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Review Article

Particle therapy for prostate cancer: The past, present and future

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Abbreviations & Acronyms
3DCRT = three-dimensional conformal radiotherapy
ADT = androgen deprivation therapy
bRFS = biochemical relapse-free survival
CIRT = carbon-ion radiotherapy
EPIC = Expanded Prostate Cancer Index Composite Instrument
FACT-P = Functional Assessment of Cancer Therapy for Prostate Cancer Patients
FFF = freedom from biochemical or clinical failure
GI = gastrointestinal
GU = genitourinary
GyE = gray equivalents
HRQOL = health-related quality of life
IMRT = intensity-modulated radiation therapy
JASTRO = Japanese Society for Radiation Oncology
PBT = proton beam therapy
PFS = progression-free survival
QOL = quality of life
RP = radical prostatectomy
RT = radiotherapy
SOBP = spread-out Bragg peaks
TOI = Trial Outcome Index
WPI = whole pelvis irradiation

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Abstract: Although prostate cancer control using radiotherapy is dose-dependent, dose–volume effects on late toxicities in organs at risk, such as the rectum and bladder, have been observed. Both protons and carbon ions offer advantageous physical properties for radiotherapy, and create favorable dose distributions using fewer portals compared with photon-based radiotherapy. Thus, particle beam therapy using protons and carbon ions theoretically seems suitable for dose escalation and reduced risk of toxicity. However, it is difficult to evaluate the superiority of particle beam radiotherapy over photon beam radiotherapy for prostate cancer, as no clinical trials have directly compared the outcomes between the two types of therapy due to the limited number of facilities using particle beam therapy. The Japanese Society for Radiation Oncology organized a joint effort among research groups to establish standardized treatment policies and indications for particle beam therapy according to disease, and multicenter prospective studies have been planned for several common cancers. Clinical trials of proton beam therapy for intermediate-risk prostate cancer and carbon-ion therapy for high-risk prostate cancer have already begun. As particle beam therapy for prostate cancer is covered by the Japanese national health insurance system as of April 2018, and the number of facilities practicing particle beam therapy has increased recently, the number of prostate cancer patients treated with particle beam therapy in Japan is expected to increase drastically. Here, we review the results from studies of particle beam therapy for prostate cancer and discuss future developments in this field.

Key words: biochemical relapse-free survival, carbon-ion radiotherapy, prostate cancer, proton beam therapy, toxicity.

Background of external beam RT for prostate cancer

Approximately 165 000 people develop prostate cancer per year in the USA, with 29 000 prostate cancer-related deaths per year.[1] In Japan, the annual number of newly diagnosed patients increases every year, and prostate cancer is currently the cause of death of >12 000 patients.[2] As recent advances in prostate cancer screening and treatment have led to an improvement in patient outcomes, the treatment goals have changed from merely tumor control to preservation of the daily activities and QOL of patients as important end-points in comparisons of the various treatment options. In particular, it is important that treatment is as minimally invasive as possible for elderly patients.

According to recent large-scale comparative studies evaluating several end-points, such as prostate cancer-specific mortality rate, disease progression, metastasis and all-cause mortality rate, external beam RT produces outcomes comparable with those of surgery; RT has thus been established as a curative treatment for prostate cancer.[3] Reports have shown that as the radiation dose used for prostate cancer is increased, a dose–response relationship is observed between the RT dose and tumor control.[4,5] Conversely, increasing the RT dose leads to concerns about adverse events in the rectum and bladder, and decreasing the RT dose and

volume in these organs decreases the incidence of adverse events, according to several studies that carried out dose–volume histogram analyses.[6–8] Thus, if the RT dose to the prostate can be increased without increasing the irradiated volume in the rectum and bladder, treatment outcomes will improve.

With X-ray-based RT regimens, a dose build-up effect occurs 1–2 cm from the body surface. After delivery of the peak dose, the deeper the rays penetrate into the body, the more gradual the decrease in the relative dose as the rays pass through the body. In contrast, charged particle beams differ from photon beams in that they create a better dose distribution in the target volume by specific beam modulations, such as a SOBP (Fig. 1).[9–11] Thus, the prescribed dose can be delivered to the lesion through a smaller number of beams with particle beam RT compared with photon beam RT, and consequently the irradiated volume and dose in the rectum and bladder in particle beam RT for prostate cancer can be decreased compared with photon beam RT, such as IMRT and volumetric-modulated arc therapy (Fig. 2).[12] One reason why particle beam RT is useful for treating prostate cancer is that dose escalation using modern techniques has improved tumor control rates, especially bRF or bRFS rates, in photon beam RT series, and charged particles might be even more useful for safely escalating the RT dose.[13–15]

In this article, we review the results of previous particle beam RT studies compared with photon beam RT, and introduce ongoing studies and future prospects to establish high-quality evidence for particle beam RT for prostate cancer.

Scientific statements

Concomitant photon and proton beam RT: 1990s to early 2000s

The treatment outcomes of four randomized comparative trials carried out in the 1990s (two photon beam RT studies and two studies on combination of PBT with photon beam RT) and a PBT study carried out at Loma Linda University are shown in Table 1.[6,16–19] At that time, the appropriate use of ADT combined with RT for prostate cancer was not yet established, and pelvic RT using photons was a standard treatment for latent lymph node involvement. PBT was therefore used as a RT boost to the prostate after pelvic RT. Shipley *et al.*[14] reported the results from the first randomized PBT study carried out at Massachusetts General Hospital Cancer Center. In their study, patients in the standard-dose group were treated with pelvic RT at 50.4 Gy/28 fr, followed by local photon beam RT at 16.8 Gy/8 fr (total dose 67.2 Gy/36 fr), and those in the high-dose group were treated with PBT at 25.2 GyE/12 fr together with pelvic RT (total dose 75.6 GyE/40 fr). Good local control was achieved in the high-dose PBT group, in which the 8-year local control rate was 73% compared with 59% in the standard-dose photon beam RT group.[14] Especially among the patients with poorly differentiated adenocarcinoma, the rate in the high-dose group was significantly better (84% *vs* 19%, $P = 0.0014$). Furthermore, grade 3 rectal bleeding was seen in just 2.9% of the patients in the high-dose group. In contrast, the Radiation Therapy Oncology Group carried out a randomized trial using photon beam RT (RTOG9413), designed as a 2×2 factorial study using ADT sequencing as one stratification factor and the radiation field as the other factor. In a secondary analysis, pelvic RT combined with neoadjuvant ADT was added for disease control of patients who had an estimated risk of lymph node involvement of >15%, according to the equation: percentages of positive lymph nodes = (2/3) PSA + [(GS − 6) × 10] or T2c–T4 diseases, and showed an improvement in PFS compared with prostate-only RT; however, despite using a 70.2 Gy dose (5.4 Gy lower than the aforementioned 75.6 Gy PBT dose), grade 3 GI toxicities were noted in 4.3% of patients[15] (Table 1).

The effect of a high-dose PBT boost after local photon beam RT on the outcomes of patients with stage T1–2 prostate cancer was evaluated in the PROG95-09 trial.[16] A PBT boost of either 19.8 GyE/11 fr (standard-dose group) or 28.8 GyE/16 fr (high-dose group) was delivered to the prostate at a total dose of 50.4 Gy/28 fr after conformal photon beam RT. After a median observation period of 8.9 years, the 10-year biochemical failure rates were 32.4% in the standard-dose group and 16.7% in the high-dose group ($P < 0.0001$), but grade 3 GI and GU events were only noted in 1% and 2% of patients in the high-dose group, respectively. At almost the same time, long-term results from a randomized dose-escalation trial of photon beam RT for prostate cancer carried out at the MD Anderson Cancer Center were reported.[6] In that study, the treatment outcomes of the standard-dose (70 Gy/35 fr) group and high-dose (78 Gy/39 fr) group were compared (Table 1). The 10-year recurrence-free rate was 50% in the standard-dose group versus 73% in the high-dose group, showing that the higher dose produced better results ($P = 0.004$). However, grade 3 GI and GU adverse events were observed in 7% and 5% of patients, respectively, in the high-dose group, indicating higher adverse event rates compared with those induced by the 79.2 GyE dose of the high-dose group in the ROG95-09 trial described above (Table 1).[6]

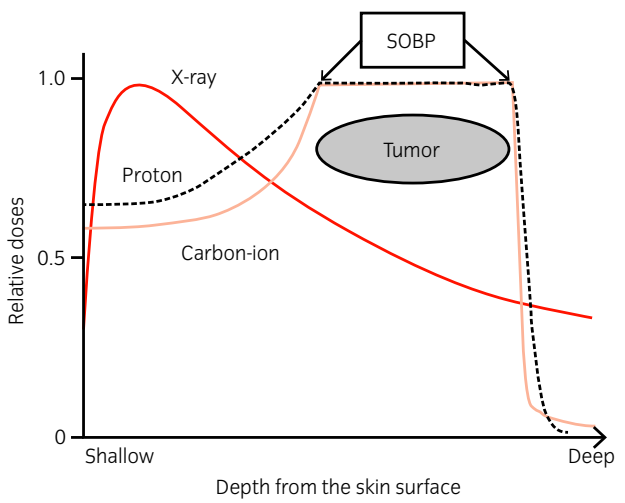


Fig. 1 A schema of relative doses from the skin surface of photon and particle beams. Dashed black and solid pink lines are the depth dose distributions of proton and carbon-ion beams, respectively. The SOBP are created by adding the contributions of some pristine Bragg peaks. A depth dose curve of a photon beam is provided for comparison.

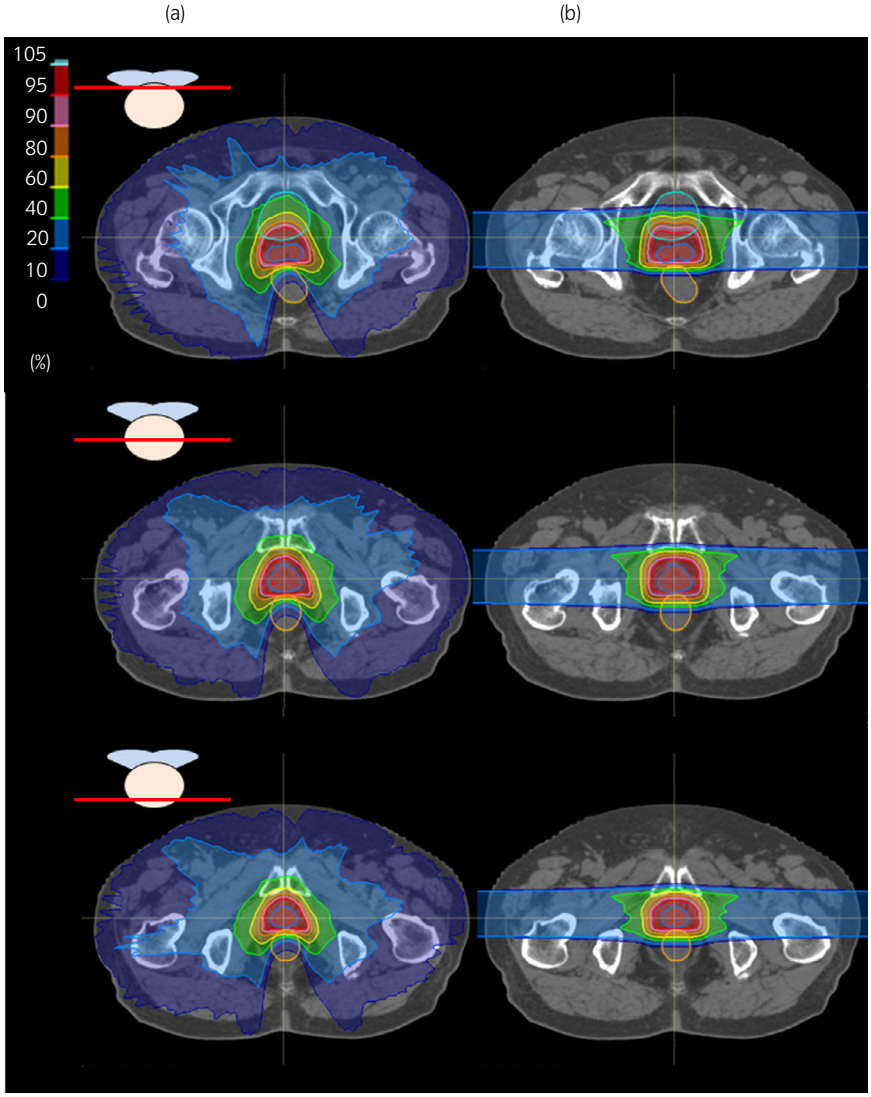


Fig. 2 Comparison of dose distribution between volumetric-modulated arc therapy and PBT. (a) In volumetric-modulated arc therapy using photons, a MLC aperture and dose rate can be simultaneously adjusted in the rotational beam of 360° to concentrate the radiation dose to the prostate. (b) However, PBT uses fewer beams to create a favorable dose distribution, thereby minimizing the irradiated volumes in the bladder and rectum at low-to-moderate doses.

In Japan, to confirm the safety of localized PBT, phase II clinical studies were carried out at the National Cancer Center Hospital East, in which 30 patients were registered over 2 years starting in 2001. Photon beam RT consisting of 50 Gy/25 fr was delivered to the prostate and bilateral seminal vesicles, followed by a PBT boost of 26 GyE/13 fr to the prostate alone. No grade 3 acute or late toxicities were observed, confirming the feasibility of high-dose RT with a PBT boost for prostate cancer.[18]

Local particle beam RT: Mainly in the 2000s

At Loma Linda University, high-dose PBT without photons was used to treat localized prostate cancer. Between 1991 and 1997, 911 cases were treated with localized PBT at a total dose of 74–75 Gy, and a 5-year bRFS of 82% was reported. No grade 3 adverse events were noted, and grade 2 toxicities included 3.5% GI and 5.4% GU events. Thus, the use of PBT alone seemed superior to photon beam RT alone or photon beam RT combined with PBT[17] (Table 1). In addition, the morbidity rates for prostate cancer have been evaluated based mainly on grade 2 GI and GU adverse events since then.

In Japan, three facilities – the National Cancer Center Hospital East, Shizuoka Cancer Center and Hyogo Ion Beam Medical Center – carried out a multicenter collaborative phase II clinical trial of local PBT, delivered at a total dose of 74 GyE/37 fr to 151 prostate cancer patients between March 2004 and March 2007. In that trial, no grade 3 adverse events occurred, and grade 2 late GI and GU toxicities were observed in 2.0% and 4.1% of patients, respectively.[19] Heavy ion RT using carbon ions for prostate cancer has been carried out at the National Institutes of Radiological Sciences in Japan since 1995; the optimal RT dose and technique were established through two phase I/II dose-escalation studies of hypofractionated CIRT carried out there.[20] In the phase II trial, which was carried out between April 2000 and October 2003, a 66 GyE/20 fr dose fractionation schedule was used based on recommendations from previous studies, which resulted in grade 2 GI and GU toxicities in 1.7% and 5.1% of patients, respectively.[21]

At the beginning of the 21st century, during which the above results were published, new radiation technologies,

Table 1 Clinical outcomes of photon and PBT trials carried out in the 1990s

Author	No. patients	Period	Total dose (Gy)	Photon (Gy)	Proton (GyE)	End-point		Late toxicity GI	Late toxicity GU
WPI and local RT									
Shipley[14]	202	1982–1992	75.6	50.4 (WPI)	25.2 (local)	Local control	73%	2.9% (G3)†	NA
			67.2	50.4 (WPI) + 16.8 (local)	–	(8 years)	59%	0% (G3)†	NA
Roach[15]	440	1995–1999	70.2	50.4 (WPI) + 19.8 (local)		PFS (7 years)	40%	4.3% (G3)	3.0% (G3)
			70.2	70.2 (local)			27%	0% (G3)	0% (G3)
Local RT									
Zietman[16]	393	1996–1999	79.2	50.4 (local)	28.8 (local)	bRF (10 years)	83%	24% (G2)	27% (G2)
								1% (G3)	2% (G3)
			70.2	50.4 (local)	19.8 (local)		67%	13% (G2)	22% (G2)
								0% (G3)	2% (G3)
Kuban[6]	301	1993–1998	78.0	78.0 (local)	–	FFF (10 years)	73%	26% (G2)	13% (G2)
								7% (G3)	5% (G3)
			70.0	70.0 (local)	–		50%	13% (G2)	8% (G2)
								1% (G3)	4% (G3)
Schulte[17]	911	1991–1996	74–75	–	74.0–75.0 (local)	bRF (5 years)	82%	3.5% (G2)	5.4% (G2)
								0% (G3)	0% (G3)

†As the details of three patients with grade ≥3 rectal bleeding are unknown, the percentages in the table are based on the assumption that all three received high-dose RT using protons.

such as IMRT and image-guided brachytherapy, became widely available as definitive RT modalities for prostate cancer. Furthermore, comparative studies and meta-analyses showed that ADT improved treatment outcomes, especially for intermediate- and high-risk prostate cancer, and the ideal duration and timing of concomitant ADT were determined.[22,23] The treatment outcomes of local high-dose RT combined with ADT were equal to or superior to those of local high-dose RT combined with pelvic or prostate RT, even for high-risk prostate cancer.[22–24] Consequently, local RT combined with effective application of ADT according to prostate cancer risk stratification has become the main treatment for prostate cancer without evidence of metastasis.

Table 2 summarizes the clinical outcomes after IMRT, PBT and CIRT, along with a comparison of the efficacies and safety parameters.[8,25–38] PBT and CIRT outcomes in Japanese patients were reported recently in a multicenter collaborative clinical study.[37,38] Iwata *et al*. reported long-term outcomes from a multi-institutional survey of PBT for prostate cancer carried out by the Japanese Radiation Oncology Study Group. In their study, 1291 patients at seven facilities received PBT between January 2008 and December 2011, mainly using the standard fractionation for RT at total doses ranging from 70 to 80 GyE. After a median follow-up period of 69 months (range 7–107 months), the 5-year bRFS rates of the low-, intermediate- and high-risk patients were 97.0%, 91.1% and 83.1%, respectively, and grade 2 GI and GU adverse events were observed in 4.1% and 4.0% of patients, respectively.[37] In another study, the treatment outcomes of 2157 patients who received CIRT at three facilities between 2003 and 2014 were analyzed.[38] Based on the results of clinical studies carried out at the National Institute of Radiological Sciences, dose fractionation schedules of CIRT have been changed from 20 sessions over 5 weeks to 12 sessions over 3 weeks step-by-step.[8,21,39] After a median observation period of 29 months, the 5-year bRFS rates of the low-, intermediate- and high-risk patients were 92%, 89% and 92%, respectively, and the rates of grade 2 GI and GU adverse events were 0.4% and 4.6%, respectively.[38] Furthermore, Okada *et al*.[39] showed no significant difference in the 5-year biochemically relapse-free rates between 16 and 20 sessions groups (88.5% and 90.2%, respectively), and the decrease in the number of CIRT fractions did not increase the incidences of the late adverse events (Table 3).[8,39,40] Thus, particle beam RT was shown to achieve well-balanced treatment outcomes in terms of both efficacy and safety.

Comparisons of RT methods in terms of HRQOL

Recent advances in RT technologies and techniques have improved the outcomes of prostate cancer. However, it is difficult to determine the optimal RT method simply by comparing bRFS and/or morbidity rates among individual treatments. Recently, HRQOL, which is measured using questionnaires, such as the FACT-P and EPIC, has become an increasingly important end-point in the evaluation of treatments for localized prostate cancer.[41,42]

Maruyama *et al*. reported long-term results of HRQOL assessments carried out at five time points (immediately before and immediately after the initiation of CIRT, and at 12, 36 and 60 months after completion of CIRT) using the FACT-P questionnaire.[43] In their study, the absolute change in the FACT-P score was minimal, and the transient decrease observed in the TOI score returned to baseline at 1 year after CIRT. Their results suggested that the changes in the HRQOL score observed after CIRT was minimal compared with the results from a previous report on photon beam RT

Table 2 Comparison of IMRT with particle beam therapy for treatment of prostate cancer

Author	Year	RT type	No. patients	Total dose (Gy/GyE)	Fractions	5-year bRF/bRFS (%)			Toxicity (grade 2)	
						Low-risk	Intermediate-risk	High-risk	GI (%)	GU (%)
IMRT										
Zelefsky[25]	2006	X-ray	561	81	45	89 (8 years)†	78 (8 years)†	67 (8 years)†	1.6	15
Kupelian[26]	2007	X-ray	770	70	28	94†	83†	72†	6	7
Vora[27]	2007	X-ray	145	70.2–77.4	39–43	88‡	73‡	60‡	24	29
Cahlon[28]	2008	X-ray	478	86.4	48	98†	85†	70†	4	16
Martin[29]	2009	X-ray	92	79.8	45	88‡	77‡	78‡	13.7	12.1
Spratt[30]	2013	X-ray	1002	86.4	48	98 (7 years)†	86 (7 years)†	68 (7 years)†	4.4	21.1
Guckenberger[31]	2014	X-ray	150	73.9–76.2	32–33	88‡	80‡	78‡	4.7	22.4
Lieng[32]	2017	X-ray	123	60–66	20–22	100‡	89‡	56‡	7.3	12.2
Takemoto[33]	2018	X-ray	348	72.8–79	33–39	93 (7 years)‡	93 (7 years)‡	80 (7 years)‡	10.1	6.0
Particle beam therapy										
Mendenhall[34]	2014	Proton	211	78–82	34–41	99‡	99‡	76‡	1.0§	0.9§
Bryant[35]	2016	Proton	1327	72–82	36–41	99†	94†	74†	0.6§	2.9§
Takagi[36]	2017	Proton	1375	74	37	99†	91†	86†	3.9	2.0
Iwata[37]	2018	Proton	1291	70–80/63–66	35–40/21–22	97‡	91‡	83‡	4.1	4.0
Ishikawa[8]	2012	Carbon	927	63–66/57.6	20/16	90†	97†	88†	1.9	6.3
Nomiya[38]	2016	Carbon	2157	63–66/57.6/51.6	20/16/12	92‡	89‡	92‡	0.4	4.6

†bRF rate. ‡bRFS rate. §Grade 3.

Table 3 Late toxicity according to dose fractionation schedule after carbon-ion therapy

Author	Dose fractionation (GyE/fr/weeks)	No. patients	Median follow-up time (months)	Rectal toxicity (%)				GU toxicity (%)			
				G0	G1	G2	G3	G0	G1	G2	G3
Ishikawa[8]	66.0/20/5	250	43.0	78.0	18.8	3.2	0	40.4	46.0	13.6	0
Ishikawa[8]	63.0/20/5	216	43.0	85.2	12.5	2.3	0	50.0	43.1	6.5	0.5
Okada[39]	57.6/16/4	198	59.3	88.9	9.6	1.5	0	58.6	39.4	2.0	0
Nomiya[40]	51.2/12/3	46	32.3	91.3	8.7	0	0	50.0	50.0	0	0

Table 4 TOI scores after different treatments for prostate cancer

	Treatment	No. patients	Median age (years)	Time after treatment			
				Baseline	1 month	12 months	36 months
Mean TOI score[43,44] (change from baseline)	RP	23	61	88.3 ± 12.3	66.2 ± 10.3 (−22.1)	88.2 ± 3.7 (−0.1)	NA
	Brachytherapy	44	67	86.9 ± 6.0	68.6 ± 7.7 (−18.3)	85.8 ± 7.3 (−1.1)	NA
	3DCRT	23	69	85.3 ± 9.1	77.6 ± 18.1 (−7.7)	84.1 ± 13.7 (−1.2)	NA
	CIRT	417	69	81.8 ± 12.0	77.8 ± 12.1 (−4.0)	80.3 ± 13.0 (−1.5)	81.6 ± 13.7 (−0.2)

and brachytherapy (Table 4).[43,44] Furthermore, a decrease in the TOI score was related to use of adjuvant ADT, onset of adverse events and biochemical recurrence.[43] One likely reason why there was little effect on the HRQOL score might be the lower rates of adverse events and biochemical recurrence after CIRT.

Gray *et al*. compared the bowel/rectal and urinary QOL after 3DCRT (n = 123), IMRT (n = 153) and PBT (n = 95).[45] During the immediate post-treatment period (2 months from the start of treatment for the IMRT cohort, and 3 months from the start of treatment for the 3DCRT and PBT cohorts), patients in the IMRT, but not the PBT, cohort reported a clinically meaningful decrease in both bowel/rectal and urinary (irritation/obstruction and incontinence) QOL. In contrast, at 12 months, patients who received PBT, but not those who received IMRT or 3DCRT, reported a clinically meaningful decrease in urinary irritation/obstruction QOL.[45] At the University of Florida (USA), 1243 patients treated with 76–78 Gy PBT were compared with 204 patients treated with nearly the same dose of IMRT (75.6–79.4 Gy) in terms of HRQOL based on the EPIC score. Urinary and sexual function did not differ during the treatment course when the

comparisons between cohorts were controlled for age, prostate size, ADT use and baseline QOL, but the frequencies of "moderate/big problems" with rectal urgency ($P = 0.02$) and bowel frequency ($P = 0.05$) were greater in the IMRT cohort.[46] In fact, Fang *et al.* assessed the associations between toxicity and PBT compared with IMRT in prostate cancer patients using a case-matched analysis; the risks of late GI and GU toxicities were not different between the two groups. However, grade ≥2 acute GI toxicities were recorded in 13 (13.8%) patients treated with IMRT and four (4.3%) patients treated with PBT, and PBT was significantly associated with a reduced risk of acute GI toxicities in univariate analysis ($P = 0.03$).[47] Based on these results, the HRQOL indicators in low- and intermediate-risk patients receiving PBT or IMRT are currently being compared (PARTIQoL trial: NCT01617161). That trial is the first to compare IMRT with PBT directly, and evaluation of the primary end-point, the EPIC mean bowel score at 24 months post-treatment, is scheduled for completion in December 2019.

To summarize these results, although no comparative study results are available at the present time, the current National Comprehensive Cancer Network guidelines on PBT state that, based on the results of many clinical studies, there is no clinical evidence supporting a benefit or disadvantage of PBT over IMRT in terms of treatment efficacy or long-term toxicities. The usefulness of PBT has been confirmed, and conventionally fractionated prostate PBT can be considered a reasonable alternative to X-ray-based regimens at clinics with the appropriate technology, physics and clinical expertise.

Future prospects

Particle beam RT for prostate cancer in Japan has changed considerably, and as of April 2018, it is eligible for insurance coverage. Of note, patients can receive particle beam RT without paying expensive fees, and the cost of this advanced medical treatment is similar to those of other RTs, such as IMRT and brachytherapy. The cost–benefit of particle beam RT was previously considered inferior to that of photon beam RT, but with development of this treatment modality, particle beam RT might now provide a potential cost-effective treatment in Japan.[48,49] However, to establish the routine use of particle beam RT worldwide, it is still necessary to further reduce the size and cost of the device for particle beam RT.

Furthermore, recent technological advances have led to changes in the beam delivery, position verification and radiation techniques of particle beam RT, which will not only improve treatment outcomes, but also reduce the cost and treatment time.[50–53] In particular, image-guided intensity-modulated particle beam RT using a new beam delivering method, known as pencil beam scanning, provides more highly conformal and precise treatments beyond what were available previously (Fig. 3).[50,51] By further decreasing the irradiated volumes and doses in the rectum and bladder, the incidence of GI and GU toxicities is expected to decrease.

With an increase in the number of patients treated with particle beam RT (Fig. 4), creating a system that allows treatment of more patients while maintaining treatment quality is critical. To overcome this issue for the future, hypofractionation is a promising strategy, especially for prostate cancer treatment, based on radiobiological models.[13] In fact, several studies of hypofractionated particle beam RT for prostate cancer have been carried out, and reported the same or lower incidences of adverse events as those seen with conventional photon beam RT using standard fractionation.[8,21,38–40,54] Further confirmation of the feasibility and efficacy of hypofractionated particle beam RT will enable an increase in patient volume and reduction in the cost per patient. Currently, the JASTRO is carrying out a multi-institutional prospective study of hypofractionated particle beam RT, using PBT for intermediate-risk and CIRT for high-risk prostate cancer. Furthermore, another multi-institutional study of IMRT for all prostate cancer risk groups is currently being carried out. Although the outcomes obtained from these prospective studies cannot be compared directly, JASTRO intends to evaluate the efficacies of the various RT modalities for prostate cancer.

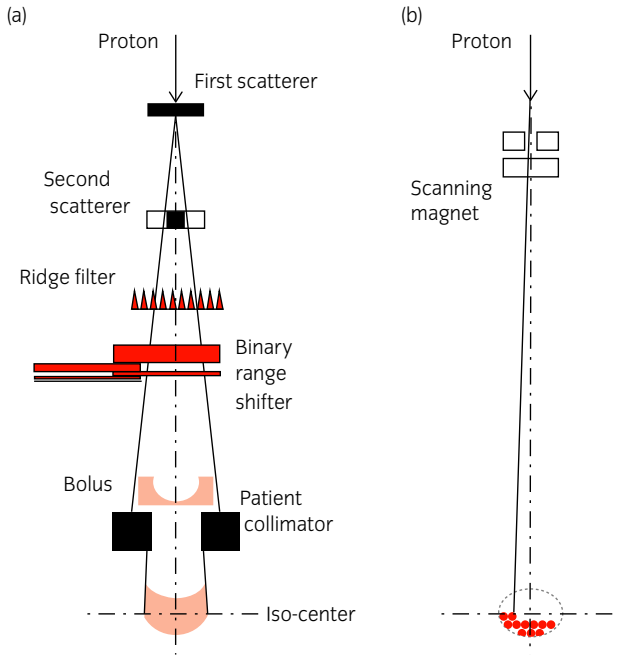
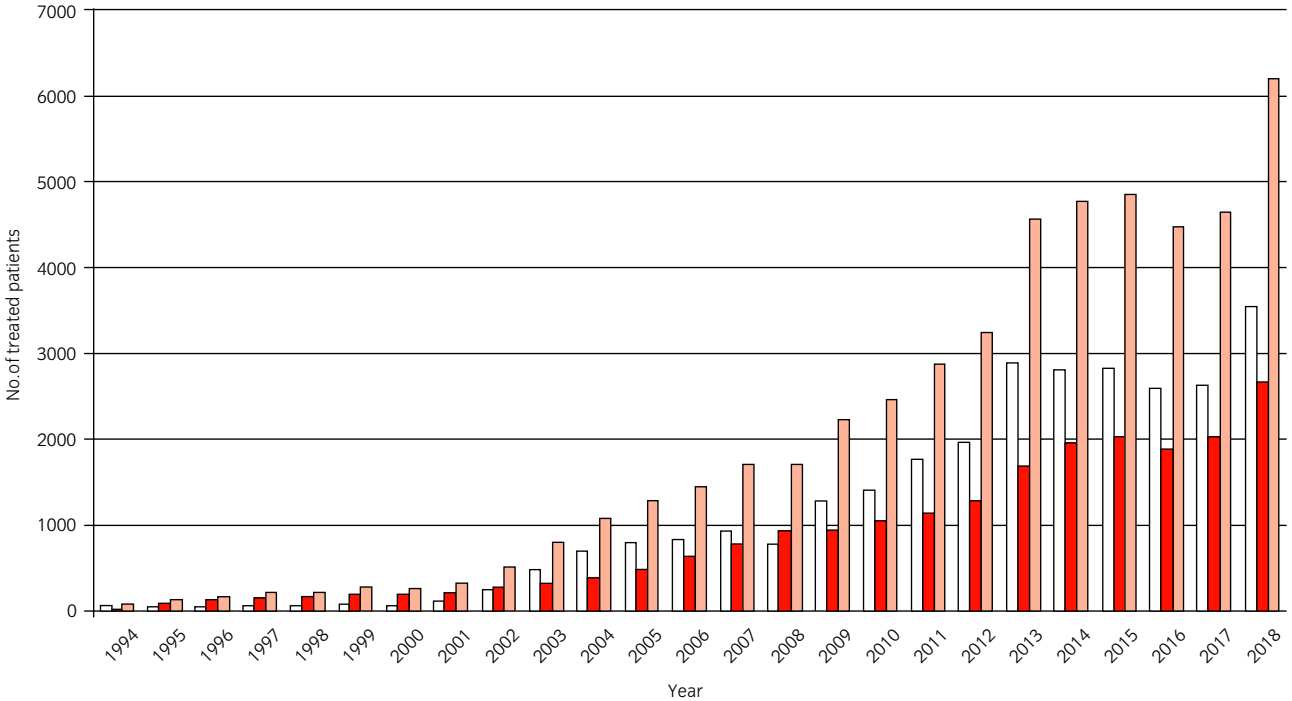


Fig. 3 Different beam delivering methods for particle beam therapy. (a) The passive scattering method for particle beam preparation: after making a broad beam of charged particles by scatterers, the SOBP is made though the ridge filter. A binary range shifter changes the beam energy, and the compensation bolus is fabricated for each patient to make the distal configuration of the SOBP similar to the target. (b) The collimator defines the irradiation field. Pencil beam scanning method. Scanning magnets are used to three-dimensionally scan narrow beams through the target. The technique enables intensity-modulated particle therapy to reduce unnecessary doses to normal tissues compared with the passive scattering method.

Conclusions

Due to a lack of direct evidence, the superiority of particle beam RT over photon beam RT for prostate cancer has not been confirmed in terms of the rates of overall survival or bRFS as end-points. However, charged particles, such as



No.of institutes																									
	2	2	2	2	2	3	3	4	4	5	5	5	5	5	6	6	7	9	9	11	13	14	15	18	23
No.of patients																									
Proton	61	47	42	58	47	83	73	115	244	474	699	803	827	923	781	1278	1421	1757	1961	2895	2813	2831	2598	2624	3547
Carbon	15	82	126	153	167	194	193	222	276	320	383	473	626	789	981	955	1048	1127	1276	1672	1964	2032	1875	2027	2656
Total	76	129	168	211	214	277	266	337	520	794	1082	1276	1453	1712	1712	2233	2469	2884	3237	4567	4777	4863	4473	4651	6203

Fig. 4 Trend of numbers of particle therapy institutes and treated patients in Japan.

protons and carbon ions, reduce the irradiated volumes and doses in the organs at risk surrounding the prostate, and previous studies have shown very low incidences of GI and GU toxicities after particle beam RT. Here, we reviewed treatment outcomes during different eras of particle beam RT, and the adverse events induced by particle beam RT have consistently been acceptable. Long-term observation in a large-scale randomized study is necessary for the most accurate evaluation of the efficacy of particle beam RT for prostate cancer, but particle beam RT seems a reasonable RT method delivering a high RT dose safely. During 2015–2017, the JASTRO committee for particle beam RT discussed this matter. At that time, particle beam RT was still considered an advanced medical treatment, and it was expected that patients would not refuse randomization in clinical trials. Therefore, we are carrying out a multi-institutional prospective study of IMRT, PBT and CIRT, and registration of all studies will be completed by April 2020. Together with the recent increase in the number of facilities offering particle beam RT in Japan (Table 5), data on treatment outcomes for various diseases including prostate cancer have accumulated, and are stored in a nationwide database. In addition, it is possible that the treatment devices will become smaller in size and less expensive in the near future. We are facing an important point at which particle beam RT can be compared directly with not only IMRT, but also other alternative treatments, such as surgery or brachytherapy, from several points of view, such as recurrence, adverse events, QOL and cost.

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Conflict of interest

Mikio Sugimoto receives lecture fees from Janssen, Takeda and AstraZeneca. Nobuo Shinohara received research grants from Astellas and Ono, and honoraria from GlaxoSmithKline, Novartis, Pfizer, Ono, Takeda, Chugai and Bayer. Hiroki Shirato receives grants from Hitachi and Shimadzu Corporation, and has a licensed patent titled “Moving body pursuit irradiating device and positioning method using this device” and a licensed patent titled “Charged particle beam system” (US 14/524 495). Hitoshi Ishikawa, Hiroshi Tsuji, Shigeyuki

Table 5 Particle beam RT facilities in Japan

Prefecture	City	Institute	Particle	Start of treatment (year)
In operation				
Ibaraki	Tsukuba	University of Tsukuba	Proton	1983
Chiba	Kashiwa	National Cancer Center Hospital East	Proton	1998
Hyogo	Tatsuno	Hyogo Ion Beam Medical Center	Proton/carbon	2001
Shizuoka	Nagaizumi	Shizuoka Cancer Center	Proton	2003
Fukushima	Koriyama	Southern Tohoku Proton Therapy Center	Proton	2008
Fukui	Fukui	Fukui Prefectural Hospital	Proton	2011
Kagoshima	Ibusuki	Medipolis Proton Therapy and Research Center	Proton	2011
Aichi	Nagoya	Nagoya City West Medical Center	Proton	2013
Nagano	Matsumoto	Aizawa Hospital	Proton	2014
Hokkaido	Sapporo	Hokkaido University	Proton	2014
Okayama	Tsuyama	Tsuyama Chuo Hospital/ Okayama University	Proton	2016
Hokkaido	Sapporo	Sapporo Teishinkai Hospital	Proton	2017
Hyogo	Kobe	Kobe Proton Center	Proton	2017
Osaka	Osaka	Hakuhokai Osaka Proton Therapy Clinic	Proton	2017
Aichi	Toyohashi	Narita Memorial Proton Center	Proton	2018
Hokkaido	Sapporo	Hokkaido Ohno Memorial Hospital	Proton	2018
Nara	Tenri	Kouseikai Takai Hospital	Proton	2018
Kyoto	Kyoto	Kyoto Prefectural University of Medicine	Proton	2018
Chiba	Chiba	National Institutes for Quantum and Radiological Science and Technology	Carbon	1994
Gunma	Maebashi	Gunma University	Carbon	2010
Saga	Tosu	SAGA Heavy ion medical accelerator in Tosu	Carbon	2013
Kanagawa	Yokohama	Kanagawa Cancer Center	Carbon	2015
Osaka	Osaka	Osaka Heavy Ion Therapy Center	Carbon	2018
Under construction				
Kanagawa	Kamakura	Shonan Kamakura General Hospital	Proton	2020
Yamagata	Yamagata	Yamagata University	Carbon	2020

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