Carbon-ion Radiotherapy for Prostate Cancer: Analysis of Morbidities and Change in Health-related Quality of Life

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Abstract. *Aim: To prospectively evaluate the feasibility of carbon-ion radiotherapy (C-ion RT) for prostate cancer using a new compact-sized accelerator. Patients and Methods: Seventy-six patients underwent C-ion RT at our center using a recommended dose fractionation of 57.6 GyE in 16 fractions established at the National Institute of Radiological Sciences. Health-related Quality of Life (HRQOL) assessment was also performed using the Medical Outcome Study 8-items Short Form Health Survey (SF-8) questionnaire. Results: The median follow-up time was 51 months (range=8-58 months). Grade 2 gastrointestinal and genitourinary complications developed in 1 (1.3%) and 5 (6.6%) patients, respectively. Recurrences occurred in 4 patients, and the 4-year biochemical relapse-free rate was 94.6%. The HRQOL scores after C-ion RT were objectively well-maintained. Conclusion: Irrespective of the small number of patients of the study, C-ion RT for prostate cancer using the first commercial-based accelerator reproduced the toxicity outcomes at the NIRS.*

Three-dimensional conformal radiation therapy (RT) with image-guided radiotherapeutic modalities such as brachytherapy, intensity-modulated radiotherapy (IMRT),

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and charged particle beam radiotherapy for prostate cancer can deliver a large dose to the tumor and allow sparing of surrounding normal tissues; these combined modalities have yielded better disease control with minimum morbidity compared to previous conventional RT (1-6). Due to the spread of prostate-specific antigen (PSA) screening and rapid changes in lifestyle in Japan, the incidence of prostate cancer has increased every year (7); thus, RT now plays a much more important role in the curative treatment of patients with prostate cancer.

Carbon ion (C-ion) beams are known to have physical and biological advantages in RT (8-10). They exhibit a spread-out Bragg peak (SOBP) and allow a desirable dose distribution to the target volume using limited numbers of portals by specified beam modulations, as well as protons (10, 11). They also have a high relative biological effectiveness (RBE) resulting from high linear energy transfer (LET), similarly to that of neutron beams; it is estimated that the cytocidal effect of C-ions is about three-times those of photons and protons (8, 11). As the LET of C-ion beams increases steadily from the point of entrance into the body with increasing depth to reach a maximum in the peak region, in contrast to neutron beams with uniform LET at any depth in the body, C-ion RT would be an ideal modality from a therapeutic viewpoint (8, 11, 12).

The efficacy and feasibility of C-ion RT for localized prostate cancer have been well-confirmed through three phase I/II and two phase II clinical trials using the Heavy Ion Medical Accelerator in Chiba (HIMAC) at the National Institute of Radiological Sciences (NIRS) beginning in 1995 (9, 13, 14). The appropriate dose fractionation schedule of C-ion RT and use of androgen-deprivation therapy (ADT)

according to tumor risk group were also determined (9, 14, 15). In addition, a therapeutic technique involving a shrinking field of C-ion RT was established to reduce gastrointestinal (GI) morbidity (14). Consequently, updated data from 972 patients treated with C-ion RT at the NIRS showed that grade 2 rectal bleeding developed in 16 (1.5%) patients, but no grade 3 or worse GI morbidities were experienced (9).

The Gunma University Heavy Ion Medical Center (GHMC) has installed a new compact-sized accelerator designed by NIRS teams that can accelerate C-ions with a maximum energy level of 400 MeV per nucleon, which is almost equivalent to those provided by the HIMAC (16). Since March 2010, GHMC has performed C-ion RT for prostate cancer using a dose fractionation of 57.6 photon Gray equivalent (GyE) [physical carbon ion (Gy) $\times$ RBE, which was estimated to be 3.0] doses in 16 fractions, which was the recommended fractionation for prostate cancer determined at the NIRS (17). Herein we report preliminary results of C-ion RT for prostate cancer using a compact-sized accelerator, with special regard to normal tissue morbidities.

Materials and Methods

Study design. The purpose of the phase II trial GUNMA0702 is to confirm the feasibility and efficacy of C-ion RT for prostate cancer and to reproduce similar clinical outcomes reported by the NIRS using a compact-size and commercial-base accelerator for C-ion RT installed at GHMC. The primary endpoint is the biochemical relapse-free (bRF) rate, and secondary endpoints are local control (LC), overall survival (OS), cause-specific survival (CSS), normal tissue morbidity, and quality of life (QOL) after C-ion RT.

Patients were stratified into low-, intermediate-, and high-risk groups according to the three major clinical risk factors for prostate cancer: T stage, the initial PSA (iPSA) value, and the Gleason score (GS) of the tumor. All biopsy specimens were centrally re-evaluated by one urological pathologist (JH) at Gunma University Hospital before the start of C-ion RT to avoid interobserver variability. If patients with T1c-T2bN0M0 disease according to the TNM classification of the International Union Against Cancer (UICC) 2009 (18) had an iPSA <10 ng/ml and GS ≤6, they were allocated to the low-risk group. In contrast, patients with T3 or iPSA ≥20 ng/ml or GS ≥8 were assigned to the high-risk group. The remaining patients were assigned to the intermediate-risk group.

ADT, consisting of medical or surgical castration with or without anti-androgens, was delivered according to our prostate cancer risk group criteria. For patients in the low-risk group, C-ion RT was performed without ADT. In contrast, neoadjuvant ADT was given to patients in the intermediate- and high-risk groups for 6 months before the start of C-ion RT. Adjuvant ADT without anti-androgens was continued only for high-risk patients, in whom ADT was administered for 24 months. If patients with T1c-T2b disease had a GS of 7 (3+4) and iPSA value <10 ng/ml, they were considered to have intermediate-risk cancer but received C-ion RT without ADT.

The study protocol was designed by the Working Group of Genitourinary Tumors of the GHMC and was approved by the

Table I. *Patients' characteristics.*

Characteristic	No. of patients (%)
Age (years) Median 66 (range=53-88)	
T-Stage	
T1c	23 (30%)
T2a-b	16 (21%)
T2c	10 (13%)
T3a	24 (32%)
T3b	2 (3%)
T4	1 (1%)
PSA (ng/ml) Median 9.61 (range=2.14-116.00)	
<10.00	41 (54%)
10.00-19.99	16 (21%)
≥20.00	19 (25%)
Gleason score	
<6	4 (5%)
7 (3+4)	23 (30%)
7 (4+3)	19 (25%)
≥8	30 (40%)
Tumor risk group	
Low	3 (4%)
Intermediate	29 (38%)
High	40 (53%)
Castration-resistant	4 (5%)
Use of androgen-deprivation therapy	
No	7 (9%)
Yes	69 (91%)

PSA, Prostate-specific antigen.

Ethical Committee (approval number: 693) and registered with the University Medical Information Network (UMIN) Clinical Trial Registry, number 000003827. A written informed consent form developed according to institutional guidelines was individually assigned before registration.

Patient eligibility. Patients ranging in age from 20 to 80 years with pathologically confirmed adenocarcinoma of the prostate with tumor stage T1c-3bN0M0 were eligible for this trial. Patients who previously received pelvic irradiation or experienced other malignancies within 5 years were not allowed to register into the trial. In addition, patients with a life expectancy of less than 6 months due to other coexisting diseases were also ineligible.

Patients who were ineligible for the trial due to advanced age (>80 years old), bladder invasion without rectal invasion (T4N0M0), or inappropriate use of ADT as defined by the protocol, were treated with another protocol–GUNMA0702Ex–as a non-clinical trial, although no difference in C-ion RT treatment strategy exists between the GUNMA0702 and GUNMA0702Ex protocols.

Patient characteristics. The current study included 76 consecutive patients treated in the first year (between March 2010 and February 2011) of C-ion RT at the GHMC for evaluation of acute and late toxicities and changes in QOL after treatment. Patient characteristics are summarized in Table I. Out of these 76 patients, 32 patients were registered into GUNMA0702, but the remaining 44 patients were treated with the GUNMA0702EX protocol. The initial 12
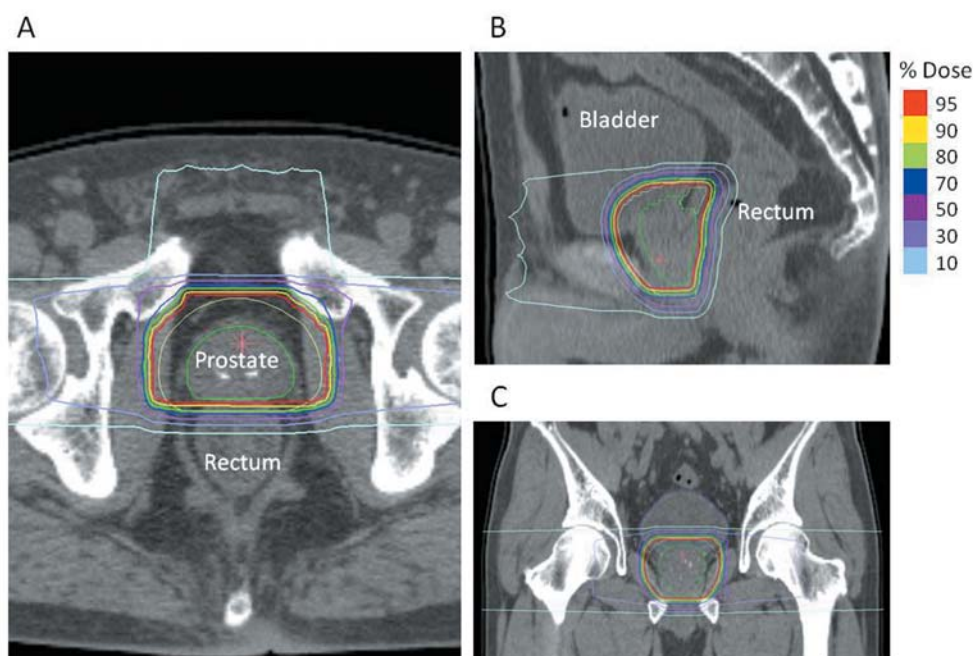
Figure 1. *A representative dose distribution of carbon-ion radiotherapy: axial view (A), sagittal view (B), and coronal view (C). Contours by light-yellow, green, and light-green lines indicate the initial planning target volume, prostate, and proximal seminal vesicles, respectively.*

patients, who had been treated before approval of "Advanced Medical Technology" under the title of "Carbon Ion Radiotherapy for Solid Cancer" were registered into the GUNMA0702Ex study between March 2010 and April 2010. The remaining 32 patients were also enrolled in GUNMA0702EX due to their advanced age (n=3), bladder invasion without rectal invasion (n=1), or inappropriate use of ADT as defined by the GUNMA0702 protocol (n=28), including 4 (5%) patients who had castration-resistant prostate cancer during ADT prior to the start of C-ion RT, but in whom diagnostic reevaluation did not reveal any prostate cancer involvement to lymph nodes or distant organs. The median patient age was 66 years, ranging from 53 to 88 years, and three (4%), 29 (38%), and 40 (53%) patients were classified into the low-, intermediate-, and high-risk groups, respectively.

Carbon-ion radiation therapy. A technique for C-ion RT for prostate cancer that has been previously reported by the NIRS was used (9, 17). The head and feet of the patients were positioned in a customized cradle (Moldcare; Alocare, Tokyo, Japan) and the pelvis was immobilized with a low-temperature thermoplastic sheet (Shellfitter; Keraray, Co., Ltd., Osaka, Japan) in the supine position both during the planning CT and actual treatment. At CT simulation, the bladder was filled with 100 ml sterilized water and the rectum was emptied using an enema. At our institution, magnetic resonance imaging (MRI) was routinely performed to produce computed tomographic (CT)/MRI fusion images for treatment planning immediately after acquiring CT images. The bladder was also filled with the same volume of water at each treatment session from the anterior direction. Before all sessions, the rectum was emptied as much as possible by the patient's own effort, and a laxative or enema was used, if necessary.

A treatment planning system (Xio-N) newly developed for the compact carbon therapy technique using the platform of Xio (Elekta AB, Stockholm, Sweden) was installed at the GHMC, in which the dose calculation engine (K2DOSE) communicates with the platform to display the dose distributions seamlessly at the Xio platform (16). Three-dimensional treatment planning was conducted using CT images of 3-mm thickness fused with MRI images. The clinical target volume (CTV) included the prostate and the proximal seminal vesicles (SVs), but whole SVs were included if tumors invaded to the vesicles (T3b). The initial planning target volume (PTV1) was automatically created by adding 10-mm anterior and lateral margins, 6-mm cranial and caudal margins, and a 5-mm posterior margin to the CTV, but lateral margins to SVs were reduced to 3 mm. According to the NIRS reports, boost therapy was performed using the second PTV (PTV2), in which the posterior edge was set in front of the anterior wall of the rectum after the completion of nine fractions; however, the other margins remained the same as those for PTV1 (17). Each portal was shaped by a multi-leaf collimator with a 3.75-mm width. The compensation bolus for each patient was also facilitated to make the distal configuration of the SOBP similar to the PTV. To maintain a positioning error of <1 mm, the field was verified at every treatment session by a computer-aided on-line positioning system at the NIRS, and patient positioning was three-dimensionally corrected using the same treatment couch used at the NIRS (16, 19).

Irradiation doses were expressed in GyE doses at the distal part of the SOBP (9, 11). C-ion RT was performed at a total dose of 57.6 GyE in 16 fractions over 4 weeks, with a fractional dose of 3.6 GyE for 4 fractions per week. One port was used for each session, with five irregularly shaped ports, including one anterior-posterior port and a pair of lateral ports for PTV1 and another pair of lateral ports

for PTV2. Before carrying out the actual treatment, all members of the GHMC treatment team including radiation oncologists, oncology nurses, medical physicists, radiation therapists routinely checked all treatment plans at the institutional conference by referring to dose constraints of the rectum determined at the NIRS using dose–volume histogram (DVH) analysis (9, 20). A representative dose distribution of C-ion RT is shown in Figure 1.

Follow-up and evaluation for toxicity and quality of life. Patients were followed up by both the referring urologist and a radiation oncologist at 1 and 3 months after C-ion RT and three monthly intervals thereafter, and an interview, physical examination, measurement of PSA value, and urine screening were conducted at every follow-up. CT and MRI were performed at least once a year. If tumor recurrence was suspected, other assessments including bone scintigraphy were added. Acute and late toxicities were assessed for each patient both during the C-ion RT treatment period and the follow-up period according to the National Cancer Institute Common Toxicity Criteria (Version 4.03) (21), and biochemical recurrence was defined by the Phoenix definition based on a rise of 2 ng/ml greater than the PSA nadir (22).

Health-related quality of life (HRQOL) assessment was performed for all 76 patients at the following four time points: before initiation of C-ion RT, immediately after completion of C-ion RT, and at 3 and 12 months after initiation of C-ion RT. HRQOL assessment was performed using the Japanese version of the Medical Outcome Study 8-items Short Form Health Survey (SF-8) questionnaire (23, 24). The SF-8 questionnaire consists of two summary scores with eight items: the physical component summary (PCS) and mental component summary (MCS) scores. Each SF-8 summary score can be scored on the same Norm-Based Scoring (NBS) as summary scores of the medical outcome study 36-item Short-Form health survey (SF-36) (25, 26). NBS is adjusted to 50 as the public standard value, with 10 used as the standard deviation. Statistics were calculated using SPSS version 21 (SPSS, Chicago, IL, USA). Linear mixed models were used to compare HRQOL data between baseline and each assessment time point. Individual summary scores were compared between baseline and each assessment time point and between individual scores, and the Bonferroni method was used for adjustment for multiple comparisons. If the *p*-value fell below 0.05, differences using two-sided tests were considered significant.

Results

Treatment and recurrence. All treatments were completed successfully. Overall treatment times for all but one patient were within 30 days. Intra-cranial bleeding accidentally occurred in a patient during the course of C-ion RT, and his symptoms were immediately resolved with medication only. As a result, C-ion RT was completed with a delay of 5 days from the planned schedule for this patient.

All patients were periodically followed-up, with a median follow-up period of 51 months (range=8-58 months). Up to the last follow-up examination, two patients had died of disease recurrence or suicide. A 72-year-old patient with castration-resistant prostate cancer died of prostate cancer recurrence; he had T1cN0M0 prostate cancer with a GS of 9
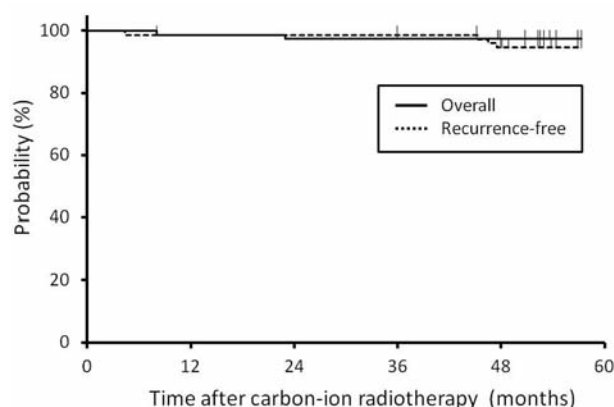

Figure 2. *Overall survival and recurrence-free survival curves after carbon-ion radiotherapy for prostate cancer.*

and a PSA value of 8.065 ng/ml based on his initial examination. He had received ADT as initial treatment, and the nadir of the PSA value was 0.096 ng/ml. Three years later, his tumor became resistant to ADT, with a gradual increase in PSA level. Diagnostic re-evaluation by transrectal ultrasonography, CT, MRI, and bone scintigraphy did not reveal any prostate cancer involvement to the rectum, lymph nodes, or distant organs before the start of C-ion RT at our Institute. The PSA values at the start and completion of C-ion RT were 3.94 ng/ml and 4.00 ng/ml, respectively, but rapidly increased again due to multiple metastases to bone and iliac lymph nodes 4 months later. Consequently, he died of prostate cancer 11 months after C-ion RT. Another patient died due to suicide 8 months after C-ion RT without any signs of recurrence.

Biochemical disease recurrences were observed in four patients treated under the GUNMA0702Ex protocol, and clinical recurrence developed in all of them. In contrast, no recurrences were observed in patients registered onto GUNMA0702. Sites of recurrence in the GUNMA0702Ex protocol included the lymph nodes (n=2), bone (n=1), and both lymph nodes and bone (n=1). Two out of four patients with recurrence were recognized as having castration-resistant prostate cancer before C-ion RT, and the remaining two patients had high-risk prostate cancer according to our criteria but were not ineligible for GUNMA0702 due to extended use of ADT before C-ion RT. The 4-year bRF and OS rates for all patients were 94.6% [95% confidence interval (CI)=89.4-99.8%] and 97.4% (95% CI=93.8-100.0%), respectively (Figure 2).

Morbidities. Table II summarizes acute and late genitourinary (GU) and GI morbidities after C-ion RT. No grade 3 or more severe morbidities were observed in the
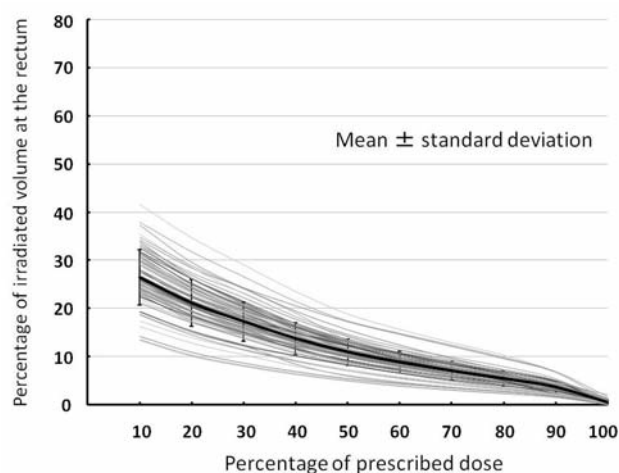
Figure 3. *Normalized rectal volume receiving 10% (V10) to 100% (V100) of the prescribed dose for all treatment plans. The averages of the rectal V30, V50, V70, and V90 in the present study were 17.2±4.1%, 10.9±2.7%, 7.0±2.0%, and 3.6±1.2%, respectively.*

Table II. *Acute and late morbidities after carbon-ion radiotherapy.*

	No. of patients (%)			
Grade	0	1	2	≥3
Acute				
Genitourinary	26 (34%)	43 (57%)	7 (9%)	0 (0%)
Gastrointestinal	75 (99%)	1 (1%)	0 (0%)	0 (0%)
Late (maximum)				
Genitourinary	36 (47%)	35 (46%)	5 (7%)	0 (0%)
Gastrointestinal	69 (91%)	6 (8%)	1 (1%)	0 (0%)
Late (last follow-up)				
Genitourinary	62 (82%)	13 (17%)	1 (1%)	0 (0%)
Gastrointestinal	76 (100%)	0 (0%)	0 (0%)	0 (0%)

Table III. *Changes in scores of SF-8 after carbon-ion radiotherapy (C-ion RT).*

	Before C-ion RT	After C-ion RT		
		1 Month	3 Months	12 Months
Mean±95% CI				
PCS	51.14±1.85	51.14±1.85	50.76±1.87	47.71±1.84*
MCS	49.18±1.96	48.45±1.96	51.63±1.98	49.75±1.95

CI: Confidence interval; PCS: Physical Component Summary; MCS: Mental Component Summary. *$p<0.05$ in comparison with the corresponding baseline scores after Bonferroni correction. C-ion RT, carbon-ion radiotherapy.

present study. Grade 1 and 2 GU toxicities were observed in 53 (69.7%) and 7 (9.2%) patients, respectively, whereas no grade 2 GI toxicities were experienced.

With respect to late morbidity, grade 2 GU toxicities occurred in 5 (6.6%) patients, but for all but one of them, observed symptoms were immediately relieved with medication. Grade 2 GI toxicity was accidentally and iatrogenically observed in a 72-year-old patient after he underwent colonoscopy and biopsy of the rectum for colorectal cancer screening at another hospital, but the bleeding was also resolved with medication within 4 weeks.

Change in QOL. Changes of PCS and MCS scores using the SF-8 questionnaire are summarized in Table III. Data before initiation of C-ion RT, immediately after completion of C-ion RT, and at 3 months after C-ion RT were obtained from all 76 patients, but only 74 (97%) were able to respond to the questionnaire at 12 months because two patients had died, as mentioned above.

PCS scores slightly decreased with the passage of time, and the score at 12 months after initiation of C-ion RT was significantly worse than that at baseline ($p<0.05$). In contrast, MCS scores at all three points after C-ion RT were maintained in comparison to the corresponding baseline scores.

Discussion

Clinical trials of C-ion RT have been conducted to confirm the efficacy of carbon ions for determining the optimal dose level and fractionation schedule for prostate cancer at the NIRS (9, 13, 14, 17), and a recent article reporting the results

of a phase I/II study of shortening the treatment period through more intense hypofractionated C-ion RT in 12 fractions over 3 weeks was also published (27). As the recommended dose fractionation at the time was 57.6 GyE in 16 fractions over 4 weeks as treatment for more than 1, 300 patients with prostate cancer (9, 17), the same dose fractionation schedule was used for patients with prostate cancer at the GHMC to assess whether C-ion RT using a new compact-sized accelerator could reproduce the results at the NIRS. The present study evaluated clinical outcomes of C-ion RT for prostate cancer using the new accelerator, with special regard to toxicities and changes in HRQOL, with a median follow-up time of 51 months; 72 (95%) patients have undergone follow-up examinations for more than 4 years.

Grade 2 late GU toxicities developed in 6.6% of patients evaluated in the present study; this rate appears to be higher than the 2.0% rate reported by the NIRS when the same fractionation schedule was used (17). However, it is possible that the incidence of GU toxicities after definitive RT for prostate cancer may change depending on the follow-up period, as several reports have indicated that rectal bleeding frequently occurred within 3 years after RT, but GU

complications continued to develop after 3 years (3, 4, 15, 17, 20, 28-30). Although the median follow-up time data for the 57.6 GyE group in the article by the NIRS were not reported, the minimum follow-up times for surviving patients in their study and in the present study were 1 and 3 years, respectively (17). In fact, they also reported that grade 2 toxicities occurred in 6.5% of patients treated with 63.0 GyE in 20 fractions, the dose previously used for prostate cancer treatment at the NIRS and equivalent to 57.6 GyE in 16 fractions based on the linear-quadratic model (9, 17, 31). Additionally, symptoms in four out of five patients with grade 2 toxicity were resolved at the last follow-up.

With respect to GI toxicity, grade 2 rectal bleeding developed in only one patient in the present study after biopsy of the rectum for colorectal cancer screening during colonoscopy. Fortunately, the bleeding was completely resolved 4 weeks after use of a laxative. Thus, this bleeding was most likely iatrogenic. Consequently, the incidence of grade 2 rectal bleeding in the present study was almost equivalent to that reported by the NIRS (1.3% in the present study, and 1.5% at the NIRS) (17). In addition to the physical advantage of C-ions in cancer treatment, another likely reason for the favorable results in the present study is the dose constraints of the rectum determined at the NIRS using DVH analysis (20). In the study reported by the NIRS, the percentage of rectal volume receiving 50% of the prescribed dose (V50) as well as use of anticoagulant therapy were significant risk factors for grade 1-2 rectal bleeding after C-ion RT for prostate cancer (13.2±5.6% in patients who experienced toxicity; 11.4±4.0% in patients who did not experience toxicity; p=0.046). The rectal V50 of all patients in the present study was slightly lower than that of patients without toxicity in the previous study (10.9±2.7%, Figure 3). Therefore, we believe that it is very important to confirm rectal doses using DVH analysis before the start of each treatment.

We also tried to examine changes in patient conditions objectively after C-ion RT due to limitations in the ability to subjectively grade small changes in adverse events according to the toxicity criteria. In fact, no grade 3 or severe toxicities were observed, and grade 2 GI and GU adverse events developed in only 1 (1.3%) and 5 (6.6%) patients, respectively. In contrast, grade 1 GI and GU adverse events were observed in 6 (7.9%) and 35 (46.0%) patients, respectively. Because it is difficult to accurately assess these minor events, particularly in the GU system, we therefore conducted a prospective longitudinal assessment of HRQOL, which is thought to be an effective tool for comprehensively assessing physical and mental changes after prostate cancer treatment (32, 33).

In the present study, all MCS scores and PCS scores at 1 and 3 months after initiation of C-ion RT were unchanged from baseline (before C-ion RT). In contrast, the PCS score at

12 months after C-ion RT was significantly decreased compared to baseline scores, although the difference also appeared to be small (Table III). Monga *et al.* reported no significant changes in HRQOL scores at 12 months after external-beam RT using self-administered Functional Assessment of Cancer Therapy questionnaires (34); however, a previous study of HRQOL assessment demonstrated a similar decrease in physical well-being scores in patients treated with C-ion RT at the NIRS (35). Furthermore, ADT has been suggested to have an adverse effect on HRQOL scores as well as late GU morbidity (15, 36-39). A probable reason for the tendency of PCS scores to be lower 12 months after C-ion RT compared to baseline in the present study is that the present study included 70 (92%) out of 76 patients who received ADT combined with C-ion RT. Although long-term follow-up results are needed, both the PCS and MCS scores appeared to be maintained at 1, 3, and 12 months after C-ion RT.

GHMC installed the third C-ion RT accelerator for clinical use in Japan following the NIRS and the Hyogo Ion Beam Medical Center in 2010. The diameter of the accelerator at the GHMC is much smaller than those of the other institutes, with emphasis placed on being a downsized facility to reduce the cost of C-ion RT worldwide (16). The GHMC accelerator can accelerate carbon ions with a maximum energy level of 400 MeV per nucleon, which is almost equivalent to those provided by the HIMAC at the NIRS. In addition, the Kyushu International External Beam Radiotherapy Center in Saga started C-ion RT using the same accelerator as that used at the GHMC in 2013, and a new C-ion RT facility in Yokohama, which will begin actual treatment in 2016, is under construction. Irrespective of the small subject number and short follow-up time of the present study, this is the first report to reproduce the NIRS C-ion RT treatment outcomes for prostate cancer using the same dose fractionation schedule. Furthermore, the utility of a compact-sized accelerator for C-ion RT has been validated.

In conclusion, the first commercial-based and compact-sized accelerator at the GHMC will most likely reproduce the lower GU and GI toxicity rates of C-ion RT for prostate cancer using the recommended fractionation at a total dose of 57.6 GyE in 16 fractions, although long-term follow-up results for a large number of treated patients is required.

Conflicts of Interest

The Authors have no potential conflicts to disclose.

Acknowledgements

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