T. A review of update clinical results of carbon ion radiotherapy. *Jpn J Clin Oncol* 2012;42:670–85.
8. Ando K, Koike S, Nojima K, et al. Mouse skin reactions following fractionated irradiation with carbon ions. *Int J Radiat Biol* 1998;74:129–38.
9. Kanai T, Endo M, Minohara S, et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. *Int J Radiat Oncol Biol Phys* 1999;44:201–10.
10. Kanai T, Furusawa Y, Fukutsu K, et al. Irradiation of mixed beam and design of spread-out Bragg peak for heavy-ion radiotherapy. *Radiat Res* 1997;147:78–85.
11. Karasawa K, Wakatsuki M, Kato S, et al. Clinical trial of carbon ion radiotherapy for gynecological melanoma. *J Radiat Res* 2014;55:343–50.
12. Nomiya T, Tsuji H, Maruyama K, et al. Phase I/II trial of definitive carbon ion radiotherapy for prostate cancer: evaluation of shortening of treatment period to 3 weeks. *Br J Cancer* 2014;110:2389–95.
13. Shinoto M, Yamada S, Yasuda S, et al. Phase 1 trial of preoperative, short-course carbon-ion radiotherapy for patients with resectable pancreatic cancer. *Cancer* 2013;119:45–51.
14. Takahashi W, Nakajima M, Yamamoto N, et al. A prospective nonrandomized phase I/II study of carbon ion radiotherapy in a favorable subset of locally advanced non–small cell lung cancer (NSCLC). *Cancer* 2015;121:1321–7.
15. Kato S, Ohno T, Tsujii H, et al. Dose escalation study of carbon ion radiotherapy for locally advanced carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 2006;65:388–97.
16. Nakano T, Suzuki M, Abe A, et al. The phase I/II clinical study of carbon ion therapy for cancer of the uterine cervix. *Cancer J Sci Am* 1999;5:362–9.
17. Wakatsuki M, Kato S, Kiyohara H, et al. Clinical trial of prophylactic extended-field carbon-ion radiotherapy for locally advanced uterine cervical cancer (Protocol 0508). *PLoS One* 2015;10: e0127587.
18. Wakatsuki M, Kato S, Ohno T, et al. Dose-escalation study of carbon ion radiotherapy for locally advanced squamous cell carcinoma of the uterine cervix (9902). *Gynecol Oncol* 2014; 132:87–92.
19. Wakatsuki M, Kato S, Ohno T, et al. Clinical outcomes of carbon ion radiotherapy for locally advanced adenocarcinoma of the uterine cervix in phase 1/2 clinical trial (protocol 9704). *Cancer* 2014;120:1663–9.
20. Wakatsuki M, Kato S, Ohno T, et al. Difference in distant failure site between locally advanced squamous cell carcinoma and adenocarcinoma of the uterine cervix after C-ion RT. *J Radiat Res* 2015;56:523–8.
21. Inaniwa T, Kanematsu N, Matsufuji N, et al. Reformulation of a clinical-dose system for carbon-ion radiotherapy treatment planning at the National Institute of Radiological Sciences, Japan. *Phys Med Biol* 2015;60:3271–86.
22. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European

Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–6.
23. Biewenga P, Mutsaerts MA, Stalpers LJ, et al. Can we predict vesicovaginal or rectovaginal fistula formation in patients with stage IVA cervical cancer? *Int J Gynecol Cancer* 2010;20:471–5.
24. Kramer C, Peschel RE, Goldberg N, et al. Radiation treatment of FIGO stage IVA carcinoma of the cervix. *Gynecol Oncol* 1989;32:323–6.
25. Moore KN, Gold MA, McMeekin DS, et al. Vesicovaginal fistula formation in patients with Stage IVA cervical carcinoma. *Gynecol Oncol* 2007;106:498–501.
26. Perez CA, Breaux S, Madoc-Jones H, et al. Radiation therapy alone in the treatment of carcinoma of uterine cervix. I. Analysis of tumor recurrence. *Cancer* 1983;51:1393–402.
27. Fowler JF. The linear–quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989;62:679–94.
28. Forrest JL, Ackerman I, Barbera L, et al. Patient outcome study of concurrent chemoradiation, external beam radiotherapy, and high-dose rate brachytherapy in locally advanced carcinoma of the cervix. *Int J Gynecol Cancer* 2010;20:1074–8.
29. Lim A, Sia S. Outcomes of chemoradiotherapy in cervical cancer—the Western Australian experience. *Int J Radiat Oncol Biol Phys* 2012;82:1431–8.
30. Nakano T, Arai T, Morita S, et al. Radiation therapy alone for adenocarcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1995;32:1331–6.
31. Eifel PJ, Morris M, Oswald MJ, et al. Adenocarcinoma of the uterine cervix. Prognosis and patterns of failure in 367 cases. *Cancer* 1990;65:2507–14.
32. Kodaira T, Fuwa N, Toita T, et al. Comparison of prognostic value of MRI and FIGO stage among patients with cervical carcinoma treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;56:769–77.
33. Hall EJ, Giaccia AJ. *Radiobiology for the Radiologist.* (7th edn.). Philadelphia: Wolters Kluwer Health, Lippincott Williams & Wilkins, 2012.
34. Palcic B, Skarsgard LD. Reduced oxygen enhancement ratio at low doses of ionizing radiation. *Radiat Res* 1984;100:328–39.
35. Suzuki Y, Nakano T, Ohno T, et al. Oxygenated and reoxygenated tumors show better local control in radiation therapy for cervical cancer. *Int J Gynecol Cancer* 2006;16:306–11.
36. Kizaka-Kondoh S, Inoue M, Harada H, et al. Tumor hypoxia: a target for selective cancer therapy. *Cancer Sci* 2003;94:1021–8.
37. Hirayama R, Uzawa A, Takase N, et al. Evaluation of SCCVII tumor cell survival in clamped and non-clamped solid tumors exposed to carbon-ion beams in comparison to X-rays. *Mutat Res* 2013;756:146–51.
38. Nakano T, Suzuki Y, Ohno T, et al. Carbon beam therapy overcomes the radiation resistance of uterine cervical cancer originating from hypoxia. *Clin Cancer Res* 2006;12:2185–90.