Dose Escalated Carbon Ion Radiotherapy for Localized Prostate Cancer in Shanghai Proton and Heavy Ion Center: Toxicity and Efficacy Outcomes At Two Years.

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Research Article

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Abstract

Purpose: The purpose of this study was to prospectively analyze the safety and feasibility of spot scanning carbon ion radiotherapy (CIRT) for patients with localized prostate cancer.

Methods: 118 localized prostate cancer patients treated with spot scanning CIRT at Shanghai Proton and Heavy Ion Center (SPHIC) were enrolled in this dose escalated study. The dose was gradually increased from 59.2GyE to 65.6GyE in 16 fractions. The primary endpoint was the acute and late toxicities. Secondary endpoints were biochemical relapse free survival (bRFS), distant metastasis free survival (DMFS), prostate cancer-specific survival (PCSS), and overall survival (OS).

Results: The median follow-up time was 30.2 months (4.8-62.7 months). Acute grade 1 and 2 genitourinary (GU) toxicities were 15.3% and 18.6%, while acute grade 1 and 2 gastrointestinal (GI) toxicities were 2.5% and 0%, respectively. Late grade 1 and 2 GU toxicities were 4.2% and 1.7%, respectively. No late GI toxicity were observed. There were no cases of severe acute or late toxicity ($\geq$ grade 3). The significant association was not found between the factors and the acute GU toxicities except for CTV volume ($p=0.031$) on multivariate analysis. The 2-year bRFS, DMFS, PCSS, OS were 100%, 100%, 100% and 98.8%, respectively.

Conclusion: The 2 years' outcomes are encouraging, providing additional and useful information on the feasibility and safety of spot scanning CIRT for prostate cancer. Long term follow-up and prospective multi-institutional data are warranted to reinforce the role of CIRT in the management of localized prostate cancer.

Trial registration: Clinicaltrial, NCT02739659. Registered 15 April 2016

Introduction

Radiotherapy is an important radical treatment option for localized prostate cancer. Randomized studies have established that dose escalated radiotherapy improve the cancer control (Dearnaley et al. 2014; Heemsbergen et al. 2014). However, increasing the radiation dose leads to concerns about the toxicities in organ at risks (OARs), such as rectum and bladder. Thus, if the dose to prostate can be increased without increasing the dose to the OARs, the treatment outcome and quality of life of patients will be improved.

Carbon ion radiotherapy (CIRT) has the potential to minimizing radiation dose to OARs while increasing the biologically effective dose delivery to prostate (Takakusagi et al. 2020; Nomiya et al. 2016). According to the data from Particle therapy co-operative Group (PTCOG) (<https://www.ptcog.ch/>), by June 2021, around 40,000 patients have been treated with CIRT at twelve carbon ion centers worldwide. The higher relative biological effectiveness (RBE) and greater cytocidal effect on cancer cells offer CIRT advantages over conventional radiotherapy (Tinganelli et al. 2020). Additionally, carbon ion beams produce the Bragg Peak through the release of enormous energy at the end of their range (Shioyama et al. 2015), allowing for maximizing destructive energy to the tumor site while minimizing unwanted damage to the surrounding normal tissues (Schulz-Ertner et al. 2007; Akakura et al. 2004). These biological and physical advantages make CIRT theoretically efficient in improving tumor control and reducing radiation-related toxicity.

The first CIRT clinical trial for prostate cancer was started at Chiba, Japan in 1995 (Akakura et al. 2004). This phase I/II dose escalation study established the efficacy and safety of CIRT. The following studies in Japan further confirmed the effectiveness of the CIRT with 16 fractions regimens (Nomiya et al. 2016; Okada et al. 2012).

However, different model to predict the relative biological effectiveness were used in different institutes. There are two major RBE models have been applied clinically in CIRT, the Japanese model (the original mixed beam model and the modified micro-dosimetric kinetic model [MKM]) and GSI model (local effect model [LEM]) (Fossati et al. 2012; Fossati et al.2018). Comparative studies shown that the LEM predicts a 5–15% higher RBE in the spread out Bragg peak (SOBP) of a carbon ion beam, relative to the MKM (Koto, et al.2020). Our previous studies also indicated that the RBE-weighted doses using MKM for targets and OARs should be converted to LEM doses using conversion curves for prostate cancer treated with CIRT (Wang et al. 2020). Which make the exchange of experience between different CIRT facilities is severely hampered by the use of disparate RBE models. Which dose should be prescribed when using LEM model to achieve results similar to those reported by Japanese facilities?

In 2014, Shanghai Proton and Heavy Ion Center (SPHIC) started the first prostate cancer CIRT treatment in China. Until Jan 2021, more than 300 prostate cancer patients have been treated by particle therapy in our institute, including localized prostate cancer, oligo-metastatic prostate cancer, prostate cancer with pelvic lymph nodes metastasis, and postoperative prostate cancer. In order to establish the optimal dose for CIRT in LEM model, dose escalated clinical trials of CIRT for localized prostate cancer were started in January 2016 at our center (NCT02739659, NCT04724577). Here, we report the two years' toxicity and efficacy of the dose escalated clinical trial in 16 fractions with CIRT.

Materials And Methods

Study design and patient eligibility

This is a dose escalation study with spot scanning carbon ion beam for localized prostate cancer. Patients who met all the following conditions were included: 1) histological diagnosis of prostate adenocarcinoma; 2) cT1N0M0 to cT4N0M0 according to the 7th American Joint Committee on Cancer (AJCC) classification; 3) Karnofsky Performance Score ≥ 70 ; 4) without any previous surgery or radiotherapy for prostate cancer; 5) and the presence of written informed consent. Patients did not meet all of the above criteria were excluded.

This dose escalated study was approved by the institutional review board of SPHIC and registered with ClinicalTrials.gov, NCT02739659. Eligible patients provided written informed consent for CIRT as well as for future anonymous use of clinical data. All patients were treated by spot scanning CIRT combined with or without hormone therapy in our institute. According to the National Comprehensive Cancer Network (NCCN) guideline, patients with low-risk prostate cancer had no hormone therapy, while intermediate-risk patients received 4-6 months of hormone therapy, and high or very risk patients received hormone therapy for 2-3 years. The hormone therapy regimens were combined androgen blockade (CAB).

Carbon ion radiotherapy

The methods of preparing of bladder and rectum, immobilizing the patients, setting clinical target volume (CTV) and planning target volume (PTV) were described previously (Li et al. 2021). Briefly, the CTV routinely included the prostate and seminal vesicle (seminal vesicle were not included for low risk), and pelvic lymph nodes were not included in this study. Two opposite lateral beams were used for each fraction treatment. CIRT was given once a day, 5 fractions per week. The treatment position was adjusted prior to each fraction with orthogonal X ray scans as image guides. Since May 2020, The daily in room computed tomography (CT) were applied to guild the CIRT. The doses were measured by the gray equivalent (GyE, carbon physical dose in Gy multiplied by RBE). The carbon ion was administered at a five dose level of 59.2/60.8/62.4/64/65.6 GyE in 16 fractions. OAR required for all the

patients were the rectum, bladder. The dose constraints of the rectum are as follow: Dmax (the max dose) <105% prescription dose (PD), V_{60} (volume receiving ≥ 60 GyE) <3 cc, V_{55} (volume receiving ≥ 55 GyE) <7cc, and V_{50} (volume receiving ≥ 50 GyE) <10cc, which were refer from our previous dose conversion study (Wang et al. 2020; Li et al. 2021). The dose constraints on the bladder were Dmax <105% PD and V_{60} (volume receiving ≥ 60 GyE) <10%, V_{55} (volume receiving ≥ 55 GyE) <15%, and V_{30} (volume receiving ≥ 30 GyE) <30%.

Follow-up

To closely monitor the patients, the patient's follow up was performed every week during treatment, and every three months until 3 years after CIRT, then 6 monthly. A rise of prostate-specific antigen (PSA) by at least 2 ng/mL above the nadir (the Phoenix definition) is considered as biochemical failure (Roach et al. 2006). For each patient, baseline parameters for genitourinary (GU) and gastrointestinal (GI) functions were assessed and acute and late toxicities were scored by a physician using common terminology criteria for adverse events (CTCAE) v.4.03 and Radiation Therapy Oncology Group (RTOG) Classification (Cox et al.1995). Acute toxicities, which were defined as side effects occurring within 3 months after the start of CIRT. Toxicities that occurred 3 months after the start of CIRT were considered as late toxicities.

Statistics

The biochemical relapse free survival (bRFS), distant metastasis free survival (DMFS), prostate cancer-specific survival (PCSS), and overall survival (OS) were evaluated using the Kaplan-Meier method. The bRFS DMFS, PCSS and OS were calculated from the start date of CIRT. The Chi-square test was used to examine the difference of acute GU toxicities between the low dose (59.2-60.8GyE) and high dose (62.4-65.6GyE) groups. Logistic and Cox regression identified univariate and multivariate associations between toxicities and clinical / dosimetric characteristics. A two-sided $p < 0.05$ was considered statistically significant. All the analyses were performed using SPSS software (version 22.0; IBM Corp).

Results

Patients characteristics

Between Jan 2016 and Dec 2020, 118 patients with clinically localized and histologically confirmed prostate cancer, treated by CIRT at SPHIC, were enrolled in this study. The patient characteristics are displayed in Table 1. The median age of the patients was 71 years old (range, 46–86 years). The median follow-up time was 30.2 months (4.8–62.7 months). According to the 7th AJCC classification, the number of patients with T1, T2, T3, and T4 was 5 (4.2%), 94 (79.7%), 17 (14.4%), and 2 (1.7%), respectively. The number of patients with Gleason score of 6, 7 and ≥ 8 was 32 (27.1%), 46 (39.0%), and 40 (33.9%), respectively. Before treatment, 45 patients had a PSA level < 10 ng/mL, 42 had a PSA level ranging from 10 ng/mL to 20 ng/mL, and 31 had a PSA level > 20 ng/mL. According to the National Comprehensive Cancer Network (NCCN) guideline, the number of patients of low risk, intermediate risk and high / very high risk patients was 9 (7.6%), 45 (38.1%), and 64 (54.2%), respectively. The number of patients were irradiated with a total dose of 59.2 GyE, 60.8 GyE, 62.4 GyE, 64GyE, and 65.6GyE was 43 (36.4%), 10 (8.5%), 9 (7.6%), 25 (21.2%), and 31 (26.3%). All patients had completed the spot scanning CIRT.

Table 1
patients' characteristics

Characteristics	59.2 GyE	60.8 GyE	62.4 GyE	64 GyE	65.6 GyE	Total
Patient number	43 (36.4%)	10 (8.5%)	9 (7.6%)	25 (21.2%)	31 (26.3%)	118(100%)
BED ($\alpha/\beta = 1.5$ Gy)	205.2 GyE	214.8 GyE	224.6 GyE	237.4 GyE	244.9 GyE	NA
Age (year)						
Median (range)	69 (50–84)	73 (69–79)	68 (62–74)	72 (47–86)	73 (50–86)	71 (46–86)
T stage						
T1	4 (9.3%)	0 (0%)	0 (0%)	0 (0%)	1 (3.2%)	5 (4.2%)
T2	32 (74.4%)	8 (80.0%)	8 (88.9%)	22 (88.0%)	24 (77.4%)	94 (79.7%)
T3	5 (11.6%)	2 (20.0%)	1 (11.1%)	3 (12.0%)	6 (19.4%)	17 (14.4%)
T4	2 (4.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.7%)
Initial PSA (ng/mL)						
<10	13 (30.2%)	5 (50.0%)	4 (44.4%)	10 (40.0%)	13 (41.9%)	45 (38.1%)
≥10 and ≤ 20	16 (37.2%)	2 (20.0%)	2 (22.2%)	11 (44.0%)	11 (35.5%)	42 (35.6%)
>20	14 (32.6%)	3 (30.0%)	3 (33.3%)	4 (16.0%)	7 (22.6%)	31 (26.3%)
Gleason Score						
6	13 (30.2%)	3 (30.0%)	2 (22.2%)	4 (16.0%)	10 (29.1%)	32 (27.1%)
7	19 (44.2%)	3 (30.0%)	4 (44.4%)	8 (32.0%)	12 (40.0%)	46 (39.0%)
≥8	11 (25.6%)	4 (40.0%)	3 (33.3%)	13 (52.0%)	9 (30.9%)	40 (33.9%)
Risk (NCCN)						
low	4 (9.3%)	0 (0%)	1 (11.1%)	1 (4.0%)	3 (9.7%)	9 (7.6%)
intermediate	14 (32.6%)	4 (40.0%)	3 (33.3%)	10 (40.0%)	14 (45.2%)	45 (38.1%)
high/very High	25 (58.1%)	6 (60.0%)	5 (55.6%)	14 (56.0%)	14 (45.2%)	64 (54.2%)
Complications						
Diabetes mellitus	7 (16.3%)	0 (0%)	1 (11.1%)	7 (28.0%)	4 (12.9%)	19 (16.1%)
Abbreviations: BED: Biological equivalent dose; PSA: Prostate-specific antigen; NCCN: National Comprehensive Cancer Network; TURP: Transurethral resection of the prostate						

Characteristics	59.2 GyE	60.8 GyE	62.4 GyE	64 GyE	65.6 GyE	Total
Internal use of anticoagulanti	6 (14.0%)	0 (0%)	0 (0%)	3 (12.0%)	4 (12.9%)	13 (11.0%)
TURP	4 (9.3%)	1 (10%)	0 (0%)	2 (8.0%)	3 (9.7%)	10 (8.5%)
Abbreviations: BED: Biological equivalent dose; PSA: Prostate-specific antigen; NCCN: National Comprehensive Cancer Network; TURP: Transurethral resection of the prostate						

Acute Toxicities

All patients were included in the analysis of acute and late toxicities. The acute toxicities are summarized in Table 2. The incidence of grade 1 and 2 acute GU toxicities were 15.3% and 18.6%, respectively. 8 (15.1%) and 5 (9.4%) patients developed grade 1 and 2 acute GU toxicities in low dose group, and 10 (15.4%) and 17 (26.2%) patients developed grade 1 and 2 acute GU toxicities in high dose group. The incidence of grade 2 acute GU toxicities of high dose group appeared to be higher than low dose group, but no significant difference was found between two groups ($p = 0.059$). There were no significant differences in the frequency of acute GU toxicities including hematuria, urinary frequency, urgency, retention and urinary tract pain between groups (Table 2). CTV volume, bladder V60, V61, V62, V63 were associated with $\geq$ grade 1 acute GU toxicities on univariate analysis, but only CTV volume was associated with $\geq$ grade 1 acute GU toxicities on multivariate analysis (Table 3).

Table 2
Acute toxicity between low dose and high dose groups.

Total dose	59.2-60.8GyE (n = 53)				62.4-65.6GyE (n = 65)				P value
Toxicity (Grade)	0	1	2	≥ 3	0	1	2	≥ 3	
GU									
Max toxicity	40 (75.5%)	8 (15.1%)	5 (9.4%)	0 (0%)	38 (58.5%)	10 (15.4%)	17 (26.2%)	0 (0%)	0.059
Urinary frequency	43 (81.1%)	5 (9.4%)	5 (9.4%)	0 (0%)	41 (63.1%)	9 (13.8%)	15 (23.1%)	0 (0%)	0.081
Urinary urgency	47 (88.7%)	3 (5.7%)	3 (5.7%)	0 (0%)	57 (87.7%)	2 (3.1%)	6 (9.2%)	0 (0%)	0.622
Urinary tract pain	52 (98.1%)	1 (1.9%)	0 (0%)	0 (0%)	62 (95.4%)	1 (1.5%)	2 (3.1%)	0 (0%)	0.433
Hematuria	51 (96.2%)	2 (3.8%)	0 (0%)	0 (0%)	61 (93.8%)	3 (4.6%)	1 (1.5%)	0 (0%)	0.644
Urinary retention	52 (98.1%)	0 (0%)	1 (1.9%)	0 (0%)	60 (92.3%)	3 (4.6%)	2 (3.1%)	0 (0%)	0.258
GI									
Max toxicity	52 (98.1%)	1 (1.9%)	0 (0%)	0 (0%)	63 (96.4%)	2 (3.6%)	0 (0%)	0 (0%)	0.683
Hematochezia	52 (98.1%)	1 (1.9%)	0 (0%)	0 (0%)	64 (98.2%)	1 (1.8%)	0 (0%)	0 (0%)	0.884
Diarrhea	53 (100%)	0 (0%)	0 (0%)	0 (0%)	64 (98.2%)	1 (1.8%)	0 (0%)	0 (0%)	0.364
Abbreviations: GU: genitourinary, GI: gastrointestinal									

Table 3
Univariate and multivariate clinical and DVH associations with acute GU toxicities ($\geq$ grade 1)

Variable	Univariate Cox regression		Multivariate Cox regression	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age	1.001 (0.956–1.047)	0.976	1.003 (0.952–1.056)	0.925
Diabetes mellitus	1.531 (0.509–4.605)	0.448	3.703 (0.881–15.564)	0.074
Internal use of anticoagulanti	0.559 (0.174–1.790)	0.327	0.370 (0.077–1.775)	0.214
TURP	2.171 (0.439–10.745)	0.342	1.871 (0.275–12.730)	0.522
CTV volume	1.016 (1.004–1.029)	0.011	1.016 (1.001–1.031)	0.031
Bladder volume	1.005 (0.997–1.013)	0.212	1.002 (0.992–1.013)	0.673
Bladder Dmax	1.105 (0.985–1.240)	0.090	1.038 (0.919–1.173)	0.549
Bladder V30	1.022 (0.983–1.063)	0.275	0.878 (0.463–1.664)	0.690
Bladder V40	1.030 (0.982–1.080)	0.224	1.031 (0.319–3.336)	0.959
Bladder V50	1.045 (0.982–1.111)	0.164	1.700 (0.489–5.912)	0.404
Bladder V55	1.059 (0.985–1.138)	0.122	0.503 (0.167–1.513)	0.221
Bladder V60	1.092 (1.004–1.187)	0.040	1.311 (0.443–3.881)	0.624
Bladder V61	1.106 (1.006–1.215)	0.038	1.193 (0.147–9.673)	0.869
Bladder V62	1.129 (1.009–1.264)	0.034	0.701 (0.135–3.647)	0.672
Bladder V63	1.178 (1.019–1.362)	0.027	1.432 (0.642–3.192)	0.380
Bladder V65	1.227 (0.908–1.658)	0.182	0.762 (0.442–1.313)	0.328
Abbreviations: DVH: dose-volume histograms, GU: genitourinary				

Three (2.5%) patients developed grade 1 acute GI toxicities. 1 patient in low dose group, which was not significantly different from 2 patients in high dose group ($p = 0.683$). There were no significant differences in the frequency of acute GI toxicities including hematochezia and diarrhea. No patients demonstrated grade 2 or worse acute GI toxicity.

Late Toxicities

Grade 1 late GU toxicities did not differ significantly between low dose group (2 [3.2%] of 62 patients) and high dose group (2 [3.6%] of 56 patients) ($p = 0.158$). In total, 5 patients developed grade 1 GU toxicities. 3 patients had urinary frequency, and 2 patients had microscopic hematuria. And there were 2 patients developed grade 2 late GU toxicity who had gross hematuria. No grade ≥ 3 late GU toxicity was found in any of the patients from both of the groups. There was no patient suffer from GI toxicity within the follow-up period (Table 4).

Table 4
Late toxicities between low dose and high dose groups.

Dose regimens	Number of patients	Number of patients (%) with GU toxicity grade					Number of patients (%) with GI toxicity grade				
		0	1	2	≥ 3	p value	0	1	2	≥ 3	p value
59.2-60.8GyE	53	60 (98.1%)	1 (1.9%)	0 (0%)	0 (0%)	0.158	62 (100%)	0 (0%)	0 (0%)	0 (0%)	NA
62.4-65.6GyE	65	59 (90.8%)	4 (6.2%)	2 (3.1%)	0 (0%)		56 (100%)	0 (0%)	0 (0%)	0 (0%)	
Total	118	111 (94.1%)	5 (4.2%)	2 (1.7%)	0 (0%)		118 (100%)	0 (0%)	0 (0%)	0 (0%)	
Abbreviations: GU: genitourinary, GI: gastrointestinal											

Efficacy

The median follow-up was 30.2 months (4.8–62.7 months). At the end of follow-up, five of the patients developed biochemical relapse, two patients received re-biopsy, but there was no evidence of tumor cells, and the PSA were stable without any treatment such as hormone therapy. One patient received hormone therapy immediately after the diagnosis of PSA failure. Two patients who were classified as high and very high risk groups experienced bone metastases at 27.4 and 32.1 months after CIRT, respectively. And one 72-year-old patient died at 20.6 months after CIRT due to cerebrovascular accident. No patients died due to prostate cancer until during the observation period. The 2-year bRFS, DMFS, PCSS, OS was 100%, 100%, 100% and 98.8%, respectively (Fig. 1). The 2-year bRFS in low risk, intermediate risk and high/very high risk was 100%, 100% and 100%, respectively ($p = 0.782$) (Fig. 2).

Discussion

The improvement in biochemical relapse free and overall survival of patients with prostate cancer were found to be dose-dependent (Kalbasi et al. 2015; Kuban et al. 2008). Several studies have shown the great potential of CIRT in the management of prostate cancer (Akakura et al. 2004; Ishikawa et al. 2006; Nomiya et al. 2016; Okada et al. 2012; Takakusagi et al. 2020), most of these studies were from Japanese institutes. However, the biological model used in European and our center (LEM model) were different from Japanese institutes (MKM model) (Molinelli et al. 2016). And our previous studies shown that the RBE-weighted doses at our center is too conservative compare with Japanese institutes, and the RBE-weighted doses using MKM for targets and OARs should be converted to LEM doses using conversion curves for prostate cancer treated with CIRT (Wang et al. 2020). The clinical study also found that the 5-year local control (71%) of skull base chordoma treated with CIRT at CANO is inferior to the results reported by Japanese centers (76–92%) using the same prescription dose, and they found that 92% of the local recurrences were attributable to suboptimal target dose in regions close to the brainstem or optic pathways (Iannalfi et al. 2020; Koto et al. 2020; Takagi et al. 2018). These studies indicated that we cannot replicate the prescription dose from Japanese experiences for prostate cancer CIRT. Until now, the optimal dose for CIRT with LEM model in localized prostate cancer remain unknown.

The first dose escalation clinical trial of CIRT for prostate cancer was started in Japan. The 5-year bRFS of the 57.6 GyE/16 fractions regimen was 88.5% (Okada et al. 2012). In a multi-institutional study, which collected and re-analyzed data from prospective clinical trials conducted in 3 institutions in Japan, the 5-year bRFS in low-risk, intermediate-risk, and high-risk patients was 92%, 89%, and 92%, respectively (Nomiya et al. 2016). At first, 63/66 GyE in 23/24 fractions was applied to treat the prostate cancer patients in our institute. The dose regimens were well tolerated and without any $\geq$ grade 2 late GI and GU toxicity. To determine the optimal radiation dose, we prospectively evaluated the safety and feasibility of dose escalated CIRT for patients with localized prostate cancer (NCT02739659). A total of 118 patients treated by CIRT in our institute achieved satisfactory short-term biochemical control without developing serious adverse events. As we known, this is the first dose escalated clinical trial in prostate cancer received CIRT with LEM model.

In the current study, five dose levels were used in this study. 118 patients were treated by 59.2 GyE (n = 43), 60.8 GyE (n = 10), 62.4 GyE (n = 9), 64.0 GyE (n = 25) and 65.6 GyE (n = 31). Five patients developed biochemical relapse, all of them were in the 59.2GyE group. None of the patients developed biochemical relapse in the $\geq$ 60.8 GyE groups within the follow-up period. The comparative analysis for efficacy between low dose and high dose group was not performed maybe due to the relatively short follow-up. The prescribed dose was 57.60 Gy (RBE) in 16 fractions in NIRS. Our previous study shown that 3.60 Gy (RBE) per fraction for 16 fractions in MKM, could be converted to 4.21 Gy (RBE) per fraction for 16 fractions in LEM (Wang et al. 2020). Hence it is expected that a better tumor control of the patients treated by high dose groups will be achieved. And we have enrolled 43 patients into the phase 2 clinical trial with the fixed dose at 65.6GyE in 16 fractions. The primary endpoint of the phase 2 study is to evaluate the efficacy of the dose regimen in LEM model system.

In terms of acute toxicity, according to the results from Radiation Therapy Oncology Group (RTOG) 0126 clinical trial (Michalski et al. 2018), 751 patients treated with 79.2Gy photon therapy, the incidence of grade 1, 2 and 3 acute GU toxicity was 19%, 16% and 1%, respectively, and the incidence of grade 1, 2 and 3 acute GI toxicity was 7%, 7% and $< 1\%$, respectively. Ion Prostate Irradiation (IPI) study from Heidelberg Ion-Beam Therapy Center (HIT) (Habl et al. 2016), 91 patients treated with 66GyE in 20 fractions carbon ion or proton, which shown that the incidence of grade 1, 2 and 3 acute GU toxicity was 34.1%, 17.6% and 0%, respectively, and the incidence of grade 1, 2 and 3 acute GI toxicity was 60.4%, 7.7% and 2.2%, respectively. In our study, there were no significant differences between groups for acute GU and GI toxicities (Table 2). Patients in the high dose group seems experienced higher rates of acute grade 2 GU toxicities than those in the low dose group (26.2% vs. 9.4%). No $\geq$ grade 3 GU toxicity was observed. The incidence of acute GU toxicities in our study is consistent with 79.2Gy arms in RTOG 0126 study, but is lower than the IPI study. The incidence of acute GI toxicity in our study is very rare, and is significantly lower than IPI study. Possible explanation for differences may lie in half patients received proton therapy in IPI, and daily in room CT was applied in our center since 2020. The association between the candidate prognostic factors and the acute toxicities has been investigated in the current study. We found CTV volume was associated with acute GU toxicities, Previous studies also indicated that patients with a large prostate volume have a great risk of irritative/obstructive symptoms (particularly dysuria) in the acute radiotherapy phase (Pinkawa et al. 2008). This may be due to more bladder volume were irradiated and lower urinary bother score before CIRT for patient with large prostate. So, for patients with large prostate, neoadjuvant hormone therapy is often recommended to reduce prostate volume.

Late toxicities tend to be more problematic than acute toxicities in radiotherapy for prostate cancer. The incidence of late grade 2 and 3 GU toxicity after radiotherapy has been reported as 11% and 3% in RTOG 0126 trial (79.2Gy arm) (Michalski et al. 2018). According to the results from a multi institutional study from Japan Carbon Ion

Radiation Oncology Study Group (J-CROS) analyzing 2157 patients treated with CIRT, the incidence of late grade 2 and 3 GU toxicity was 4.2% and 0% (Nomiya et al.2016). In the present study, the incidence of late grade 2 and 3 GU toxicity was 1.7% and 0%, respectively. The incidence of late grade 2 and 3 GI toxicity was 16% and 5% in RTOG 0126 trial (79.2Gy arm). The incidence of late grade 2 and 3 GU toxicity was 0.5% and 0% in J-CROS trial, which was more favorable than photon therapy. And in our study, there was no patient suffer from GI toxicity within the follow-up period, that may be due to the short follow-up time. Ishikawa's study shown that 81% late toxicities occurred within 2 years after CIRT. the median follow-up time of patients in low dose and high dose group was 49 and 17 months, respectively (Ishikawa et al.2006). Therefore, toxicities were evaluated for a sufficient period in low dose group, but were not sufficient in high dose group.

The limitations in this study include short follow up time, low sample size and single institution study. With 30.2 months follow up, we were only able to assess acute and early late toxicity, were too short to evaluate the long time outcome for prostate cancer.

Conclusion

In conclusion, the short-term results of spot scanning carbon ion therapy in the management of localized prostate cancer are encouraging. Our current results provide additional and useful information on the feasibility and safety of CIRT with LEM model for localized prostate cancer. Longer follow-up and prospective multi-institutional data are warranted to confirm the biochemical control and survival benefit of this promising radiotherapy technique.

Declarations

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Contributions

PL, XG, SF and QZ conceived and designed the study; PL contributed data analysis and reagents; YL performed the physical data analysis; PL and ZH participated in patient treatment and follow up; PL wrote the manuscript; XG, SF and QZ reviewed the manuscript and contributed to the final version of the manuscript, All authors have read and approved the manuscript.

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Ethics declarations

Conflicts of interest

The authors declare no conflict of interest or financial interest related to this publication.

Ethics approval and consent to participate

This study was approved by the ethical review board of Shanghai Proton and Heavy Ion Center (approval reference number 1510-03-03-1907). All patients provided written informed consent before enrollment. The informed consent form also contained an agreement for the publication of the study results.

Availability of data and materials

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

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Figures

Fig.1

Figure 1

The 2-year bRFS, DMFS, PCSS, OS was 100%, 100%, 100% and 98.8%, respectively (Figure 1).

Fig.2

Figure 2

The 2-year bRFS in low risk, intermediate risk and high/very high risk was 100%, 100% and 100%, respectively (p=0.782) (Figure 2).