Prostate-Specific Antigen Dynamics After Carbon Ion Radiotherapy for Prostate Cancer

Yosuke Takakusagi (y-takakusagi@kcch.jp)
Kanagawa Cancer Center
Takahiro Oike
Gunma University Graduate School of Medicine
Kio Kano
Kanagawa Cancer Center
Wataru Anno
Kanagawa Cancer Center
Keisuke Tsuchida
Kanagawa Cancer Center
Nobutaka Mizoguchi
Kanagawa Cancer Center
Itsuko Serizawa
Kanagawa Cancer Center
Daisaku Yoshida
Kanagawa Cancer Center
Tadashi Kamada
Kanagawa Cancer Center
Hiroyuki Katoh
Kanagawa Cancer Center

Research

Keywords: PSA dynamics, prostate cancer, carbon ion radiotherapy

Posted Date: June 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-32254/v1

Abstract

Background This study aimed to explain the dynamics of prostate-specific antigen (PSA) levels in patients with prostate cancer who were treated with carbon ion radiotherapy (CIRT) and neoadjuvant androgen-deprivation therapy (ADT).

Methods Eighty-five patients with intermediate-risk prostate cancer who received CIRT and neoadjuvant ADT from December 2015 to December 2017 were analyzed in the present study. The total dose of CIRT was set at 51.6 Gy (relative biological effectiveness) delivered in 12 fractions over 3 weeks. The PSA bounce was defined as a ≥0.4 ng/ml increase of PSA levels from the nadir, followed by any decrease. PSA failure was defined using the Phoenix criteria.

Results The median patient age was 68 (range, 48–81) years. The median follow-up duration was 33 (range, 20–48) months. The clinical T stage was T1c, T2a, and T2b in 26, 44, and 14 patients, respectively. The Gleason score was 6 in 3 patients and 7 in 82 patients. The median pretreatment PSA level was 7.37 (range, 3.33–19.0) ng/ml. All patients received neoadjuvant ADT for a median of 6 (range, 2–116) months. PSA bounces were observed in 39 patients (45.9%), occurring a median of 12 (range, 6–30) months after CIRT. PSA failure was observed in eight patients (9.4%), occurring a median of 21 (range, 15–33) months after CIRT. The 3-year PSA failure-free survival rate was 88.5%. No clinical recurrence was observed during the follow-up period. Younger age was a significant predictor of PSA bounces and PSA failure.

Conclusions The dynamics of PSA levels after CIRT was investigated in the present study. Further follow-up is needed to reveal the clinical significance of PSA dynamics.

Background

Among cancers, prostate cancer ranks second globally in morbidity and fifth in mortality [1]. Radiotherapy is one of the definitive treatments for localized or locally advanced prostate cancer. The number of patients treated with radiotherapy for prostate cancer has been increasing in Japan according to a structural survey conducted by the Japanese Society for Therapeutic Radiology and Oncology [2]. Brachytherapy, intensity-modulated radiotherapy (IMRT), and particle beam radiotherapy are the radiotherapy modalities used for patients with prostate cancer [3–6].

The first carbon ion radiotherapy (CIRT) clinical trial for prostate cancer was initiated in 1995 at the National Institute of Radiological Sciences (Chiba, Japan) [7]. CIRT offers biological and physical advantages over conventional photon radiotherapy with X-rays. Regarding the biological aspect, carbon ion beams have an estimated 2–3-fold higher relative biological effectiveness (RBE) than X-rays [8, 9]. In terms of the physical aspect, a more conformal dose distribution can be delivered via CIRT based on the ability of accelerated carbon ions to release a maximal amount of energy at the end of their track, resulting in a Bragg peak [10]. These features have led to favorable clinical outcomes for CIRT in prostate cancer [6, 11]. The first clinical treatment for prostate cancer at the ion-beam Radiation Oncology Center

in Kanagawa (i-ROCK) in Japan was performed in 2015 [12]. In i-ROCK, similar to previous studies of CIRT for prostate cancer, a favorable clinical outcome was achieved for prostate cancer treated with CIRT [13].

Serum prostate-specific antigen (PSA) is a sensitive marker of treatment outcomes for prostate cancer [14]. Fluctuation of PSA levels is often observed after radiotherapy without any clinical recurrence [15–17].Such benign PSA fluctuation, which was first reported in 1997, is known as the PSA bounce [18]. PSA bounces can be disconcerting for patients and physicians [19], and they may lead to unnecessary salvage treatment for cases that meet the definition of PSA failure. Therefore, accurate clinical interpretation of PSA dynamics after radiotherapy for prostate cancer is necessary to avoid patient anxiety or a false-positive diagnosis of relapse, which can instigate unnecessary treatment [20].

PSA bounces have been observed after various radiotherapy modalities for prostate cancer, such as low-dose-rate brachytherapy (LDR-BT), high-dose-rate brachytherapy (HDR-BT), IMRT, and stereotactic radiotherapy (SRT). However, only one study has reported PSA dynamics after CIRT [21]. In that study, although PSA dynamics after CIRT alone was revealed, that after CIRT using androgen-deprivation therapy (ADT) was not investigated. Thus, the present study aimed to explain the dynamics of PSA in patients with prostate cancer who were treated with CIRT and ADT.

Methods

Patients

In total, the cases of 85 consecutive patients with intermediate-risk prostate cancer who received CIRT at i-ROCK between December 2015 and December 2017 were analyzed in the present study. The patients were classified using the D'Amico risk group classification [22]. The eligibility criteria for this study were as follows: (i) histological diagnosis of prostate adenocarcinoma, (ii) cT1cN0M0 to T2bN0M0 according to the 7th UICC classification, (iii) performance status of 0–2, (iv) age of 20 years or older, (v) no previous treatment for prostate cancer excluding ADT, and (vi) followed up at least 1 year post-CIRT. Clinical records were collected in December 2019. The study was approved by the institutional review board of Kanagawa Cancer Center (approval number: 2019–171□). Written informed consent was obtained from all patients.

CIRT

Patients were placed in the supine position on a vacuum mattress (BlueBAG: Elekta AB, Stockholm, Sweden) and immobilized using thermoplastic shells (Shellfitter: Kuraray, Tokyo, Japan). Enema was used before computed tomography (CT) for CIRT planning. The rectum was emptied as much as possible using a laxative and an antiflatulent before each session, and enema was performed if the patient did not defecate within 24 h of treatment. The patients urinated and drank water 60 min before CT. A set of CT images with 2-mm-thick slices was taken for treatment planning.

Contouring of the target volumes and normal tissues was performed using MIM maestro software version 5.6 (MIM Software Inc., Cleveland, OH, USA). Dose calculation and optimization were performed using the Monaco version 5.20 system (Elekta AB).

The prostate volume was measured via CT imaging. The gross tumor volume was not defined. The clinical target volume (CTV) included the entire prostate and proximal seminal vesicles. Planning target volume (PTV) 1 was created by adding anterior and lateral margins of 10 mm and a posterior margin of 5 mm to the CTV. Boost therapy was performed using PTV2, in which the posterior edge was set in front of the anterior wall of the rectum to reduce the rectal dose in the ninth course of treatment [23, 24]. The rectum was delineated as the organ at risk from 10 mm above the upper margin of the PTV to 10 mm below the lower margin of the PTV.

The total dose was set at 51.6 Gy (RBE). After the first eight fractions were delivered using PTV1, boost therapy was performed using PTV2 in the latter four fractions. The PTV was covered by ≥95% of the prescribed dose, and the maximum PTV dose was limited to <105% of the prescribed dose. The dose constraint for the rectum aimed at V80% < 10 ml.

CIRT was administered once daily for 4 days a week for 3 weeks. All patients were treated using the spot scanning method. CIRT was performed from both the right and left sides of the patient. One port was used for each treatment session. Verification of the patient position was performed using in-room CT during the first, fifth, and ninth treatment sessions. In each treatment session, a computer-aided online positioning system was employed to verify the positioning accuracy to less than 1 mm.

ADT

Urologists administered ADT. Neoadjuvant ADT was administered for 4–8 months through the end of CIRT. ADT was performed via combined androgen blockade with an antiandrogen plus medical castration in principle.

Follow-Up

A urologist and a radiation oncologist conducted patient follow-up at 3-month intervals for the first 3 years after CIRT and at 6-month intervals thereafter. PSA was measured at each follow-up visit. In the present study, the PSA bounce was defined as a PSA increase of at least 0.4 ng/ml from the nadir PSA level, followed by any decrease [25, 26]. PSA failure was defined using the Phoenix definition, namely, the nadir PSA level plus 2 ng/ml [27]. The time to the event was calculated from the start of CIRT to the date of the event.

Statistical Analysis

Statistical analysis was performed using STATA software (version 13.1, TX, USA). The correlation of clinical variables with PSA dynamics was assessed via logistic regression. Comparative analyses for continuous variables of the two groups were examined using the Mann–Whitney U test. Comparative analyses for categorical variables of the two groups were examined using the chi-squared test. A *p* value of <0.05 was considered significant. The PSA failure-free survival rate was estimated using the Kaplan–Meier method.

Results

Patient Characteristics

Patient characteristics are summarized in *Table 1.* The median patient age was 68 (range, 48–81) years. The median follow-up duration was 33.1 (range, 20.1–48.3) months. All patients completed CIRT on schedule. Neoadjuvant ADT was administered to all patients, and the median duration of ADT was 6.2 (range, 2.3–116.9) months. Pre-CIRT PSA levels were measured a median of 15 (range, 0–40) days before the start of CIRT.

Characteristics	n (%)
Follow-up duration, months, median (range)	33.1 (20.1-48.3)
Age, years, median (range)	68 (48-81)
T stage	
1c	27 (31.8%)
2a	44 (51.8%)
2b	14 (16.5%)
Pretreatment PSA, ng/ml, median (range)	7.37 (3.33-19.0)
< 10	147 (58.1%)
10 ≤ 20	73 (28.9%)
Gleason score	
6	3 (3.5%)
7	82 (96.5%)
D'Amico classification	
intermediate	85 (100.0%)
ADT	
neoadjuvant	85 (100.0%)
duration, month, median (range)	6.2 (2.3-116.9)
Prostate volume, cc, median (range)	26.9 (11.9-88.2)
pre-CIRT PSA, ng/ml, median (range)	0.31 (0.01-3.28)
Time to nadir PSA, month, median (range)	3 (3-24)
PSA: prostate specific antigen, ADT: androgen deprivation therapy	

Table 1
Patient characteristics (n = 85)

PSA Dynamics

PSA dynamics for all patients is presented in *Fig. 1(a).* The average PSA dynamics based on the presence or absence of the PSA bounce is presented in *Fig. 1(b).* The average PSA level in the PSA bounce group was significantly higher than that in the PSA bounce-free group beyond 3 months after CIRT ($p < 0.05$). The average PSA dynamics for the presence or absence of PSA failure is presented in *Fig. 1(c).* The

average PSA level in the PSA failure group was significantly higher than that in the PSA failure-free group before CIRT and at all time points between 6 and 36 months after CIRT, excluding 30 months ($p < 0.05$).

PSA bounces were observed in 39 patients (45.9%) a median of 12 (range, 6–30) months after CIRT. Predictive significance of clinical variables for the occurrence of PSA bounces was assessed via logistic regression (*Table 2)*.. In the univariate analysis, younger age and lower T stage were statistically significantly associated with the occurrence of a PSA bounce ($p = 0.001$ and 0.027, respectively). The median ages of patients with and without PSA bounces were 68 (range, 48–79) and 70 (range, 55–81) years, respectively ($p = 0.001$). The T stage in the PSA bounce group was T1c, T2a, and T2b in 16 (41.0%), 20 (51.3%), and 3 (7.7%) patients, respectively, versus 11 (23.9%), 24 (52.2%), and 11 (23.9%) patients, respectively, in the PSA bounce-free group ($p = 0.027$). In the multivariate analysis, only younger age was significantly associated with the occurrence of a PSA bounce ($p = 0.003$).

	Univariate			Multivariate		
	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
Age	0.89	(0.83-0.96)	**0.001**	0.88	(0.81-0.96)	**0.003**
T stage	0.47	(0.24-0.92)	**0.027**	0.46	(0.21-1.06)	0.068
Gleason score	0.41	(0.04-4.71)	0.475	0.70	(0.04-11.48)	0.801
initial PSA	0.96	(0.85-1.09)	0.517	0.99	(0.84-1.16)	0.902
Prostate volume	1.03	(0.99-1.07)	0.106	1.04	(0.99-1.09)	0.153
ADT duration	1.01	(0.97-1.06)	0.494	1.05	(0.98-1.14)	0.185
pre-CIRT PSA	1.40	(0.79-2.47)	0.247	0.87	(0.37-2.05)	0.751
PSA nadir	8682.40	(0.02-3.1e+9)	0.165	5029.79	(0.01-2.3e+9)	0.200
Time to PSA nadir	0.95	(0.79-1.09)	0.349	0.95	(0.80-1.12)	0.548
PSA: prostate specific antigen, ADT: androgen deprivation therapy, CIRT: carbon ion radiotherapy, OR: Odds ratios, CI: confidence interval						

Table 2
Predictive significance of clinical factors for PSA bounce occurrence
PSA failure was observed in eight patients (9.4%). As shown in *Fig. 2,* the 3-year PSA failure-free rate was 88.5%. PSA failure occurred a median of 21 (range, 15–33) months after CIRT. No clinical recurrence was observed. In seven of eight patients with PSA failure, the PSA level decreased without any treatment such as ADT. The remaining patient received ADT immediately after the occurrence of PSA failure without radiological confirmation of clinical recurrence.

The predictive significance of clinical variables for the occurrence of PSA failure was assessed via logistic regression (*Table 3)*.. In the univariate analysis, younger age, higher pre-CIRT PSA levels, and PSA

bounces were significantly associated with the occurrence of PSA failure (p = 0.004, 0.010, and 0.037, respectively). The median ages of patients with and without PSA failure were 61 (range, 50–68) and 69 (range, 48–81) years, respectively (p = 0.001). The median pre-CIRT PSA levels of patients with and without PSA failure were 1.24 (range, 0.30–3.97) and 0.25 (range, 0.01–3.28) ng/ml, respectively (p = 0.009). PSA bounces were observed in 7 patients (87.5%) with PSA failure versus 32 patients (41.6%) without PSA failure (p = 0.013). In the multivariate analysis, only younger age was statistically significantly associated with the occurrence of PSA failure (p = 0.019).

	Univariate			Multivariate		
	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
Age	0.85	(0.76-0.95)	**0.004**	0.81	(0.69-0.97)	**0.019**
T stage	1.07	(0.36-3.12)	0.902	2.08	(0.39-11.17)	0.392
Gleason score	NA	-	-	NA	-	-
initial PSA	1.13	(0.94-1.36)	0.180	1.27	(0.95-1.70)	0.100
Prostate volume	1.03	(0.99-1.07)	0.149	1.05	(0.98-1.13)	0.171
ADT duration	0.91	(0.65-1.26)	0.555	0.97	(0.66-1.43)	0.895
pre-CIRT PSA	2.73	(1.27-5.87)	**0.010**	1.28	(0.35-4.73)	0.707
PSA nadir	7.49	(0.60-93.75)	0.119	3.51	(0.12-106.89)	0.470
Time to PSA nadir	0.82	(0.51-1.32)	0.409	1.03	(0.63-1.67)	0.906
PSA bounce	9.84	(1.15-83.98)	**0.037**	4.95	(0.35-70.37)	0.238
PSA: prostate specific antigen, ADT: androgen deprivation therapy, CIRT: carbon ion radiotherapy, OR: Odds ratios, CI: Confidence interval, NA: not available						

Table 3
Predictive significance of clinical factors for PSA failure occurrence

Discussion

We investigated the dynamics of PSA in patients with prostate cancer who were treated with CIRT and neoadjuvant ADT in the present study. Both PSA bounces and PSA failure were correlated with younger age. To the best of our knowledge, this is the first report of PSA dynamics after CIRT with neoadjuvant ADT.

Multiple definitions of the PSA bounce have been reported, and no consensus has been established. Several studies used the definition of an increase of >0.2 ng/ml in PSA levels followed by a spontaneous decrease to the pre-bounce level or lower [14, 17, 21, 28–29]. In the present study, no patient met this definition, as the nadir PSA level was extremely low because of the use of neoadjuvant ADT. Thus, we

defined the PSA bounce as an increase of at least 0.4 ng/ml followed by any decrease, in line with previous studies [25, 26]. In a study of PSA bounces in patients treated with conventional external radiotherapy, the bounce was defined as an increase of 0.5 ng/ml [30]. Conversely, the PSA bounce was defined as an increase of 0.1 ng/ml followed by two consecutive decreases after IMRT [31].

PSA bounces have been mainly reported after brachytherapy. PSA bounces were observed in 28–49% of patients after LDR-BT [15]. In two other studies, PSA bounces were observed in 43 and 48% of patients treated with HDR-BT, respectively [32, 33]. In a study of PSA dynamics after HDR-BT combined with conventional external beam radiotherapy, PSA bounces were detected in 31% patients [34].

PSA bounces have also been observed in patients treated with external beam radiotherapy alone. After IMRT, the occurrence rate of PSA bounces ranged 30%–32% [25, 31]. Recently, SRT has been performed for the definitive treatment of prostate cancer, and PSA bounces were also observed after SRT. In a multi-institutional analysis of PSA dynamics, PSA bounces were noted in 26% of patients [19]. Only one study of PSA dynamics after particle beam radiotherapy has been reported [21]. In that study, PSA bounces were observed in 55.7% of patients treated with CIRT alone for prostate cancer.

Age was one of the first and most frequently described predictive factors for PSA bounces after brachytherapy [15].Age was a significant consistent predictor of PSA bounces after IMRT [25, 31]. Regarding other treatment modalities, namely, SRT or HDR-BT combined with external beam radiotherapy, younger age was a significant predictor for PSA bounces [19, 34]. In addition, age was detected as a predictive factor for PSA bounces after CIRT [21]. Similar results were observed in the present study, as younger age was a predictive factor for PSA bounces and PSA failure. Therefore, it is suggested that age is a predictor for PSA bounce regardless of the radiotherapy modality.

Despite the accumulation of data on post-radiotherapy PSA dynamics, its relevance to clinical outcomes remains unclear. One study suggested that PSA bounces did not predict biochemical recurrence or clinical disease recurrence [31]. Another study reported that PSA bounces after external beam radiotherapy were correlated with PSA failure [26]. By contrast, some reports stated that the PSA bounce was a good predictive factor for PSA failure [20].Hinnen et al. found that PSA bounces after LDR-BT were predictive of better outcomes [35]. A long-term analysis suggested that the PSA bounce was a significant factor for better overall survival [36]. In CIRT, PSA bounce positivity was a significant predictor of favorable 5-year PSA failure-free survival [21]. In the present study, we found a correlation between PSA bounces and PSA failure only in univariate analysis. Longer follow-up is warranted to further explain this issue.

Some patients who exhibited PSA bounces experienced increases in PSA levels of 2 ng/ml or more, which met the Phoenix criteria. The PSA bounce exceeds the 2 ng/ml limit in approximately 10% of patients after brachytherapy [14].Approximately 1% of patients treated with SRT experienced a PSA increase of >2 ng/ml above the nadir [19]. However, PSA levels spontaneously decreased without any treatment in those patients. A similar clinical course was observed in the present study, as most patients experienced spontaneous decreases of PSA levels. Therefore, even among patients with PSA increases exceeding 2 ng/ml, which met the PSA failure criteria, continuous close PSA surveillance should be considered to

confirm the PSA bounce without immediate treatment such as ADT. These findings may provide important information for both patients and physicians to understand PSA dynamics after CIRT.

The present study had several limitations, such as its single-institutional nature, small number of patients, short observation period, and lack of cases of clinical recurrence. Although the correlation between PSA bounces and androgen production in younger age patients was suggested [37], serum androgen levels were not measured in the present study.

Conclusions

We observed the dynamics of PSA in patients with prostate cancer who were treated with CIRT and neoadjuvant ADT in the present study. PSA levels should be examined after treatment to survey for clinical recurrence. Further follow-up is needed to reveal the clinical significance of PSA dynamics.

Abbreviations

IMRT: intensity-modulated radiotherapy; CIRT: carbon ion radiotherapy; RBE: relative biological effectiveness; i-ROCK: ion-beam Radiation Oncology Center in Kanagawa; PSA: prostate-specific antigen; LDR-BT: low-dose-rate brachytherapy; HDR-BT: high-dose-rate brachytherapy; SRT: stereotactic radiation therapy; ADT: androgen-deprivation therapy; CT: computed tomography; CTV: clinical target volume; PTV: planning target volume

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of Kanagawa Cancer Center (approval number: 2019-171)

Consent for publication

Written informed consent was obtained from all patients.

Availability of data and material

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

Competing interests

The authors declare that they have no competing interests.

Funding

There is no funding to declare.

Authors' contributions

YT collected and analyzed the data and drafted the manuscript. KK, WA, and KT collected the data. NM and IS analyzed the data. TO and HK aided in writing the manuscript and contributed to the final draft of the manuscript. DY and TK analyzed the data and contributed to the final draft of the manuscript. All authors read and approved the final manuscript.

Acknowledgments

None

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359–86.
2. Shibuya H, Tsujii H. The structural characteristics of radiation oncology in Japan in 2003. Int. J. Radiat. Oncol. Biol. Phys. 2005;62:1472–6.
3. Smith GD, Pickles T, Crook J, Martin AG, Vigneault E, Cury FL, Morris J, Catton C, Lukka H, Warner A, Yang Y, Rodrigues G. Brachytherapy improves biochemical failurefree survival in low- and intermediate-risk prostate cancer compared with conventionally fractionated external beam radiation therapy: a propensity score matched analysis. Int J Radiat Oncol Biol Phys 2015;91:505–16.
4. Deutsch I, Zelefsky MJ, Zhang Z, Mo Q, Zaider M, Cohen G, Cahlon O, Yamada Y. Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT. Brachytherapy 2010;9:313–8.
5. Bryant C, Smith TL, Henderson RH, Hoppe BS, Mendenhall WM, Nichols RC, Morris CG, Williams CR, Su Z, Li Z, Lee D, Mendenhall NP. Five-Year biochemical results, toxicity, and patient-reported quality of life after delivery of dose-escalated image guided proton therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2016;95:422–34.
6. Nomiya T, Tsuji H, Kawamura H, Ohno T, Toyama S, Shioyama Y, Nakayama Y, Nemoto K, Tsujii H, Kamada T. 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). Radiother Oncol. 2016;121:288–93.

7. Akakura K, Tsujii H, Morita S, Tsuji H, Yagishita T, Isaka S, Ito H, Akaza H, Hata M, Fujime M, Harada M, Shimazaki, J. Phase I/II clinical trials of carbon ion therapy for prostate cancer. Prostate 2004;58:252–8.
8. Kanai T, Endo M, Minohara S, Miyahara N, Koyama-ito H, Tomura H, Matsufuji N, Futami Y, Fukumura A, Hiraoka T, Furusawa Y, Ando K, Suzuki M, Soga F, Kawachi K. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int J Radiat Oncol Biol Phys. 1999;44:201–10.
9. Kanai T, Matsufuji N, Miyamoto T, Mizoe J, Kamada T, Tsuji H, Kato H, Baba M, Tsujii H. Examination of GyE system for HIMAC carbon therapy. Int J Radiat Oncol Biol Phys. 2006;64:650–6.
10. Schulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. J Clin Oncol. 2007;25:953–64.
11. Ishikawa H, Tsuji H, Kamada T, Akakura K, Suzuki H, Shimazaki J, Tsujii H. Carbon-ion radiation therapy for prostate cancer. Int J Urol. 2012;19:296–305.
12. Nakayama Y, Minohara S, Nonaka T, Nomiya T, Kusano Y, Takeshita E, Mizoguchi N, Hagiwara Y. The Ion-Beam Radiation Oncology Center in Kanagawa (i-ROCK) Carbon Ion Facility at the Kanagawa Cancer Center. Int J Part Ther. 2016;2:478–80.
13. Takakusagi Y, Katoh H, Kano K, Anno W, Tsuchida K, Mizoguchi N, Serizawa I, Yoshida D, Kamada T. Preliminary result of carbon-ion radiotherapy using the spot scanning method for prostate cancer. Radiat Oncol. 2020;15:127
14. Caloglu M, Ciezki J. Prostate-specific antigen bounce after prostate brachytherapy: review of a confusing phenomenon. Urology 2009;74:1183e90
15. Burchardt W, Skowronek J. Time to PSA rise differentiates the PSA bounce after HDR and LDR brachytherapy of prostate cancer. J Contemp Brachytherapy. 2018;10:1–9.
16. Crook J, Gillan C, Yeung I, Austen L, McLean M, Lockwood G. PSA kinetics and PSA bounce following permanent seed prostate brachytherapy. Int J Radiat Oncol Biol Phys 2007;69:426–33.
17. Patel C, Elshaikh MA, Angermeier K, Ulchaker J, Klein EA, Chehade N, Wilkinson DA, Reddy CA, Ciezki JP. PSA bounce predicts early success in patients with permanent iodine-125 prostate implant. Urology 2004;63:110-–13
18. Wallner KE, Blasko J, Dattoli MJ. Evaluating cancer status. Prostate brachytherapy made complicated. Smart Medicine Press; Seattle 1997
19. Jiang NY, Dang AT, Yuan Y, Chu FI, Shabsovich D, King CR, Collins SP, Aghdam N, Suy S, Mantz CA, Miszczyk L, Napieralska A, Namysl-Kaletka A, Bagshaw H, Prionas N, Buyyounouski MK, Jackson WC, Spratt DE, Nickols NG, Steinberg ML, Kupelian PA, Kishan AU. Multi-Institutional Analysis of Prostate-Specific Antigen Kinetics After Stereotactic Body Radiation Therapy. Int J Radiat Oncol Biol Phys. 2019;105:628–36.

20. Åström L, Sandin F, Holmberg L. Good prognosis following a PSA bounce after high dose rate brachytherapy and external radiotherapy in prostate cancer. Radiother Oncol. 2018;129:561–6.
21. Darwis NDM, Oike T, Kawamura H, Kawahara M, Kubo N, Sato H, Miyasaka Y, Katoh H, Ishikawa H, Matsui H, Miyazawa Y, Ito K, Suzuki K, Gondhowiardjo S, Nakano T, Ohno T. Kinetics of Prostate-Specific Antigen after Carbon Ion Radiotherapy for Prostate Cancer. Cancers (Basel). 2020 Mar 4;12(3).
22. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, Tomaszewski JE, Renshaw AA, Kaplan I, Beard CJ, Wein A. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998;280:969–74.
23. Tsuji H, Yanagi T, Ishikawa H, Kamada T, Mizoe JE, Kanai T, Morita S, Tsujii H. Hypofractionated radiotherapy with carbon ion beams for prostate cancer. Int J Radiat Oncol Biol Phys. 2005;63:1153–60.
24. Ishikawa H, Tsuji H, Kamada T, Yanagi T, Mizoe J.E, Kanai T, Morita S, Wakatsuki M, Shimazaki J, Tsujii, H. Carbon ion radiation therapy for prostate cancer: results of a prospective phase II study. Radiother Oncol. 2006;81:57–64.
25. Sheinbein C, Teh BS, Mai WY, Grant W, Paulino A, Butler EB. Prostate-specific antigen bounce after intensity-modulated radiotherapy for prostate cancer. Urology. 2010;76:728–33.
26. Horwitz EM, Levy LB, Thames HD, Kupelian PA, Martinez AA, Michalski JM, Pisansky TM, Sandler HM, Shipley WU, Zelefsky MJ, Zietman AL, Kuban DA. Biochemical and clinical significance of the posttreatment prostate-specific antigen bounce for prostate cancer patients treated with external beam radiation therapy alone: a multiinstitutional pooled analysis. Cancer. 2006;107:1496–1502.
27. Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH, Sandler H. Defining biochemical failure following radio therapy with clinically localized prostate cancer recommendations of the RTOG- ASTRO Phoenix Consensus Conference. Int J Radiation Oncol Biol Phys. 2006;65:965–74.
28. Mazeron R, Bajard A, Montbarbon X, Gassa F, Malet C, Rocher F, Clippe S, Bringeon G, Desmettre O, Pommier P. Permanent 125I-seed prostate brachytherapy: early prostate specific antigen value as a predictor of PSA bounce occurrence. Radiat Oncol 2012;7:46.
29. Zwahlen DR, Smith R, Andrianopoulos N, Matheson B, Royce P, Millar JL. Prostate-specific antigen bounce after permanent iodine-125 prostate brachytherapy – an Australian analysis. Int J Radiat Oncol Biol Phys 2011;79:179–87.
30. Rosser CJ, Kamat AM, Wang X, Do KA, Sanchez-Ortiz RF, Kuban DA, Lee AK, Cheung R, Chichakli R, Pisters LL. Is patient age a factor in the occurrence of prostate-specific antigen bounce phenomenon after external beam radiotherapy for prostate cancer? Urology 2005;66:327–31.
31. Tan YG, Lau Kam On W, Huang HH, Tan Wee Kiat T. Prostate specific antigen bounce after intensity-modulated radiation therapy in an Asian population. Asian J Urol. 2016;3:59–63.

32. McGrath SD, Antonucci JV, Fitch DL, Ghilezan M, Gustafson GS, Vicini FA, Martinez AA, Kestin LL. PSA bounce after prostate brachytherapy with or without neoadjuvant androgen deprivation. Brachytherapy 2010;9:137–44.
33. Mehta NH, Kamrava M, Wang PC, Steinberg M, Demanes J. Prostate-specific antigen bounce after high-dose-rate monotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2013; 86: 729–33.
34. Makarewicz R, Lebioda A, Terlikiewicz J, Biedka M, Wiśniewski T. PSA bouncing after brachytherapy HDR and external beam radiation therapy: a study of 121 patients with minimum 5-years follow-up. J Contemp Brachytherapy. 2009;1:92–6.
35. Hinnen KA, Monninkhof EM, Battermann JJ, van Roermund JG, Frank SJ, van Vulpen M. Prostate specific antigen bounce is related to overall survival in prostate brachytherapy. Int J Radiat Oncol Biol Phys 2012;82:883–8.
36. Freiberger C, Berneking V, Vögeli TA, Kirschner-Hermanns R, Eble MJ, Pinkawa M. Long-term prognostic significance of rising PSA levels following radiotherapy for localized prostate cancer - focus on overall survival. Radiat Oncol. 2017 Jun 14;12:98.
37. Stock RG, Stone NN, Cesaretti JA. Prostate-specific antigen bounce after prostate seed implantation for localized prostate cancer: descriptions and implications. Int J Radiat Oncol Biol Phys 2003;56:448e53.

Figures

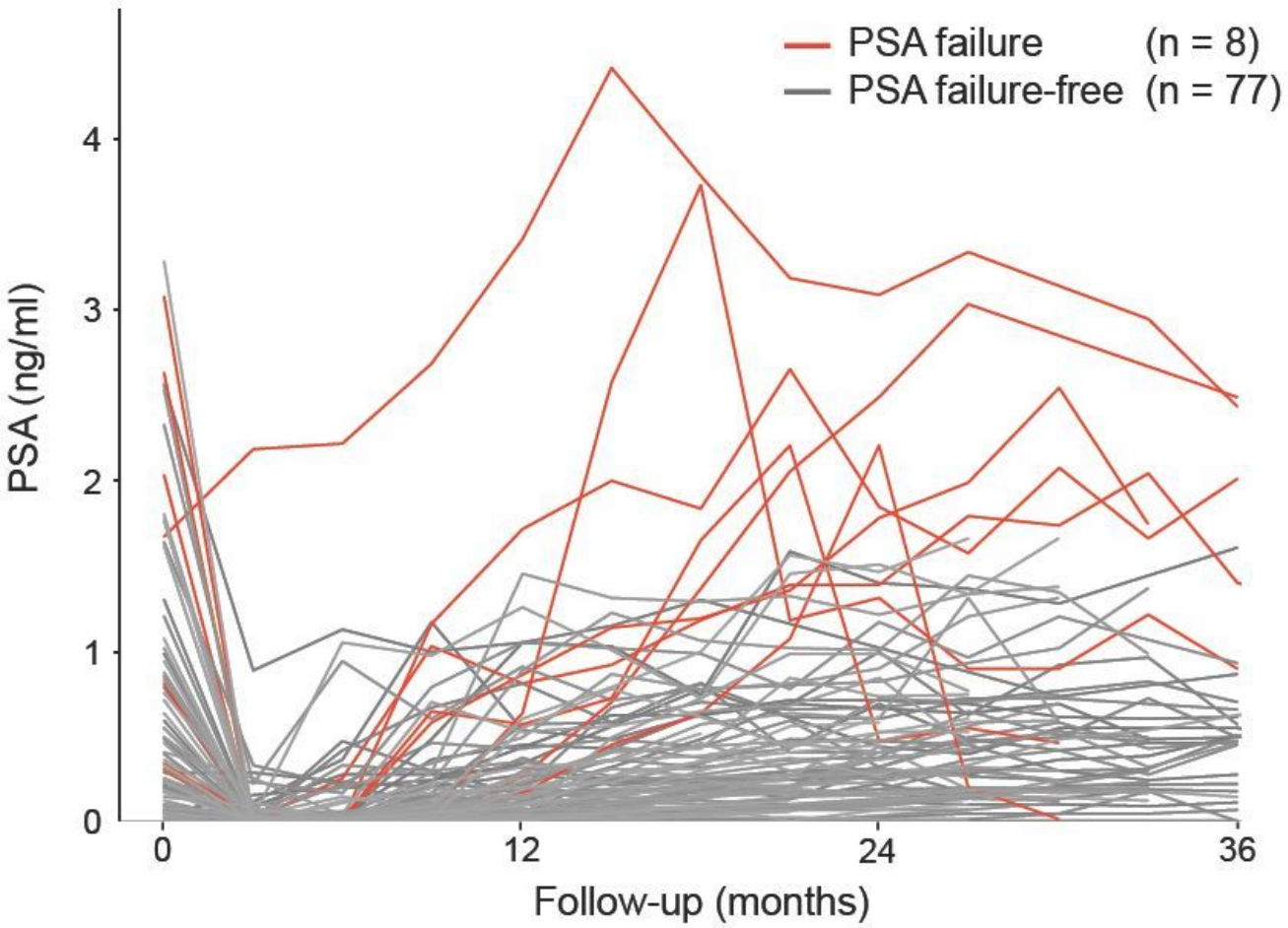

Figure 1

Prostate-specific antigen (PSA) dynamics after carbon ion radiotherapy (CIRT) for all patients. The PSA dynamics in patients with biochemical relapse is indicated by the red line. No clinical recurrence was observed

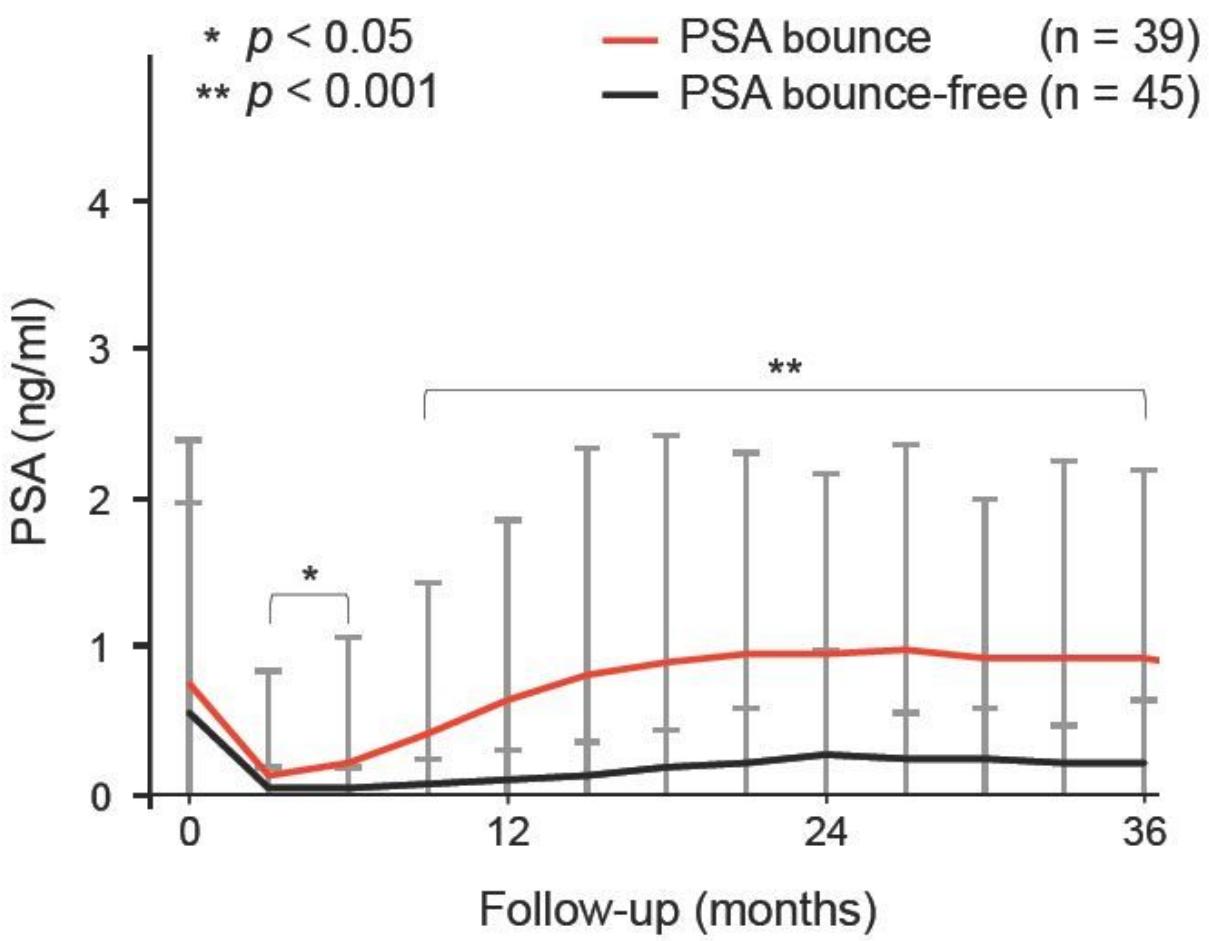

Figure 2

The average PSA dynamics in patients with or without PSA bounces

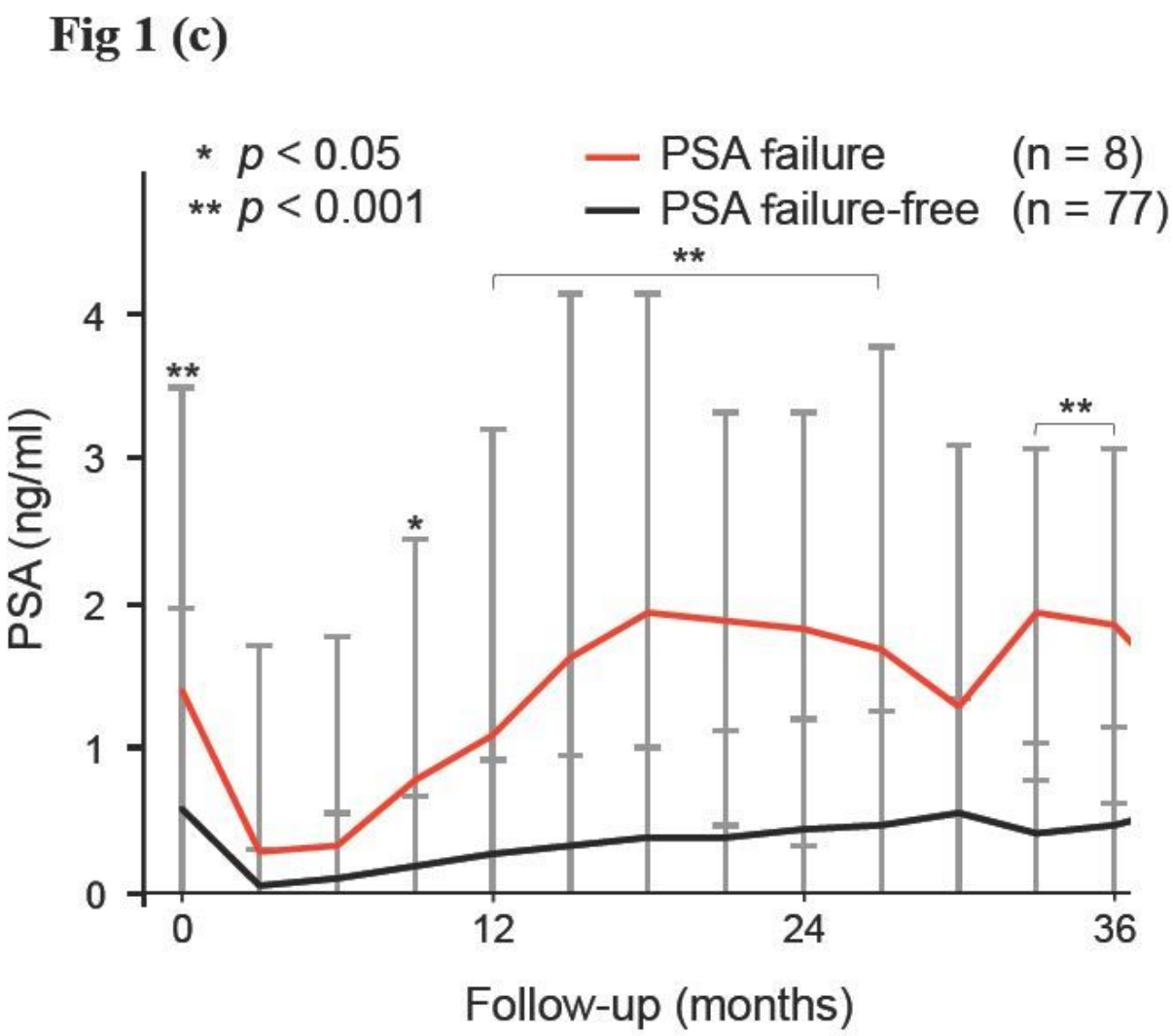

Figure 3

The average PSA dynamics in patients with or without PSA failure

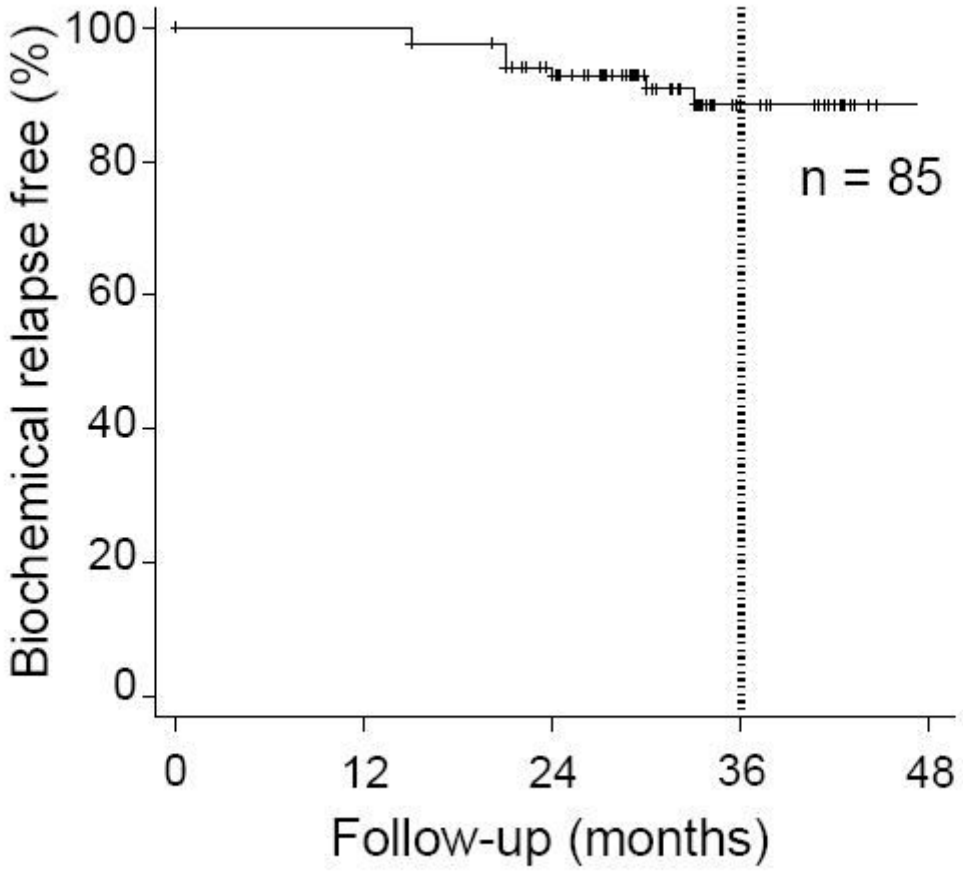

Figure 4

Prostate-specific antigen (PSA) failure-free rate. The 3-year PSA failure-free rate was 88.5%