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CLINICAL INVESTIGATION **Prostate**

ADVERSE EFFECTS OF ANDROGEN DEPRIVATION THERAPY ON PERSISTENT GENITOURINARY COMPLICATIONS AFTER CARBON ION RADIOTHERAPY FOR PROSTATE CANCER

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Purpose: To determine the risk factors for persistent late genitourinary (GU) morbidity after carbon ion radiotherapy (C-ion RT) for prostate cancer.

Methods and Materials: Between April 2000 and November 2003, a Phase II study of 175 prostate cancer patients was performed to assess C-ion RT with a dose fractionation (66 Gray equivalent in 20 fractions) established from previous Phase I-II studies. The effects of the clinical and dosimetric parameters on the occurrence of persistent GU toxicity in 172 patients who survived for >18 months after C-ion RT were examined retrospectively. C-ion RT alone was performed for 33 low-risk patients, and 139 high-risk patients received C-ion RT combined with androgen deprivation therapy (ADT).

Results: Grade 1 and 2 persistent GU toxicities developed in 36 (21%) and 3 (2%) patients, respectively. The use of long-course ADT (≥24 months) and acute GU toxicity were associated with the occurrence of persistent toxicity by multivariate analysis ($p = 0.016$ and $p = 0.048$, respectively), but short-course ADT (<24 months) had no effect on the development of toxicity ($p = 0.35$). The 5-year actuarial complication rate of 80 patients undergoing long-course ADT was 31.1%; the corresponding rate for the 92 patients who received no ADT or short-course ADT was 22.2%.

Conclusion: Adverse effects with long-course ADT on persistent GU morbidity were observed in this study. Additional investigation is needed to identify suitable ADT administration according to risk groups, but long-course ADT should not be adopted for non–high-risk prostate cancer patients to reduce the GU toxicity rate with C-ion RT. © 2008 Elsevier Inc.

Carbon ion therapy, Prostate cancer, Urinary complications, Hormonal therapy, Dose–volume histogram.

INTRODUCTION

The incidence and mortality of prostate cancer are rapidly increasing in Japan, as well as in Western countries, mainly because of the spread of mass screening using prostate-specific antigen (PSA) evaluations (1). Radiotherapy (RT) is recognized as one of the treatment choices for localized or locally advanced prostate cancer. Taking both the cytocidal effect and the radiation-induced toxicity into consideration, hypofractionated RT with a desirable dose concentration is regarded as an ideal treatment for prostate cancer because of the relatively low α/β ratio of prostate cancer cells (2–4). The successful results obtained with novel recent conformal hypofractionated RT techniques, such as high-dose-rate brachytherapy and three-dimensional conformal RT, including intensity-modulated RT have yielded encouraging results, without increasing the complication rates compared with high-dose three-dimensional conformal RT using conventional fractionation (5–9).

Carbon ion RT (C-ion RT) is a promising RT modality because of its excellent dose localization and high biologic effect on the tumor (10–12). Therefore, C-ion RT with a hypofractionation schedule can be expected to achieve better local tumor control with minimal morbidity for prostate cancer. Since 1995, C-ion RT using C-ion beams generated by the Heavy Ion Medical Accelerator in Chiba has been

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Table 1. Patient characteristics

Characteristic	Low risk (n = 33)	High risk (n = 139)		All (n = 172)
		Short ADT (n = 59)	Long ADT (n = 80)	
Age (y)				
Median (range)	71 (60–80)	70 (54–79)	70 (53–83)	70 (53–83)
≤70	16 (48%)	30 (50%)	44 (55%)	90 (52%)
≥71	17 (52%)	29 (50%)	36 (45%)	82 (48%)
T stage				
T1	22 (67%)	18 (31%)	16 (20%)	56 (33%)
T2a	11 (33%)	5 (8%)	8 (10%)	24 (14%)
T2b	0 (0%)	15 (25%)	14 (17%)	29 (17%)
T3	0 (0%)	21 (36%)	42 (53%)	63 (36%)
Gleason score				
4–5	14 (42%)	3 (5%)	2 (3%)	19 (11%)
6	19 (58%)	9 (15%)	7 (9%)	35 (20%)
7	0	35 (60%)	42 (53%)	77 (45%)
8–9	0	12 (20%)	29 (35%)	41 (24%)
PSA (ng/mL)				
≤19.9	33 (100%)	33 (56%)	32 (40%)	98 (57%)
20.0–49.9	0	18 (30%)	28 (35%)	46 (27%)
≥50.0	0	8 (14%)	20 (25%)	28 (16%)

Abbreviations: PSA = prostate-specific antigen, ADT = androgen deprivation therapy.
Data presented as number of patients, with percentages in parentheses, unless otherwise noted.

performed for prostate cancer patients at our institute (13). The clinical outcomes of the first and second Phase I-II trials have been previously reported (14). On the basis of the results of these dose-escalation studies, a Phase II trial with a hypofractionation schedule of a fixed total dose of 66 Gray equivalent (GyE) in 20 fractions with a fraction dose of 3.3 GyE was planned to further confirm the efficacy and feasibility of C-ion RT for prostate cancer (15, 16).

We recently reported the results of this Phase II trial, and the effectiveness for prostate cancer of C-ion RT has been well confirmed (16). Moreover, our study showed that the percentage of rectal volume receiving 50% of the prescribed dose (V_{50}) was significantly greater in patients with rectal toxicity than in those without toxicity (17). However, urethral toxicity is also recognized as an important late complication of RT for prostate cancer. Although many reports have been published concerning the risk factors for late rectal bleeding after RT (6, 17–22), few reports have examined late genitourinary (GU) morbidity, especially for external beam RT using a hypofractionated regimen. Furthermore, to our knowledge, no data are available for charged-particle RT at this point. Therefore, we investigated the relationship between the clinical and dosimetric parameters and the incidence of late GU morbidities in the same Phase II trial of C-ion RT.

METHODS AND MATERIALS

Protocol and patients

The protocol of this trial has been previously described (16). In brief, patients were divided into high- and low-risk groups on the basis of their various pretreatment factors (*i.e.,* T stage according to the 1997 American Joint Committee on Cancer staging system [23], initial PSA [iPSA], and Gleason score). If patients had a Stage T1-T2a tumor with an iPSA of <20 ng/mL and Gleason score <7, they were classified as low risk. Conversely, patients were assigned to the high-risk group if their tumor characteristics were recognized as Stage T2b-T3 or iPSA of ≥20 ng/mL, or Gleason score ≥7.

As mentioned in our recent report (17), 175 prostate cancer patients were enrolled in this Phase II study between April 2000 and November 2003, but the updated data of 172 patients who were followed for >18 months were evaluated. The patient characteristics are summarized in Table 1. The median patient age was 70 years (range, 53–83). Of the 172 patients, 33 were considered low risk and underwent C-ion RT alone; the 139 high-risk patients underwent androgen deprivation therapy (ADT) combined with C-ion RT.

Carbon ion therapy

Setting the target volume and the methods of patient immobilization and field verification at each treatment session have also been previously described (15, 16). In brief, the clinical target volume included the prostate and seminal vesicles, and the initial planning target volume (PTV) was created by adding 10-mm margins at the anterior and lateral sides and a 5-mm margin at the posterior side of the clinical target volume. The second PTV, in which the posterior margin was deleted to reduce the rectal dose, was adopted after the first 10 fractions, but the second PTV was covered by >90% of the prescribed dose.

Fractionation was determined on the basis of the results from previous dose-escalation studies (12). C-ion RT was administered at a fixed total dose of 66 GyE in 20 fractions within 5 weeks, with a fraction dose of 3.3 GyE, and it was performed once daily, 4 fractions weekly.

Androgen deprivation therapy

Patients in the high-risk group received ADT combined with C-ion RT. ADT consisted of luteinizing hormone-releasing