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Prostate carbon ion therapy

A multi-institutional analysis of prospective studies of carbon ion radiotherapy for prostate cancer: A report from the Japan Carbon ion Radiation Oncology Study Group (J-CROS)

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ABSTRACT

Background and purpose: A multi-institutional observational study (J-CROS1501PR) has been carried out to analyze outcomes of carbon-ion radiotherapy (CIRT) for patients with prostate cancer.
Patients and methods: Data of the patients enrolled in prospective studies of following 3 CIRT institutions were analyzed: National Institute of Radiological Sciences (NIRS; Chiba, Japan), Gunma University Heavy Ion Medical Center (GHMC; Gunma, Japan), and Ion Beam Therapy Center, SAGA HIMAT Foundation (HIMAT; Saga, Japan). Endpoints of the clinical trial are biochemical recurrence-free survival (bRFS), overall survival (OS), cause-specific survival (CSS), local control rate (LCR), and acute/late adverse effects.
Results: A total of 2157 patients' data were collected from NIRS (n = 1432), GHMC (n = 515), and HIMAT (n = 210). The number of patients in low-risk, intermediate-risk, and high-risk groups was 263 (12%), 679 (31%), and 1215 (56%), respectively. The five-year bRFS in low-risk, intermediate-risk, and high-risk patients was 92%, 89%, and 92%, respectively. The five-year CSS in low-risk, intermediate-risk, and high-risk patients was 100%, 100%, and 99%, respectively. The incidence of grade 2 late GU/GI toxicities was 4.6% and 0.4%, respectively, and the incidence of $\geqslant$G3 toxicities were 0%.
Conclusions: Favorable overall outcomes of CIRT for prostate cancer were suggested by the analysis of the first multi-institutional data.
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The incidence and mortality of prostate cancer have been reported to be 14.8% and 7.8%, respectively, according to the worldwide cancer database [1]. The outcomes of radiotherapy (RT) for prostate cancer have improved over the years due to the introduction of new treatment modalities, such as conventional RT, three dimensional conformal RT, and intensity-modulated RT (IMRT) [2–4]. The outcomes of RT for prostate cancer are suggested to be equal to or better than surgery [5]. Recently, robot-associate radical prostatectomy has been developed. Although the problem of surgical margin and learning curve are remaining, the outcomes of the surgery has been improving [6,7]. Besides that, low-dose rate (LDR) or high-dose rate (HDR) brachytherapy, combination of brachytherapy and IMRT, and proton beam therapy are also available for patients with prostate cancer [8–10]. Heavy ion (carbon ion) RT (CIRT) for cancer treatment in humans has been started in Japan in 1994, and the first CIRT clinical trial for prostate cancer was started in 1995 in Japan [11]. The advantages of CI beam are the focused dose distribution by an energy surge known as a spread-out Bragg-peak (SOBP) at a certain depth and its high biological effectiveness. Because these advantages have been extensively discussed in the literature, the characteristics and mechanism of CI beam will not be described in detail here [12,13].

Since its implementation >20 years ago, CIRT is currently available in eight institutions across four countries [14]. There are many challenges to conduct multi-institutional studies of CIRT due to the small number of CIRT institutions, almost all of which are specialized centers rather than general hospitals. However, due to the evidence of favorable outcomes with low incidence of adverse effects reported by CIRT studies, the number of CIRT institutions has been steadily increasing [11,14–18].

Here, we report the results of the first multi-institutional study of its kind that analyzed the data on the outcomes of CIRT for prostate cancer conducted in three institutions in Japan.

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Materials and methods

The Japan Carbon-ion Radiation Oncology Study Group (J-CROS)

The J-CROS is a study group including all four CIRT institutions currently in Japan. The following three institutions, the National Institute of Radiological Sciences (NIRS, Chiba), Gunma University Heavy Ion Medical Center (GHMC, Gunma), and Ion Beam Therapy Center, SAGA HIMAT Foundation (HIMAT, Saga) participated in this multi-institutional study on prostate cancer. The other one institution did not participate in this study because carbon-ion beam was not used for prostate cancer due to accelerator specification issues.

Patients and risk classification

All patients who were enrolled in prospective clinical trials of CIRT in each institution between December 2003 and December 2014 were included in the study. The inclusion criteria were as follows: pathologically confirmed prostate adenocarcinoma, stage T1–T3N0M0 (Union for International Cancer Control [UICC] 7th eds.), no other primary malignancies, no history of treatments for prostate cancer, performance status between 0 and 2, and the presence of written informed consent. Patients who did not meet all of the above criteria were excluded. The detailed criteria of each institution are shown in Table 1. The collected patient data were reclassified according to the D'Amico's classification [19]: low-risk = T1–T2a, initial prostate-specific antigen (iPSA) $\leqslant$ 10 ng/mL, and Gleason sum (GS) $\leqslant$ 6; intermediate-risk = not low-risk and not high-risk; high-risk = T2c–T3b or iPSA > 20 ng/mL or GS $\geqslant$ 7. Because not all institutions used the D'Amico classification, the initial risk categorization of patients treated in each institution was not always the same as the reclassified risk categorization in this multi-institutional analysis.

Treatments

CIRT was performed in accordance with the protocols of the specific prospective study conducted in each institution. The parameters of target volume and dose constraints of organs at risk were determined in accordance with each protocol. The dose constraints of the rectum are as following; D_{max}(rectum) < 60 Gy(RBE), $V80_{\%}$ (the irradiated volume of $\geqslant$80% prescribed dose) of the rectum <10 cc, $V50_{Gy(RBE)}$ of the rectum <7 cc. There are slight differences in the dose constraints of the rectum according to the institution or protocol. CIRT was delivered once per day, six to eight times per two weeks. All patients were set-up with bone matching image-guidance of daily vertical/horizontal kV fluoroscopy (without implantation of gold seed fiducial markers), and urination and defecation were controlled for set-up reproducibility. Written informed consent was obtained from all enrolled patients. Androgen deprivation therapy (ADT) was not administered to low-risk patients, while intermediate-risk patients received 4–8 months of neoadjuvant ADT, and high-risk patients received a total of 24 months of neoadjuvant plus adjuvant ADT. The hormonal therapy regimens were mostly consistent among the three institutions: maximal androgen blockade (MAB) or combined androgen blockade (CAB) were used for intermediate-risk and high-risk groups.

Endpoints and statistics

Biochemical recurrence-free survival (bRFS), overall survival (OS), cause-specific survival (CSS), local control rate (LCR), and acute/late adverse effects were defined as endpoints. The OS, CSS, LCR, and bRFS were calculated from the CIRT start date or neoadjuvant ADT start date. Biochemical failure was defined as a rise of >2.0 ng/mL above PSA nadir [20]. However, decreases in PSA level of less than nadir +2.0 ng/mL without any treatment or apparent transient PSA elevations due to benign prostatitis were not regarded as biochemical failure. The time at which adverse events occurred due to CIRT was defined as the time interval from the date CIRT began to the date of adverse event onset. Acute and late adverse events were analyzed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4 [21]. The Kaplan–Meier method was used to estimate the bRFS, LCR, CSS, and OS, and the log-rank test was used to determine statistical differences between survival curves.

This multi-institutional analysis of CIRT for prostate cancer was approved by the NIRS Institutional Review Board (IRB) in June 2015, and the IRB approvals from other institutions have also been obtained.

Results

Between December 2003 and December 2014, the total number of enrolled patients in all three institutions was 2157 (HIMAC: n = 1432, GHMC: n = 515, HIMAT: n = 210). According to the D'Amico classification, the number of patients with T1b–T2a, T2b, and T2c–T3b was 1210 (56%), 73 (3.4%), and 874 (41%), respectively. The number of patients with GS of $\leqslant$6, 7, and $\geqslant$8 was 414 (19%), 1074 (50%), and 669 (31%), respectively. Finally, the number of low-risk, intermediate-risk, and high-risk patients was 263 (12%), 679 (32%), and 1215 (56%), respectively (Table 2). The number of patients receiving ADT, including neoadjuvant and adjuvant ADT, was 1754 (81%).

All patients in this analysis had completed the scheduled CIRT. In all 2157 patients, 1724 patients were treated with the broad-beam irradiation method, and 433 patients were treated with the scanning irradiation method (only at NIRS). The target volume

Table 1
Definitions of the risk classification and hormonal therapy according to the institutions.

Institution	Risk	Conditions	ADT
NIRS (Phase II study)	Low*1	<T2a, iPSA < 10, GS $\leqslant$ 6	Not applied
	Intermediate	Other than Low/High risk	NAADT 4–6 months
	High*2	$\geqslant$T3a, iPSA $\geqslant$ 20, GS $\geqslant$ 8	NAADT + adjv. ADT total $\geqslant$ 24 months
GHMC (Prospective observational study)	Low*1	<T2a, iPSA < 10, GS $\leqslant$ 6	Not applied
	Intermediate	Other than Low/High risk	NAADT 6-8 months
	High*2	$\geqslant$T3a, iPSA $\geqslant$ 20, GS $\geqslant$ 8	NAADT + adjv. ADT total 24 months
HIMAT (Phase II study)	Low*1	<T2a, iPSA < 10, GS $\leqslant$ 6	Not applied
	Intermediate	Other than Low/High risk	NAADT 4-8 months
	High*2	$\geqslant$T2c, iPSA $\geqslant$ 20, GS $\geqslant$ 8	NAADT + adjv. ADT total 24-36 months

*1: satisfy all the conditions, *2: satisfy any of the conditions. *Abbreviations*; ADT: Androgen Deprivation Therapy, NAADT: neo-adjuvant ADT, adjv ADT: adjuvant ADT, iPSA: initial PSA, NIRS: National Institute of Radiological Sciences (Chiba), GHMC: Gunma University Heavy-ion Medical Center (Gunma), HIMAT: Saga Heavy-Ion Medical Accelerator in Tosu.

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