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Five-year quality of life assessment after carbon ion radiotherapy for prostate cancer

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ABSTRACT

The aim of this study was to prospectively assess 5-year health-related quality of life (HRQOL) of patients treated with carbon ion radiotherapy (C-ion RT) for clinically localized prostate cancer. A total of 417 patients received carbon ion radiotherapy at a total dose of 63–66 Gray-equivalents (GyE) in 20 fractions over 5 weeks, and neoadjuvant and adjuvant androgen deprivation therapy (ADT) were administered for intermediate and high-risk patients. A HRQOL assessment was performed at five time points (immediately before the initiation of C-ion RT, immediately after, and at 12, 36 and 60 months after completion of C-ion RT) using Functional Assessment of Cancer Therapy (FACT) questionnaires. FACT-G and FACT-P scores were significantly decreased; however, the absolute change after 60 months was minimal. The transient decreases in the Trial Outcome Index (TOI) score returned to their baseline levels. Use of ADT, presence of adverse events, and biochemical failure were related to lower scores. Scores of subdomains of FACT instruments indicated characteristic changes. The pattern of HRQOL change after C-ion RT was similar to that of other modalities. Further controlled studies focusing on a HRQOL in patients with prostate cancer are warranted.

KEYWORDS: prostate cancer, carbon ion radiotherapy, quality of life, prospective study

INTRODUCTION

Definitive treatment modalities such as radical prostatectomy, external beam radiotherapy (EBRT) and interstitial brachytherapy are preferred for clinically localized prostate cancer. By using modern radiotherapy modalities, such as intensity-modulated radiation therapy, high-dose-rate (HDR) brachytherapy or charged particle radiotherapy, hypofractionated and high-dose irradiation have become available [1–4].

Unique characteristics of carbon ion beams, such as a high relative biological effectiveness (RBE) in Bragg peak, and higher linear energy transfer (LET) than protons or photons, enable us to deliver a sufficient dose to the target volume, while minimizing the dose to the surrounding normal tissues. In 1994, clinical trials using carbon ion beams generated from the Heavy-Ion Medical Accelerator in Chiba (HIMAC) were begun at the National Institute of Radiological Sciences (NIRS). We started a Phase II study in 2000,

and reported good clinical outcomes with a low incidence of toxicities [5].

On the other hand, quality of life (QOL) is an important factor in therapeutic decision-making for patients and is commonly used as an end-point in clinical trials. Many studies for QOL assessment have been carried out; however, few long-term prospective studies have been reported.

In our Phase II study, QOL was investigated as a secondary endpoint. We previously reported the 12- and 36-month results of a QOL assessment in prostate cancer with carbon ion radiotherapy (C-ion RT), with a total dose of 63–66 GyE given in 20 fractions over 5 weeks [6, 7]. In this article, we describe the results of our trial at a follow-up of 5 years.

MATERIALS AND METHODS

Patients enrolled in a Phase II clinical study and those who received the same treatment method as for the study of April 2000 to January 2007 were analyzed. Patients eligible for the study had a proven diagnosis of prostatic adenocarcinoma, localized Stage T1–3 cancer according to the 1997 American Joint Committee on Cancer staging system [8], and a primary tumor without radiologically detectable involvement of regional lymph nodes or distant organs. All patients were also required not to have undergone previous treatment for prostate cancer except for hormone therapy. Patients with T1/T2aN0M0, an initial prostate-specific antigen (iPSA) level of <20 ng/ml, and a Gleason score (GS) of ≤6 were allocated to the low-risk group, those with T3 or iPSA level ≥20 ng/ml or GS ≥ 8 were assigned to the high-risk group, and the remainder were assigned to the intermediate-risk group [9]. All patients signed an informed consent form approved by the local institutional review board.

Carbon ion radiotherapy

Patients were treated with C-ion beams generated by the HIMAC. Details of the treatment protocol have been provided elsewhere [9–11]. Briefly, C-ion RT was performed once daily, 4 days per week. Patients were treated with five ports, one anterior–posterior port, a pair of lateral ports, and a second pair of lateral ports with a reduced rectal field [12]. One port was used in each session. The irradiated dose was 63.0 or 66.0 Gy equivalents (GyE) in 20 fractions, with a fraction dose of 3.15 or 3.3 GyE [5]. The patients were hospitalized just before the start of C-ion RT and discharged just after the end of the treatment.

Androgen deprivation therapy

Patients in both the intermediate- and high-risk groups received androgen deprivation therapy (ADT) in combination with C-ion RT. ADT was administered for a total duration of 6 months for intermediate-risk patients and for more than 24 months for high-risk patients. Neoadjuvant ADT was administered for 2–6 months in both groups.

QOL questionnaire

The assessment of health-related quality of life (HRQOL) was performed using the Functional Assessment of Cancer Therapy-General (FACT-G) and for Prostate Cancer Patients (FACT-P) questionnaire version 4 (Japanese version) [13].

The FACT-P, a validated questionnaire that has been frequently used to assess QOL in men with clinically localized and advanced prostate cancer, consists of the FACT-G questionnaire and the Prostate Cancer Subscale (PCS). The FACT-G instrument is a self-report questionnaire consisting of 27 question items, and it comprises four subdomains: physical well-being (PWB), functional well-being (FWB), social/family well-being (SFWB), and emotional well-being (EWB). Each item is scored from 0 to 4, with a higher score representing a better QOL.

The prostate cancer subscale (PCS) contained in the FACT-P consists of 12 questions particularly designed to measure the HRQOL in patients with prostate cancer. The FACT-P score is the combination of the four subdomains of the FACT-G and the PCS. The Trial Outcome Index (TOI) is created by summing the PWB, FWB, and PCS, and is considered to be a sensitive index focusing on the physical aspects of HRQOL [14].

HRQOL assessment was prospectively performed at the following five time points: before the initiation of C-ion RT, immediately after, and 12 and 36 and 60 months after completion of C-ion RT. The questionnaire sheet was given to each subject in person before and immediately after C-ion RT, whereas the investigation was performed by mail at 12, 36 and 60 months after C-ion RT.

Each subdomain score could be calculated if >50% of items were answered.

The missing items, if any, were prorated from the answered items. Subjects whose subscales were sufficient to calculate each index were used for analysis.

Follow-up

Patients were followed at 3-month intervals during the first 5 years after C-ion RT and at 3- to 6-month intervals thereafter. Late toxicities caused by C-ion RT were scored according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) toxicity criteria [15]. The late reaction scores were recorded at each follow-up. Biochemical failure (BF) was defined according to the Phoenix criteria [16].

Statistical analysis

Subdomains of the FACT-P and combined scores (FACT-G, FACT-P, TOI) were tested by the paired *t* test using SPSS version 23 software (SPSS Inc., Chicago, IL). Those scores after C-ion RT were compared with their baseline scores.

Subjects were divided by the presence of ADT, or any relapse or late morbidities at each assessment time point to perform a subset analysis between two subgroups. In the subgroup analysis, QOL scores were analyzed using the unpaired *t*-test. Results were considered significant at a P value of <0.05. The Bonferroni method was used for adjustment for multiple comparisons.

RESULTS

A total of 417 males with prostate cancer were enrolled into the Phase II study between April 2000 and January 2007 at NIRS.

Patient characteristics are shown in Table 1. The median age was 69 years (ranging from 47 to 92 years). The clinical stage (according to the 1997 UICC TNM classification) was T1 in 109 subjects, T2a in 87, T2b in 81, and T3 in 140. The Gleason score reassessed by a central pathologist was ≤6 in 119 subjects, 7 in 183, and ≥8 in 115. The median pretreatment PSA was 14.0 ng/ml (ranging from 2.1 to 260 ng/ml). The numbers of patients classified into the low-, intermediate- and high-risk groups were 79 (19%), 86 (21%) and 252 (60%), respectively. At 60 months after C-ion RT, 6 subjects had died of prostate cancer and 17 had died of other diseases.

QOL questionnaire submission rate

The response rate of the QOL questionnaire and the number of available data are also shown in Table 2. Overall, responses to >90% of questions were available for calculating FACT-G, FACT-P and TOI scores.

Table 1. Participant characteristics

Median age (range)	69 years	(47–92)
Median PSA (range)	14.0 ng/ml	(2.1–260)
No. of patients (%)		
T Stage (UICC 1997)		
≤T1c	109	(26.1)
T2a	87	(20.9)
T2b	81	(19.4)
T3a–b	140	(33.6)
Gleason Score		
≤6	119	(28.5)
7	183	(43.9)
≥8	115	(27.6)

QOL scores

The means and standard deviations of the individual subdomains—FACT-G, FACT-P and TOI—obtained from all subjects are shown in Table 3 and Fig. 1 (see Supplementary Fig. 1).

In comparison with the corresponding baseline scores, a significant decrease was observed in PWB, PCS and TOI scores at completion of C-ion RT; however, these scores returned to the baseline levels, and there was no significant difference in the scores at baseline and 60 months after C-ion RT. At 60 months after treatment with C-ion RT, the SFWB, FACT-G and FACT-P scores remained lower than the baseline levels. On the other hand, the EWB subscale score significantly increased immediately after C-ion RT, and remained higher than the baseline level. The FWB score changed very little during 60 months.

In the group with C-ion RT in combination with ADT, significant decreases were observed in FACT-G, FACT-P and TOI scores at 12 months compared with those of the group without ADT; however, at 36 and 60 months after C-ion RT, no significant decrease was observed in any scores between the two groups (Fig. 2a and supplementary data).

Some kind of relapse was observed in 42 subjects, who had BF and/or local recurrence, lymph node metastasis or distant metastasis. The FACT-G, FACT-P and TOI scores in the group with some kind of relapse were lower than those in the group without any relapse, although the difference was of only borderline significance (P value = 0.06–0.10) (Fig. 2b and supplementary data). The EWB score in the group with some kind of relapse was significantly decreased at 36 months and 60 months after C-ion RT (data not shown). In this study, late adverse events were assessed according to the RTOG/EORTC late morbidity criteria. Except for one subject with Grade 3 genitourinary (GU) morbidity, no severe late adverse events were observed at any assessment time point. At 12, 36 and 60 months after C-ion RT, incidents of Grade 1 or worse late adverse events were observed in 61 (15%), 132 (32%) and 89 (21%) patients, respectively (Table 4). The FACT-P and TOI scores in the group with late morbidities were significantly lower than those in the group without late morbidities at 12, 36 and 60 months after C-ion RT (Fig. 2c and supplementary data).

Table 2. Submission rate of the HRQOL questionnaire and response compliance rate

	Before C-ion RT	After C-ion RT			
		1 month	12 months	36 months	60 months
Number of living participants	417	417	416	402	394
Number of responses	401	389	402	386	365
% of responses of living participants	96.2	93.3	96.6	96.0	92.6
No. of available data for FACT-G	390	379	387	372	345
No. of available data for FACT-P	385	372	384	370	342
No. of available data for TOI	387	375	388	374	345

HRQOL = health-related quality of life, C-ion RT = carbon ion radiotherapy.

Table 3. Mean (standard deviation) of scores of the individual subdomains, FACT-P, FACT-G, and TOI obtained from all of the 417 subjects

Subdomains (full mark)	Formula	Before C-ion RT	After C-ion RT							
			1 month		12 months		36 months		60 months	
Physical well-being (28)	(1)	25.1 (3.2)	24.4*	(3.3)	24.6	(3.5)	25.1	(4.0)	25.3	(4.1)
Social/Family well-being (24)	(2)	18.8 (5.5)	18.6	(5.7)	16.8*	(6.4)	16.3*	(6.5)	15.8*	(6.9)
Emotional well-being (24)	(3)	18.8 (4.0)	19.8*	(3.7)	19.6*	(3.7)	19.5*	(3.9)	20.0*	(3.5)
Functional well-being (24)	(4)	21.3 (5.3)	20.8	(5.4)	21.6	(5.6)	21.4	(5.8)	21.0	(6.4)
Prostate cancer subscale (48)	(5)	35.3 (6.2)	32.5*	(6.4)	34.1*	(6.5)	34.8	(6.9)	34.7	(7.2)
Index (full mark)										
FACT-G (100)	(1 + 2 + 3 + 4)	84.2 (12.6)	83.7	(12.9)	82.6*	(13.7)	82.4*	(14.3)	82.7*	(15.0)
FACT-P (148)	(1 + 2 + 3 + 4 + 5)	119.5 (16.9)	116.2*	(17.1)	116.9*	(18.4)	117.5*	(19.3)	117.6*	(20.2)
TOI (100)	(1 + 4 + 5)	81.8 (12.0)	77.8*	(12.1)	80.3	(13.0)	81.6	(13.7)	81.4	(14.6)

FACT-G = Functional Assessment of Cancer Therapy-General, FACT-P = Functional Assessment of Cancer Therapy for Prostate Cancer Patients, TOI = Trial Outcome Index, C-ion RT = carbon ion radiotherapy. Asterisk indicates significant changes in comparison with the corresponding baseline scores.

DISCUSSION

In this study, we showed 5-year prospective follow-up results using a QOL questionnaire after carbon ion radiotherapy. The FACT-P and TOI scores decreased immediately after C-ion RT, but returned to near-baseline levels at 12 months. The FACT-G score showed a gradual and continual decrease after C-ion RT. The FACT-P and FACT-G scores were significantly lower than the baseline level, even at 60 months after C-ion RT, but the absolute change was only about 2 points. It is thought that the cause for decreases in the FACT-P and FACT-G scores was the decrease of the SFWB scores. The SFWB scores at 12–60 months in the present study remained significantly lower than those of the baseline. Fujimoto *et al.* indicated culture-specific QOL issues for the FACT-G questionnaire for Japanese lung cancer patients [17]. The reason why SFWB was decreasing after C-ion RT is potentially cross-cultural issues, but it is still unknown. The TOI score, not including SFWB and EWB, returned to near-baseline levels at 12 months.

Lee *et al.* carried out a prospective longitudinal study to analyze the HRQOL assessment, using FACT questionnaires for up to 12 months after external beam radiotherapy, radical prostatectomy or interstitial brachytherapy for prostate cancer. The FACT-P score decreased at 1 month, but returned to baseline levels at 12 months [18]. This study did not randomize the participants to a particular treatment; however, the HRQOL decline reported by patients in the EBRT group was smaller in magnitude than those in the prostatectomy or brachytherapy group.

Recently, some prospective, long-term follow-up results in prostate cancer patients were published. King *et al.* reported data using the Expanded Prostate Cancer Index Composite (EPIC) instrument in patients receiving stereotactic body radiation therapy. In their study, transient decline in urinary/bowel domains within 3 months returned to baseline or better within 6 months and remained. Sexual QOL decline was predominantly observed within 9 months and was not altered by androgen deprivation or age [19].

Hoskin *et al.* reported that QOL scores were maintained over a 10.5-year follow-up in prostate cancer patients randomized to EBRT alone or with an HDR brachytherapy boost [20]. There was no evidence that QOL deteriorated with increasing follow-up time in any of the four FACT domains. They also reported that mean FACT scores were significantly lower in patients with moderate to severe genitourinary morbidity than those free of morbidity.

In the present study, the presence of ≥G1 adverse events and biochemical failure worsened the scores. On the other hand, the decreases in QOL scores in patients with biochemical failure were not statistically significant. Possible reasons were the small number of BF cases, or the use of salvage therapies. In addition, medication may also affect the incidence rate of late adverse effects; however, there is no restriction about medication for late toxicities or salvage therapy for recurrent disease in our protocol.

Missing data would result in a significant overestimation. It is suggested that the longer the investigation period lasts, the more difficult it is to obtain necessary responses for a proper analysis. In this study, the response rate was ~95% at all assessment time-points. We considered that the number of missing data was small, so we handled incomplete returns according to the Functional Assessment of Chronic Illness Therapy (FACIT) guidelines. At 60 months after treatment, The FACT-G, FACT-P and TOI scores in the group with any relapse seemed to be recovered; however, the two patients with the lowest scores died in this period.

ADT is now commonly used for prostate cancer patients with intermediate or high risk. ADT is known to adversely affect quality of life, due to various symptoms including sexual dysfunction, increased fatigue, and metabolic syndrome [21].

Sanda *et al.* reported long-lasting symptoms up to 2 years, despite termination of ADT in patients receiving EBRT [22]. In the

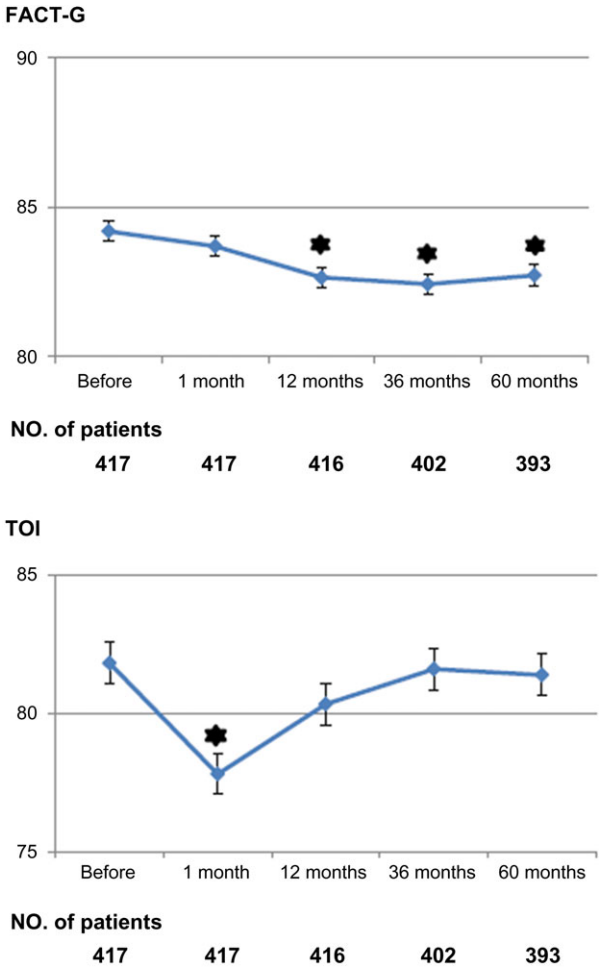

Fig. 1. Changes of QOL scores (FACT-G and TOI). Asterisk indicates significant change in comparison with baseline scores.

present study, FACT-G, FACT-P and TOI scores in patients with ADT were lower than those of patients without ADT, but significant decreases were observed at only 12 months after treatment. Symptoms due to ADT may show improvement over a longer-term follow-up period.

Our data were similar to those of other reports; however, it is impossible to directly compare results with the present study because of the use of different questionnaires or different treatment modalities. In our Phase II study protocol, which was made in 1999, the FACT questionnaire was selected since it was one of the most reliable system in HRQOL assessment at that time. Randomized trials remain the surest way of proving the utility of a new modality such as carbon ion radiotherapy. However, particle therapy for prostate cancer is not covered by the national health insurance system at this time, so it would be very difficult to compare C-ion RT with other treatment modalities.

From a longitudinal prospective study with a large number of patients, reliable data about HRQOL after C-ion RT for prostate

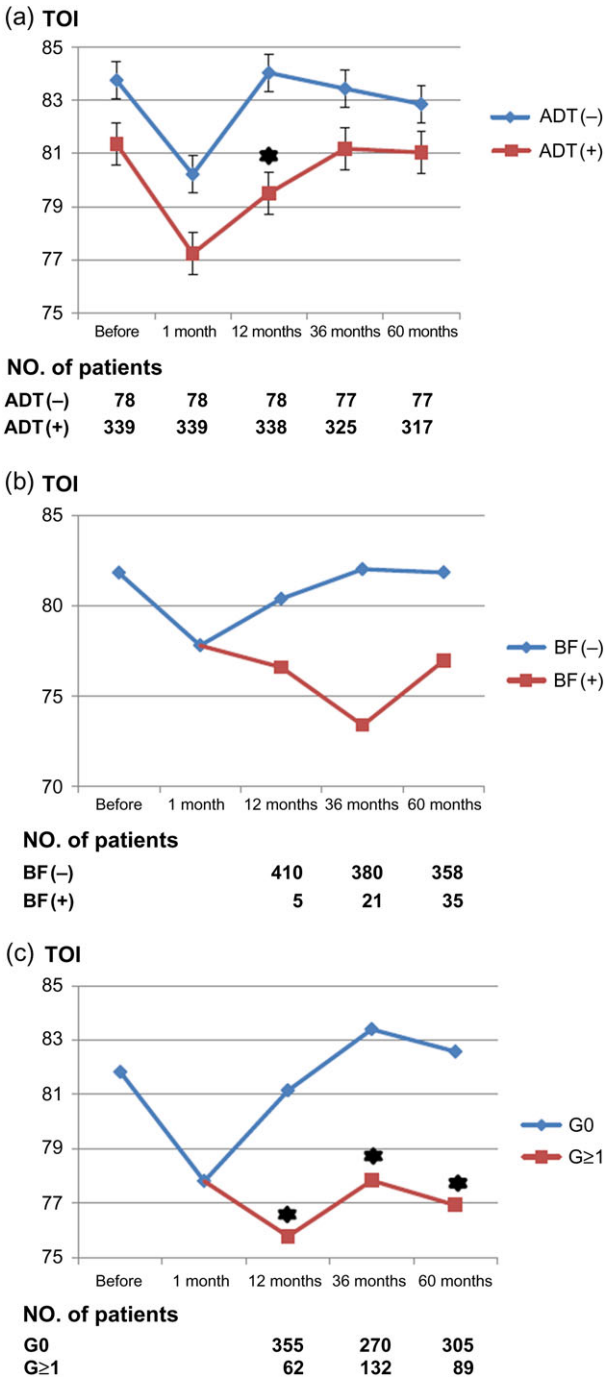

Fig. 2. (a) Comparison of changes of QOL scores (TOI) between C-ion RT alone and in combination with ADT. (b) Comparison of changes of QOL scores (TOI) between the groups with and without biochemical failure (BF). (c) Comparison of changes of QOL scores (TOI) between patients in whom no adverse events observed and those in whom ≥Grade 1 late adverse events were observed. Asterisk indicates significant difference between two groups.

Table 4. Incidence of adverse events in all of the 417 participants

No. of patients (%)	Bladder/Urethra				Rectum			
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
At 12 months	358 (86.0)	56 (13.5)	2 (0.5)	0 (0.0)	412 (99.0)	4 (1.0)	0 (0.0)	0 (0.0)
At 36 months	288 (71.6)	108 (26.9)	6 (1.5)	0 (0.0)	370 (92.0)	29 (7.2)	3 (0.7)	0 (0.0)
At 60 months	317 (80.5)	66 (16.8)	10 (2.5)	1 (0.3)	376 (95.4)	16 (4.1)	2 (0.5)	0 (0.0)
Max (>3 months)	121 (29.0)	266 (63.8)	29 (7.0)	1 (0.2)	341 (81.8)	64 (15.3)	12 (2.9)	0 (0.0)

cancer were obtained. The pattern of HRQOL change after C-ion RT was similar to those of other treatment modalities. QOL scores by FACT questionnaires were maintained at roughly the same levels during a long-term follow-up period. We believe that QOL assessment provides additional useful information for the treatment of prostate cancer patients.

SUPPLEMENTARY DATA

Supplementary data are available at *Journal of Radiation Research* online.

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CONFLICT OF INTEREST

There are no conflicts to disclose.

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