Review Article

Review of the Carbon Ion Radiotherapy for Locally Advanced Uterine Cervical Cancer

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Abstract

Carbon ion beams offer improved dose distribution, resulting in the concentration of a sufficient dose within a target volume while minimizing the dose in surrounding normal tissues. Moreover, carbon ions possess a biological advantage due to their high Relative Biological Effectiveness (RBE) in the Bragg Peak. A number of reports have demonstrated the favorable results of Carbon Ion Radiotherapy (C-ion RT) in the treatment of several malignant tumors. As for clinical trials of C-ion RT for locally advanced cervical cancer, 5 have already been completed and 2 are still ongoing.

Between June 1995 and March 2013, 197 patients with locally advanced cervical cancer in 7 protocols were treated with C-ion RT. Carbon-ion RT has been established as a safe short-term treatment for locally advanced uterine cervical cancer. Although the patient population in these trials was small, it was shown that C-ion RT has the potential to improve the treatment for locally advanced bulky squamous cell carcinoma or adenocarcinoma of the uterine cervix, with the results supporting the view that investigations should be continued to confirm the therapeutic efficacy. In addition, we are now conducting a new clinical trial of C-ion RT with concurrent chemotherapy.

ABBREVIATIONS

CCRT: Concurrent Chemoradiation Therapy; RT: Radiation Therapy; C-ion RT: Carbon-Ion Radiation Therapy; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; GTV: Gross Tumor Volume; CTV: Clinical Target Volume; PTV: Planning Target Volume; DVH: Dose Volume Histogram; GI: Gastrointestinal; GU: Genitourinary; OTT: Overall Treatment Time

INTRODUCTION

Cisplatin-based Concurrent Chemoradiation Therapy (CCRT) has become the standard treatment for locally advanced cervical cancer on the basis of several randomized phase III clinical trials in the 1990s [1-4]. Concurrent chemoradiation therapy improved survival and local control for this disease. Nevertheless, a 5-year local failure rate of 30% or more has been observed, especially in patients with stage III or IVA disease, with the pelvis being the major site of failure and this percentage increased with increasing tumor bulk. In addition, the majority of patients included in most of the clinical trials had squamous cell histology, with adenocarcinomas representing approximately 10% of the patients enrolled [5-7]. However, as uterine cervical adenocarcinoma is more radio-resistant and thus has poorer prognosis than squamous cell carcinoma, radiation therapy both with and without chemotherapy is still unsatisfactory. This means that locally advanced bulky cervical cancers as well as adenocarcinomas are in need of even more aggressive approaches. One such strategy for applying more treatment is to use drugs for radiosensitizing chemotherapy [8-10] and another is the use of particle therapy [11-15].

Heavy-charged particle radiation therapy for cancer treatment started at the National Institute of Radiological Sciences in June 1994 using carbon ions generated by the heavy-ion medical accelerator in Chiba, where all patients have been treated within prospective Phase I/II or Phase II studies. Since 1994, more than 7000 patients have been treated with carbon-ion radiation therapy (C-ion RT), demonstrating the benefit of C-ion RT over other modalities for various types of tumors in terms of high local control and survival rates [16,17]. Carbon ion beams have improved the properties of dose localization, a potentiality that

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can produce great effects on tumors while minimizing normal tissue damage. Moreover, they possess a biological advantage due to their high relative biological effectiveness in the Bragg Peak [18-20].

Since 1995, we have conducted several clinical trials for locally advanced squamous cell carcinoma or adenocarcinoma of the cervix. The purpose of these trials was to evaluate the toxicity and efficacy of C-ion RT and to confirm the optimum dose of C-ion RT for uterine cervical cancer and 4 clinical trials of the treatment with C-ion RT for locally advanced cervical carcinoma have been reported [12-15]. This review introduces the results of these clinical trials.

MATERIALS AND METHODS

Eligibility criteria

Patients were eligible for these studies if they had previously untreated and histologically proven squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma and International Federation of Gynecology and Obstetrics (FIGO 1994) Stage IIB, III, or IVA disease (> 4 cm in diameter for squamous cell carcinoma)and no rectal invasion. Bladder or rectal involvement was assessed by endoscopy. Eligible patients had World Health Organization performance status < 3, were aged < 80 years and had an estimated life expectancy of > 6 months. Patients were excluded if they had severe pelvic infection, severe psychological illness, or active synchronous cancer. Pretreatment evaluation consisted of an assessment of the patient's history, physical and pelvic examinations by gynecologists and radiation oncologists, cervical biopsy, routine blood cell counts, chemistry profile, chest X-ray, cystoscopy and rectoscopy. Computed tomography (CT) scans of the abdomen and pelvis, Magnetic Resonance Imaging (MRI) of the pelvis and Positron Emission Tomography (PET) scans were also performed for all patients. Patients were staged according to the FIGO staging system, but patients with para-aortic lymph nodes > 1 cm in minimum diameter on CT images were excluded from the studies, although those with enlarged pelvic lymph nodes only were included. Tumor size was assessed by both pelvic examination and MRI and the dimensions of the cervical tumor were measured on T2-weighted MRI images. Staging laparotomy was not performed and no histologic confirmation of CT-positive pelvic lymph nodes was obtained. No patient underwent lymph node resection. PET scans were supplementally used for detecting distant metastases. Tumor specimens were examined by working group pathologists. The treatment protocols for these clinical studies were 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.
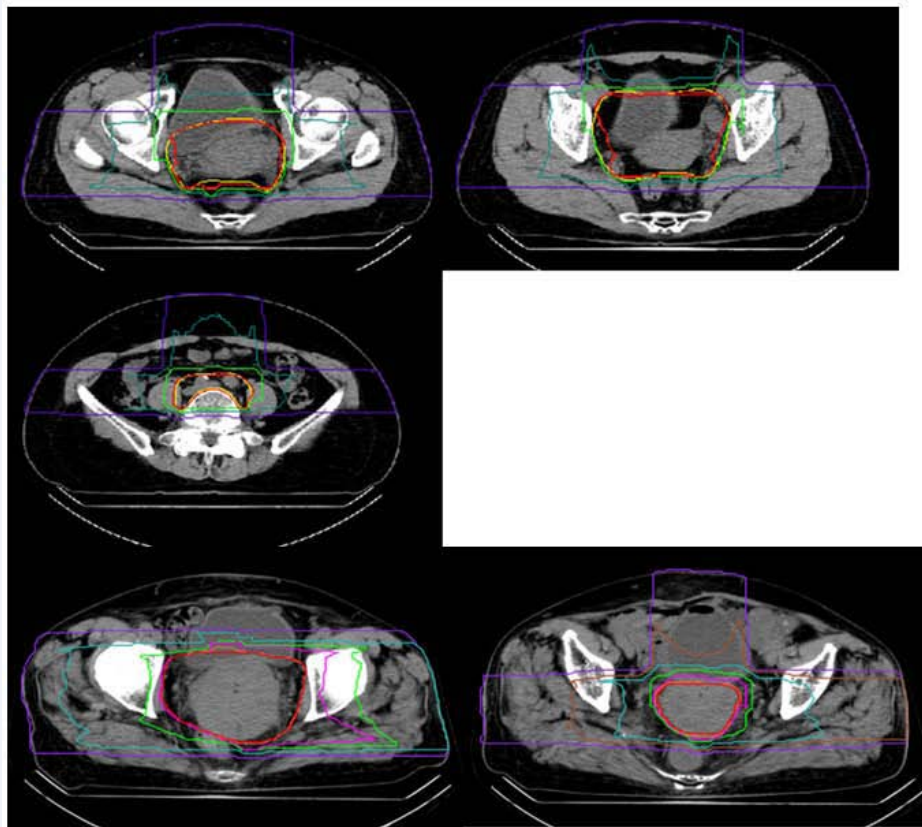
Carbon-ion radiation therapy

Patients were positioned in customized cradles and immobilized with a low-temperature thermoplastic sheet. A set of 5-mm-thick CT images was taken for treatment planning. Three-dimensional treatment planning for C-ion RT was performed using HIPLAN software (National Institute of Radiological Sciences, Chiba, Japan) [21]. Patients received C-ion RT daily for 4 days per week (Tuesday through Friday). At every treatment session, the patient was positioned on the treatment

couch with the immobilization devices and the patient's position was verified with 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 cottons for vaginal packing were soaked in a contrast medium so that the surface of the uterine cervix could be visualized by X-ray images at the treatment sessions for the last 7 fractions; the internal position of the uterine cervix could be identified by checking the position of the vaginal packing. Patients were also encouraged to use laxatives, if necessary, to prevent constipation throughout the treatment period. The radiation dose was calculated for the target volume and surrounding normal structures and was expressed in GyE, which was defined as the physical doses multiplied by the relative biologic effectiveness of the carbon ions [18,19].

The treatment consisted of whole pelvic irradiation and local boost. The Gross Tumor Volume (GTV) was defined by MRI findings and clinical examination just before each treatment planning. The Clinical Target Volume (CTV) of whole pelvic irradiation included all areas of gross and potentially microscopic disease, which consisted of the primary site (GTV, whole uterus, parametrium, at least the upper half of the vagina and ovaries) and the whole pelvic node region (common iliac, internal iliac, external iliac, obturator and presacral node regions) (CTV-1). The planning target volume (PTV-1) included CTV-1 plus a 5-mm safety margin for positioning uncertainty and the uterus plus a 1.5-cm safety margin for intra- and inter-movement. PTV-1 was covered by at least 90% of the prescribed dose. After completing whole pelvic irradiation, CTV included the primary site and enlarged lymph nodes (= CTV-2). A 5-mm or 1.5-cm margin was added to PTV-2. Finally, CTV was shrunk to GTV only (CTV-3) and no margin was added to PTV-3 (Figure 1). Normal tissue structures, such as the rectum, sigmoid colon, bladderand the small bowel in the pelvis were excluded from PTV as much as possible. If PTV-1 and PTV-2 overlapped normal tissues, priority was given to target coverage. However, in the other two clinical trials of C-ion RT for squamous cell carcinoma of the uterine cervix, 18% of the patients developed major Gastrointestinal (GI) complications after the start of the present clinical study [12]. Therefore, a revised treatment technique was used from 2001. The GI tracts were completely excluded from PTV-3 on the basis of DVH) analysis of the earlier two studies and the dose to the GI tracts was limited to < 60 GyE according to the DVH analysis of those protocols, with this limitation having higher priority than the prescription to CTV-3 as final boost irradiation [12,15].

Figure 2-A shows the treatment schedule for 9902and PTV-1, PTV-2 and PTV-3 were irradiated with 13, 5 and 2 fractions, respectively. These clinical trials (Protocol 9702 and 9902) were dose escalation trials. In Protocol 9902, based on DVH analysis of Protocols 9403 and 9702, the doses to PTV-1 and PTV-2 were fixed at 39.0 GyE in 13 fractions and 15.0 GyE in 5 fractions (3.0

Figure 1 Isodose curves of carbon ion radiotherapy for locally advanced cervical cancer superimposed on axial computed tomography images for the total irradiation plan. Highlighted are 95% (red), 90% (yellow), 80%(orange), 70% (pink), 50% (green), 30% (blue), and 10% (purple) isodose curves.

GyE per fraction), respectively. With regard to local boost, a dose-escalation study was planned with an initial dose of 10 GyE in 2 fractions to PTV-3. The dose to all GI tracts was strictly limited to < 60 GyE to prevent major late toxicities. The initial dose was determined based on the results of Protocols 9403 and 9702, in which 18% of patients developed major late GI complications and dose escalation to 18 GyE in 2 fractions was performed after careful observation of late toxicity according to discussions of the Working Group of the Gynecological Tumor on a semi-annual basis. Total dose to the cervical tumor was 64.0 – 72.0 GyE in 20 fractions (Figure 2-A).

In the treatment schedule for locally advanced adenocarcinoma of the uterus (Protocol 9704), PTV-1, PTV-2 and PTV-3 were irradiated with 12, 4 and 4 fractions, respectively (Figure 2-B). This clinical trial was a dose escalation trial. Based on the results of a previous study (Protocol 9403), the dose to PTV-1 was fixed at 36.0 GyE in 12 fractions (3.0 GyE per fraction) in this protocol. With regard to local boost, a dose-escalation study was planned with an initial dose of 26.4 GyE in 8 fractions, then gradually increasing up to 38.4 GyE in 8 fractions by 2.4 or 3.6 GyE increments. Dose escalation was performed after careful observation of acute normal tissue responses according to discussions twice per year of the Working Group of the Gynecological Tumor. Total dose to the cervical tumor was 62.4 – 74.4 GyE in 20 fractions (Figure 2-B).

RESULTS AND DISCUSSION

Locally advanced squamous cell carcinoma of the uterus (9702 and 9902)

Between December 1997 and October 2005, 36 patients of Protocols 9702 and 9902, both dose escalation studies, were treated with C-ion RT [12,15]. Patients with histories of prior chemotherapy or pelvic radiotherapy were excluded from the studies. Patient characteristics are summarized in Table 1. Histologically, all patients had squamous cell carcinoma. The numbers of patients with stage IIB, IIIB and IVA disease were 1, 27and 8, respectively. All patients with stage IVA had bladder invasion but no rectal invasion. All patients had bulky tumors 4.0 – 12.0 cm in maximum diameter, with a median of 6.5 cm. Eighteen of the 36 patients had pelvic lymph node metastases. Staging laparotomy was not performed and no histologic confirmation of CT-positive pelvic or para-aortic lymph nodes was obtained. No patient underwent lymph node resection. Twenty-three patients received 64.0 – 68.8 GyE and 13 patients had 72.0 – 72.8 GyE. Overall Treatment Time (OTT) ranged from 32 to 48 days, with a median of 36 days. The median follow-up duration was 37 months (8-181 months).

The 5-year local control rate, progression-free survival rateand overall survival rate were 72.1%, 44.4% and 47.2%, respectively (Figure 3). Recently, the standard treatment
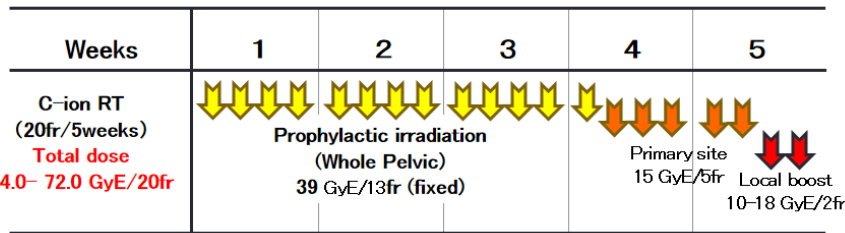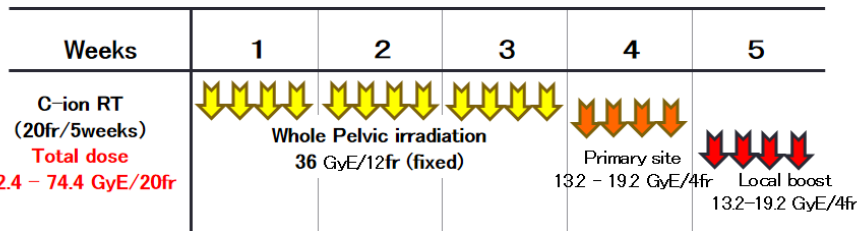
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Figure 2 Treatment schedule of protocol 9902 (A) and 9704 (B).
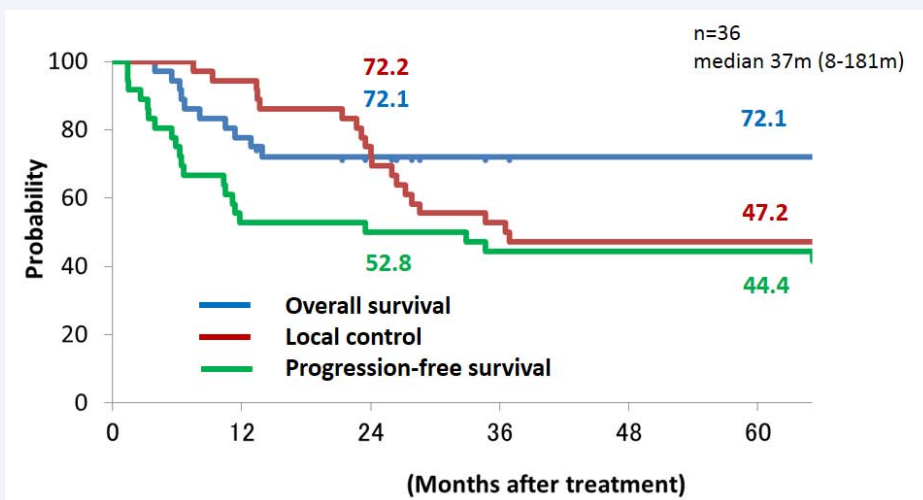

Figure 3 Overall survival, local control and progression-free survival curves in Protocol 9702 and 0508 (Sq.C.C.): Blue line is overall survival curve; red line is local control curve; green line is progression-free survival curve.

for locally advanced cervical cancer has been CCRT. Several researchers reported that local or locoregional control rates for locally advanced cervical cancer by CCRT were 67 – 84% at 4 or 5 years [6,22-25]. Toita et al. reported 2-year locoregional control rates for CCRT in patients with tumors < 50 mm, 50 – 70 mm and > 70 mm of 85%, 72% and 54%, respectively [26]. Parker et al. reported 5-year local control rates for < 50 mm and > 50 mm of 73% and 56%, respectively [24]. The current study did not include concurrent chemotherapy, being based on C-ion RT alone. The 5-year local control rate was 72.1%, even though the median tumor size of our cases was 6.5 cm (4-12 cm) and 33 of 36 tumors were over 5 cm. In addition, these protocols were dose-escalation studies. The 5-year local control rates in patients with

64.0 – 68.8 GyE (23 cases) and 72.0 – 72.8 GyE (13 cases) were 60.9% and 91.7%, respectively (Figure 4). Although the number of patients receiving 72.0 -72.8 GyE was small, these results suggested that local control rate for patients receiving 72.0-72.8 GyE might be better than with 64.0 - 68.8 GyE. Thus, C-ion RT has the potential to improve the treatment of locally advanced bulky cervical cancer with a total dose of more than 72.0 GyE.

In spite of the favorable local tumor control, distant metastases frequently occurred and the 5-year progression-free survival rate and overall survival rate were still unsatisfactory. The high rate of distant metastasis can be ascribed to the advanced stage of the tumors, which includes bulky tumors and a high rate of pelvic lymph node metastasis. To improve the survival rate as
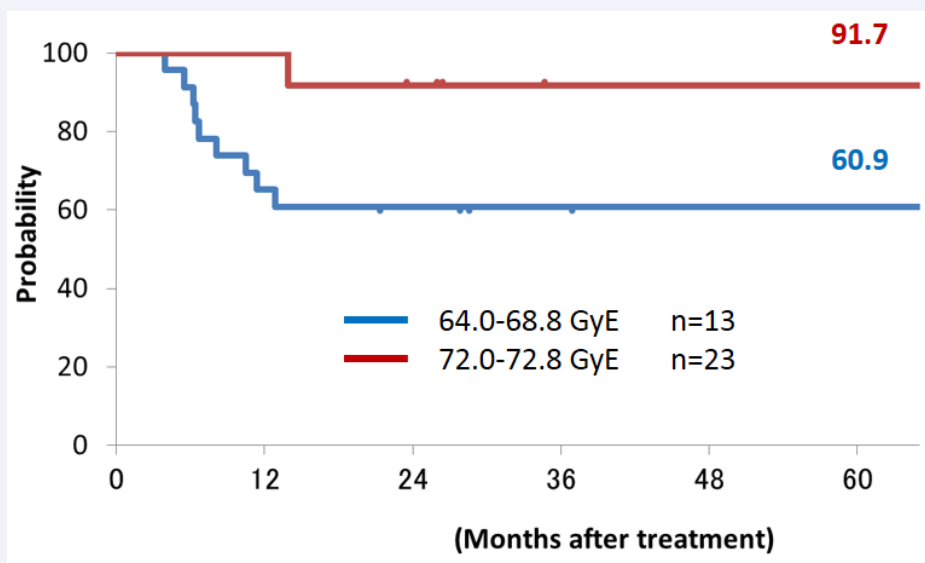
Figure 4 Local control curves in patients with 64.0 – 68.8 GyE (blue line) and 72.0 – 72.8 GyE (red line).
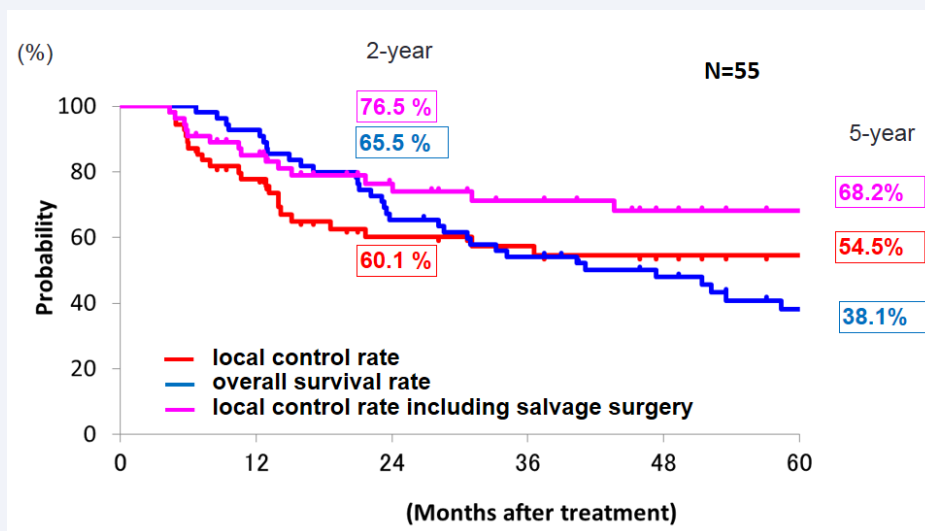

Figure 5 Local control rate, local control rate including salvage surgery and overall survival rate in Protocol 9704(Cervical adenocarcinoma): Blue line is overall survival curve, red line is local control curve, and pink line is local control curve including salvage surgery.

well as the local control rate, the use of combination regimens for systemic treatment, such as combining extended field irradiation with chemotherapy, should be further explored. Thus, we are now conducting a new clinical trial of C-ion RT for locally advanced squamous cell carcinoma of the uterus.

Locally advanced adenocarcinoma of the uterus (9704)

Between April 1998 and February 2010, 55 patients with locally advanced adenocarcinoma of the uterine cervix (Protocol 9704) were treated with C-ion RT [14]. Patient characteristics are summarized in Table 1. The numbers of patients with stage IIB, IIIB and IVA disease were 20, 33and 2, respectively. All patients with stage IVA had bladder invasion but no rectal invasion. Tumor size was 3.0 – 11.8 cm in maximum diameter (median 5.5

cm) and that of stage IIIB and IVA cases was 3.5 – 9.2 cm (median 5.8 cm). Histologically, 45 of 55 patients had adenocarcinoma and 13 patients had adenosquamous cell carcinoma. Twenty-four of the 55 patients had pelvic lymph node metastases. Seven of 55 patients received 62.4 – 64.8 GyE, 10 patients had 68.0 GyE, 21 patients had 71.2 GyE and 17 patients had 74.4 GyE. OTT ranged from 32 to 40 days, with a median of 35 days. Median follow-up duration was 38 months (range, 7 to 141 months).

The 5-year local control rate, local control rate including salvage surgery and overall survival rate in all cases were 54.5%, 68.2% and 38.1%, respectively (Figure 5). In stage IIIB and IVA cases, the rates were 57.9%, 69.2% and 42.4%, respectively (Figure 5). Several studies have reported treatment outcomes of adenocarcinoma of the uterine cervix treated with RT or CCRT (Table 2). Niibe et al. reported a 5-year local control rate of 36%

for stage IIIB by RT alone or CCRT [27]. Grigsby et al. reported 33% for stage III adenocarcinoma of the uterine cervix by RT alone [28]. Huang et al. reported 58% for stage III and 48% for stage IB-IIA bulky (> 4 cm) by RT alone or CCRT [29]. In the present study, the 5-year overall local control rate for stage IIIB or IVA was 57.9% even though the median tumor size of our cases was 5.8 cm (3.5-9.2 cm). Although the number of patients in this study was small, the local control rate was relatively better than those of the conventional studies.

On the other hand, the overall survival rate was less than satisfactory in this study (2-year: 65.5%, 5-year: 38.1%), even though the local control rate for bulky tumors was relatively favorable. Several researchers showed that locally advanced adenocarcinoma of the uterine cervix had poor prognosis, with 5-year survival rates being only 25-29% [27-30]. They suggested that the reasons were poor local control and greater distant metastases. Huang et al. reported a 5-year distant metastasis rate of 46% for stage III patients after RT alone or CCRT [29]and Eifel et al. reported that 45% of patients with stage IIB or III showed distant metastases after RT [30]. In the present study, 2-year and 5-year cumulative distant metastasis rates were 49.4% and 64.8%, respectively (Figure 6). These rates were higher than those in the other studies because our patients did not receive concurrent chemotherapy, tumor size was larger than in the other studies and the overall survival rate was also higher. Thus, to improve the distant metastasis and local control rates, the use of chemotherapy in combination with C-ion RT should receive further consideration.

Acute and late toxicities

Of the first 68 patients treated by C-ion RT between 1995 and 2001 (Protocol 9403, 9702 and 9704), 8 patients (11.8%) developed major (Grade 4) GI complications. All were surgically salvaged and remained free of intestinal problems. Based on these results, the treatment technique was revised from 2002. The dose to the GI tracts was limited to < 60 GyE according to DVH analysis [12]and this limitation had higher priority than the prescription to CTV-3 as final boost irradiation. In addition, vaginal packing for the space between tumors of the uterine cervix and rectum was placed at the time of C-ion RT (Figure 7). Since 2002, there has been no grade 3 or higher major GI complication in these clinical trials.

Acute toxicity was graded according to the National Cancer Institute - Common Toxicity Criteria version 3.0. Of 91 patients for Protocols 9702, 9704 and 9902, all of the observed acute and late toxicities are listed in Table 3. Although 36 patients (39.6%) developed acute GI toxicity (G1-G2) and 16 patients (17.6%) had acute GU toxicity (G1-G2), all patients completed the scheduled therapy. No patient developed Grade 3 or higher acute toxicity.

Late toxicity was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Twenty-seven patients (29.7%) had mild or intermediate bleeding of the rectum or sigmoid colon. Two patients (2.2%) had Grade 4 rectal complications that were surgically salvaged and one patient (1.1%) had severe rectal bleeding. These cases were treated before revision of the treatment technique. Nineteen patients (20.9%) had Grade 1 or 2 late GU toxicities and none developed Grade 3 or higher toxicity.

Overall treatment time (OTT)

Carbon-ion RT for several carcinomas has achieved shorter OTT. It is well known that OTT is an important factor of RT for several cancers including cervical cancer. Several studies reported that prolongation of OTT of RT for uterine cervical cancer had a significant impact on treatment outcome because of biological factors such as cell repopulation and increased proliferation [31,32]. Thus, they suggested that RT for patients with uterine cervical cancer should be delivered in the shortest
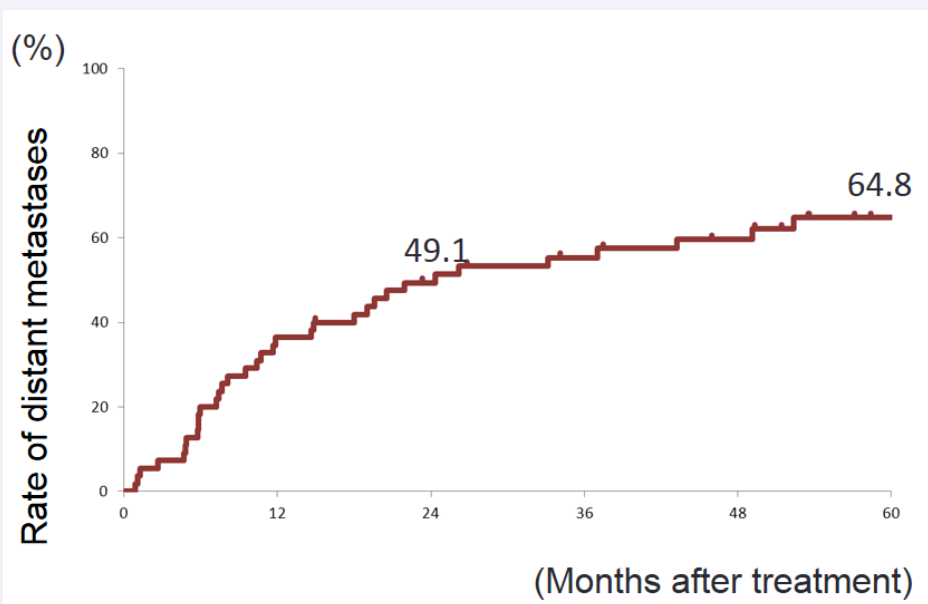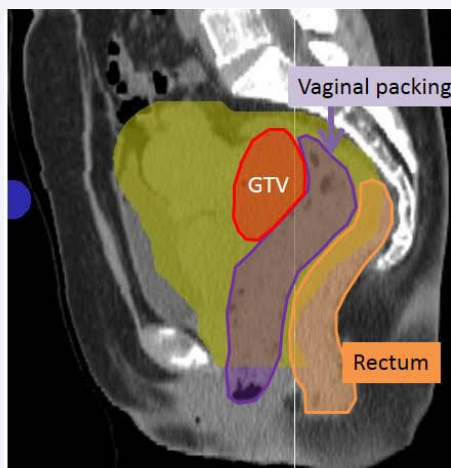

Figure 6 Cumulative distant metastasis rate of the cases in Protocol 9704 (Cervical adenocarcinoma).

Figure 7 Vaginal packing (Purple area) for spacer between tumor of uterine cervix (Red) and rectum (Orange) [Description of figures/image].

possible overall time. In addition, shorter OTT obviously offers a better quality of life for the patients. OTT ranged from 45 to 60 days in most clinical trials for uterine cervical cancer by CCRT. On the other hand, median OTT for C-ion RT in these trials was only 35 or 36 days. Even though C-ion RT was delivered in a shorter OTT, there were no higher incidences of acute or late complications than those for CCRT. This indicates that C-ion RT achieved shorter OTT in a safe manner.

CONCLUSION

Carbon-ion RT has been established as a safe short-term treatment for locally advanced uterine cervical cancer. Although the patient population in these trials was small, it was shown that C-ion RT has the potential to improve the treatment for locally advanced bulky squamous cell carcinoma or adenocarcinoma of the uterine cervix, with the results supporting the view that investigations should be continued to confirm the therapeutic efficacy. In addition, we are now conducting a new clinical trial of C-ion RT with concurrent chemotherapy.

ACKNOWLEDGEMENT

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