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Clinical Investigation: Genitourinary Cancer

Carbon Ion Radiotherapy in Advanced Hypofractionated Regimens for Prostate Cancer: From 20 to 16 Fractions

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Summary

This was a large (>700 patients) retrospective study that assessed the effects of differences in dose fractionation (16 and 20 fractions) on late radiation toxicity and biochemical control in patients with prostate cancer treated with carbon ion radiotherapy (C-ion RT). C-ion RT in 16 fractions could offer an even lower incidence of genitourinary toxicity and comparable BRF rate than in 20 fractions. Advancement in hypofractionation could be safely achieved with C-ion RT for prostate cancer.

Purpose: To assess the effects of differences in dose fractionation on late radiation toxicity and biochemical control in patients with prostate cancer treated with carbon ion radiotherapy (C-ion RT).

Methods and Materials: A total of 740 prostate cancer patients who received C-ion RT between April 2000 and February 2009 were analyzed. Of those, 664 patients followed for at least 1 year were analyzed with regard to late radiation toxicity. Biochemical relapse-free (BRF) and overall survival (OS) rates in patient subgroups with each dose-fractionation were analyzed.

Results: Only 1 case of grade 3 genitourinary (GU) morbidity was observed in 20 fractions, and none of the patients developed higher grade morbidities. The incidence of late GU toxicity in patients treated with 16 fractions was lower than that of patients treated with 20 fractions. The OS rate and BRF rate of the entire group at 5 years were 95.2% and 89.7%, respectively. The 5-year BRF rate of the patients treated with 16 fractions of C-ion RT (88.5%) was comparable to that of the patients treated with 20 fractions (90.2%).

Conclusion: C-ion RT of 57.6 GyE (the physical C-ion dose [Gy] × RBE) in 16 fractions could offer an even lower incidence of genitourinary toxicity and comparable BRF rate than that in 20 fractions. Advancement in hypofractionation could be safely achieved with C-ion RT for prostate cancer. © 2012 Elsevier Inc.

Keywords: Carbon ion radiotherapy, Hypofractionation, Prostate cancer

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Introduction

Carbon ion radiotherapy (C-ion RT) may be the ideal radiation treatment for prostate cancer because of the unique physical and biologic advantages of C-ion beams (1). C-ion beams have a high relative biological effectiveness (RBE) resulting from high linear energy transfer (LET); their cytocidal effect is estimated to be about three times those of photons and protons (2).

Moreover, C-ion beams can theoretically offer a better therapeutic ratio with hypofractionation. Experiments with neutron beams with the same high-LET components as C-ion beams have demonstrated that increasing their fraction dose tends to lower the RBE for both the tumor and normal tissues. However, the RBE for normal tissues did not decrease as rapidly as that for the tumor in these experiments (3). This result substantiates the conclusion that the therapeutic ratio in high-LET radiation increases rather than decreases, even though the fraction dose is increased. Similar results have been obtained in experiments with C-ion beams (4, 5). These results have provided biological evidence for the validity of the hypofractionation regimen in C-ion RT. The hypofractionation regimen also benefits patients, as it allows abbreviation of the treatment period.

The first clinical trial of C-ion RT for prostate cancer was initiated at the National Institute of Radiological Sciences in 1994 (6). From the beginning of this trial, a relatively hypofractionated regimen of 20 fractions over 5 weeks was used. Two phase I/II dose escalation studies were first carried out to establish an appropriate dose of 20 fractions over 5 weeks for C-ion RT of prostate cancer (6-8). A phase II clinical study was started in April 2000 with the recommended dose of 66.0 or 63.0 GyE in 20 fractions (where GyE is the physical C-ion dose [Gy] × RBE) (9). In 2003, a more hypofractionated schedule of 57.6 GyE in 16 fractions was initiated with the expectation of more favorable outcomes. Because the preliminary results with this new fractionation schedule were sufficiently satisfactory, in September 2007, we started to treat all new patients with 57.6 GyE/16 fractions over 4 weeks. Here we report the effects of two different dose fractionation regimens (20 fractions/5 weeks and 16 fractions/4 weeks) on late radiation toxicity and biochemical control in patients with prostate cancer treated with C-ion RT.

Methods and Materials

Protocol and patients

Patients were eligible if they had histologically proven prostatic adenocarcinoma, that is, stage T1, T2, or T3 primary tumors according to the 1997 American Joint Committee on Cancer staging system (10), without radiologically detectable distant metastasis (M0), involvement of regional lymph nodes (N0, pN0); or solitary, nonfixed involvement of regional lymph nodes diagnosed by staging pelvic lymphadenectomy (pN1). Eligible patients were required not to have undergone previous treatment for prostate cancer except for hormone therapy. All patients signed an informed consent form approved by the local institutional review board. Pathology specimens were reviewed centrally before registration, and those of patients enrolled in the phase I/II studies were reviewed retrospectively. In this study, patients who received C-ion RT of the recommended doses in 20 fractions or 16 fractions were followed for at least 6 months and were analyzed with special regard to difference in late radiation toxicity and biochemical control in different fractionations. Analysis of late radiation toxicity included patients who were followed for at least 12 months.

C-ion therapy

Methods for setting target volume, immobilizing the patient, and verifying the field at each treatment session were described previously (8−10). For treatment planning, the clinical target volume (CTV) included the prostate and seminal vesicle, irrespective of T-stage or other risk factors. The 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 CTV. The posterior margin was reduced during the latter half of the C-ion RT. The dose and irradiated volume of the rectum were restricted by using the dose-volume histogram (DVH). A treatment plan was required to satisfy the condition that the rectal DVH be below the reference DVH, which was an average DVH of patients who developed grade 1 or lower rectal toxicity in early dose escalation studies. That meant (eg, the V50 [volume receiving 50 Gy] of the rectum was restricted to less than 8 cc in 20-fraction treatment).

C-ion RT was given once a day, 4 days a week (Tuesday to Friday). One port was used in each session. Positioning images were compared with reference images, which were checked to confirm their match with the digitally reconstructed radiograph. Alignments were performed only to skeletal anatomy without on-site imaging of the prostate. The treatment couch was moved to the matching position until the largest deviation of all measured points was less than 2 mm.

The dose was expressed as GyE (physical C-ion dose [Gy] × RBE) (11). Irrespective of the size of the spread-out Bragg peak (SOBP), the RBE value for the C-ion was estimated to be 3.0 at the distal part of the SOBP.

The compensation bolus was fabricated for each patient to make the distal configuration of the SOBP similar to the PTV. The multileaf collimator or the customized brass collimator defined the margins of the PTV.

Dose fractionations were determined on the basis of results from previous dose-escalation studies (7). C-ion RT was administered at a total dose of 63 GyE or 66 GyE in 20 fractions for 5 weeks or a dose of 57.6 GyE in 16 fractions for 4 weeks.

Androgen deprivation therapy

Patients in both the intermediate- and high-risk groups received androgen deprivation therapy (ADT) combined with C-ion RT. Neoadjuvant ADT was administered for 2-6 months. Adjuvant ADT was continued for a total duration of 6 months for intermediate-risk patients and of more than 24-36 months for high-risk patients. ADT use did not differ by fractionation regimen.

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