Original paper

Plan reproducibility of intraoperatively custom-built linked seeds compared to loose seeds for prostate brachytherapy

Tomoya Kaneda, MD[1,2], Toshio Ohashi, MD, PhD[1,2], Masanori Sakayori, MD, PhD[1,2], Shinya Sutani, MD, PhD[1], Shoji Yamashita, MD, PhD[2], Tetsuo Momma, MD, PhD[3], Shinichi Takahashi, RT[2], Takashi Hanada, PhD[1], Naoyuki Shigematsu, MD, PhD[1]

[1]Department of Radiology, Keio University School of Medicine, Tokyo, [2]Department of Radiology, National Hospital Organization Saitama Hospital, Saitama, [3]Department of Urology, National Hospital Organization Saitama Hospital, Saitama, Japan

Abstract

Purpose: Few studies have compared the implant quality of linked and loose seeds for prostate brachytherapy. This study aimed to evaluate and compare plan reproducibility of intraoperatively built custom linked seeds and loose seeds for prostate brachytherapy.

Material and methods: Between December 2010 and March 2014, 76 localized prostate cancer patients received Iodine-125 brachytherapy with external beam radiotherapy. Linked and loose seeds were implanted in 39 and 37 patients, respectively. The primary endpoint was the mean (± standard deviation) of the absolute change in the minimum dose received by 90% of the prostate volume between intraoperative and post-operative planning (ΔD_{90}) to confirm plan reproducibility. Comparisons between the groups were evaluated using 2-sample *t* tests.

Results: The ΔD_{90} values were 6.95 ± 11.6% and –0.41 ± 8.5% for the loose and linked seed groups, respectively ($p < 0.01$). The linked seed group showed decreased post-operative D_{90} (118.8% vs. 127.2%), V_{150} (51.7% vs. 66.7%), and RV_{100} (0.44 ml vs. 0.61 ml) compared to the loose seed group ($p < 0.01$), whereas lung migration tended to be reduced (0% vs. 8%).

Conclusions: The plan reproducibility of the linked seed group was better than that of the loose seed group. Moreover, the linked seed group showed less migration and lower rectal dose.

J Contemp Brachytherapy 2018; 10, 4: 291–296
DOI: https://doi.org/10.5114/jcb.2018.77948

Key words: brachytherapy, dosimetry, linked seed, migration, prostate cancer.

Purpose

Permanent prostate brachytherapy is a standard treatment option for localized prostate cancer. In Japan, this treatment has been performed since 2003 and has recently gained popularity. Recent evidence has demonstrated an excellent biochemical control rate for patients treated with brachytherapy alone or in combination with external radiation [1,2,3,4,5,6]. Low-dose-rate prostate brachytherapy techniques have several variations, including loose vs. stranded seeds and preplan vs. intraoperative techniques. Until 2012, when stranded or linked seeds were first introduced, the most popular approach in Japan was the intraoperative technique using loose seeds [7,8]. However, problems with loose seeds include migration to distant sites (e.g., the lungs) [9,10,11,12] and possible deterioration of dosimetry due to this migration [10,11,13,14,15,16]. Zauls *et al*. [17] first reported the outline for the technique of linked seeds. With this approach, the user can create intraoperatively built custom linked seeds, using a combination of seeds, connectors, and spacers. The advantages of linked seeds include intraoperative customization, less migration, and increased stabilization due to linking, indicating the benefits of loose plus stranded seeds [18].

To date, many studies compared stranded seeds to loose seeds [9,13,14,19,20,21], but few studies have compared the implant quality of linked seeds with that of loose seeds for prostate brachytherapy [17,22,23,24,25]; however, until now, there have been no reports about the plan reproducibility of linked seeds. Generally, intraoperative dosimetry based on ultrasound would not predict biochemical outcome [26]. Post-operative D_{90} is an important dosimetric parameter for biochemical freedom from failure [27]. A recent report revealed that intraoperative magnetic resonance imaging/ultrasound fusion

Address for correspondence: Toshio Ohashi, MD, PhD, Department of Radiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan, phone: +81-3-3353-1211, fax: +81-3-3359-7425, ✉ e-mail: ohashi@rad.med.keio.ac.jp

Received: 24.12.2017
Accepted: 22.08.2018
Published: 31.08.2018

may improve prostate dosimetry [28] but post-operative computed tomography (CT)-based dosimetry remains the gold standard for the evaluation of implant quality. Therefore, the reproducibility of both intraoperative and post-operative planning is important for implant evaluation. We hypothesized that the plan reproducibility of linked seeds between intraoperative planning and post-operative planning would be good, on the assumption that linked seeds are connected to each other and do not move easily after seed placement. In the present study, to address this hypothesis, we focused on the post-operative minimum dose received by 90% of the prostate volume (D_{90}). If the absolute change in prostate D_{90} (ΔD_{90} = post-operative D_{90} – intraoperative D_{90}) is low, the plan reproducibility is considered to be high. To date, no studies on dosimetric reproducibility of linked seeds have been reported. Therefore, our study, which further investigated the usefulness of linked seeds, provides novel information on this issue.

The primary endpoint of our analysis was the mean (± standard deviation) of the ΔD_{90} as a means to confirm plan reproducibility. The secondary endpoints were the comparisons of other dosimetric parameters as well as seed migration between linked and loose seeds for prostate brachytherapy.

Material and methods

Between December 2010 and March 2014, 76 patients with localized prostate cancer receiving Iodine-125 brachytherapy combined with external beam radiation therapy (EBRT) at the National Hospital Organization Saitama Hospital were analyzed. The following risk factors related to prostate cancer were assessed: serum levels of prostate specific antigen (PSA), Gleason score, and TNM stage. The subjects were divided into low-risk (T1-2a: PSA < 10 ng/ml and Gleason score ≤ 6), intermediate-risk (T2b: PSA 10-20 ng/ml, or Gleason score = 7), and high-risk (T2c-3: PSA > 20 ng/ml, or Gleason score ≥ 8) groups. The intermediate to high-risk group patients, and the low-risk group patients with positive core needle biopsy rates > 33% received combined therapy. This retrospective study was approved by the institutional review board.

All patients underwent an ultrasonography volume study one month before implantation to determine the number of seeds needed. Loose seeds (Brachysource; CR Bard, Covington, GA, USA) were implanted in 37 patients using a Mick applicator (Mick Radio-Nuclear Instruments, Inc., Bronx, NY, USA). The mean activity per seed was 0.35 U (range, 0.29-0.46 U), and total seed activity was 19.2 U (range, 11.2-27.1 U). Linked seeds (Brachysource; CR Bard, Covington, GA, USA) were implanted in 39 patients using a Quicklink device (CR Bard, Covington, GA, USA). The mean activity per seed was 0.32 U (range, 0.27-0.38 U), and total seed activity was 18.8 U (range, 13.3-27.5 U). A medical physicist checked the intensity of Iodine-125 seed sources. Implantation was carried out using an interactive transrectal ultrasound (SSD-3500 SV; Hitachi Aloka Medical Co., Ltd.)-guided technique with a modified peripheral loading pattern by using the VariSeed 8.0 planning system (Varian Medical Systems, Inc., Palo Alto, CA, USA) [29].

The prostate, urethra, and rectal wall were contoured by a radiation oncologist. The planned target volume was defined as the entire prostate. Urethra was visualized on ultrasound images using a catheter. The width of the urethral catheter was 18 F in diameter. The prescribed dose to the planned target volume was 110 Gy for intraoperative planning. Supplemental EBRT was started one month after implantation. All patients received a median dose of 45 Gy (range, 30.6-50.4 Gy) at 1.8 Gy per fraction, using 10-MV photons delivered by a three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) with a linear accelerator (ONCOR Impression Plus; Siemens Medical Solutions, Erlangen, Germany). The prescribed EBRT dose varied according to the dosimetric findings at the time of the post-implant dosimetry.

Computed tomography of the prostate was obtained one month post-operatively in the supine position, with 20 slice detector arrays (SOMATOM Sensation Open; Siemens Medical Solutions, Erlangen, Germany). Axial computed tomography images of the pelvic area were taken at a 3-mm thickness and 3-mm intervals. The post-implant planning for dosimetric assumption in clinical dosimetry was done using the VariSeed 8.0 planning system (Varian Medical Systems, Inc., Palo Alto, CA, USA). The entire prostate, excluding the seminal vesicles, was contoured from the base to the apex. As urinary catheters were not used for the post-implant dosimetry, it was not possible to identify the urethral position. We modified the post-implant urethral position with the help of their intraoperative ultrasound findings. The rectum was contoured as a solid structure defined by the outer wall on all slices showing seeds, without attempting to differentiate the inner wall or the contents. A frontal chest plain radiograph was obtained two weeks post-operatively to check for seed migration to the lungs. The calculated dosimetric parameters included the percent volume of the post-implant prostate receiving 100% and 150% of the prescribed dose (V_{100} and V_{150}, respectively), and the D_{90}. The ΔD_{90} was also evaluated. To analyze the entire cohort (n = 76), the delivered doses were converted to percentages of the prescribed dose. In addition, the rectal dose was expressed as the rectal volume receiving > 100% of the prescribed dose (RV_{100}), and as the minimum dose received by the hottest 2 cc of the rectum, as recommended by the AAPM Task Group 137 [30].

The quantitative variables are described as arithmetic means and standard deviations. The normality of the sample has been confirmed statistically. The 2-sample t test was used for comparing the two groups. All tests and confidence intervals were two-sided, and a value of $p \leq 0.05$ was considered to indicate statistical significance. Analyses were carried out using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

The clinical characteristics of the 76 patients are shown in Table 1. Table 2 shows the dosimetric results of the intraoperative plan. The same predetermined do-

Table 1. Clinical characteristics

Factor	Loose seed group	Linked seed group	*p*
n	37	39	
Age (years)			
Median (range)	73 (62-79)	71 (52-79)	0.090
Risk category			0.27
Low	6 (16%)	3 (8%)	
Intermediate	26 (70%)	26 (67%)	
High	5 (14%)	10 (26%)	
Hormonal therapy	11 (30%)	19 (49%)	0.090

Unless otherwise specified, the values are given as numbers

Table 2. Intraoperative parameters

Factor	Loose seed group	Linked seed group	*p*
Prostate volume (ml)	21.2 (5.8)	21.2 (7.3)	0.95
Implanted seed number	55.3 (8.6)	59.3 (9.4)	0.060
Seed activity (U)	0.35 (0.032)	0.32 (0.026)	< 0.001
Total seed activity (U)	19.2 (3.7)	18.8 (4.0)	0.67
D_{90} (%)	120.3 (5.1)	119.2 (5.5)	0.40
V_{100} (%)	98.4 (1.4)	98.8 (1.1)	0.14
V_{150} (%)	47.7 (6.4)	43.0 (7.5)	< 0.01

Values are given as the mean (± standard deviation).
D_{90} – the minimum dose received by 90% of the prostate volume; V_{100} – the percent volume of the prostate receiving 100% of the prescribed dose; V_{150} – the percent volume of the prostate receiving 150% of the prescribed dose

Table 3. Post-operative parameters

Factor	Loose seed group	Linked seed group	*p*
Prostate volume (ml)	22.1 (5.9)	23.5 (7.4)	0.37
D_{90} (%)	127.2 (11.4)	118.8 (9.2)	< 0.01
V_{100} (%)	98.7 (1.4)	98.0 (1.9)	0.06
V_{150} (%)	66.7 (13.2)	51.7 (11.4)	< 0.001
ΔD_{90} (%)	6.95 (11.6)	–0.41 (8.5)	< 0.01
RV_{100} (ml)	0.61 (0.35)	0.44 (0.27)	0.03
RD_{2cc} (%)	68.1 (12.3)	64.6 (10.4)	0.18

Values are given as the mean (± standard deviation).
D_{90} – the minimum dose received by 90% of the prostate volume; V_{100} – the percent volume of the prostate receiving 100% of the prescribed dose; V_{150} – the percent volume of the prostate receiving 150% of the prescribed dose; ΔD_{90} – the postoperative D_{90} minus intraoperative D_{90}; RV_{100} – the rectal volume receiving > 100% of the prescribed dose; RD_{2cc} – the minimum dose received by 2 cc of the rectum

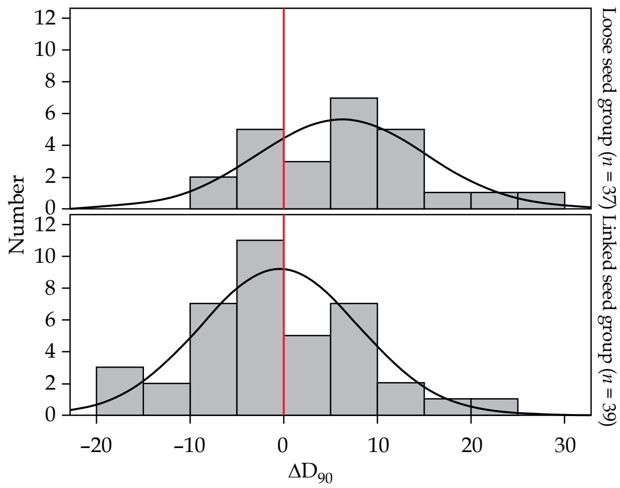

Fig. 1. Histogram of the difference in the minimum dose received by 90% of the prostate volume (ΔD_{90}) in the loose and linked seed groups

simetric parameters for prostate (110 Gy) were used in both groups, and no dose escalation for the prostate was intended for the linked seed group. Significant differences in the V_{150} and seed activity were seen between the groups. Table 3 shows the dosimetric results of the computed tomography analysis from one month post-operatively. The D_{90}, V_{150}, RV_{100}, and ΔD_{90} in the linked seed group were significantly lower compared with those in the loose seed group. Figure 1 presents a histogram of the ΔD_{90} values in the loose and linked seed groups. The ΔD_{90} in the linked seed group showed a lower mean value and narrower distribution (–0.41 ± 8.5%) than the loose seed group (6.95 ± 11.6%) ($p < 0.01$). Migration to the lungs was not seen in any patients in the linked seed group (0%), as compared to 3 patients (1-4 seeds per patient) in the loose seed group (8%; $p = 0.070$).

Discussion

Our study revealed the dosimetric advantages, including less seed migration, of linked seeds compared to loose seeds. The mean of the ΔD_{90} significantly decreased towards zero and the standard deviation of the ΔD_{90} was narrow in the linked seed group (–0.41 ± 8.5%) compared with that in the loose seed group (6.95 ± 11.6%), which showed almost identical intraoperative and post-operative D_{90} values. Since linked seeds are connected to each other, the seeds do not move easily in the prostate after implantation. Therefore, the dose distribution of the intraoperative D_{90} is stable up to post-operative planning. That is, intraoperative planning can be reproduced in the post-operative planning. In previous reports [17,24], the ΔD_{90} showed no statistically significant difference between linked and loose seeds, unlike in our study. In our study, the prostate D_{90} of the intraoperative plan was almost the same as that of the post-operative plan in the linked seed group. Hence, we can achieve a reliable plan in the intraoperative phase. Our study is distinct from previous studies because we focus on dosimetric reproducibility of linked seeds using ΔD_{90} as an indicator. Therefore, it newly shows that intraoperative custom-built linked seeds are valuable in prostate brachytherapy.

In the present study, the post-operative prostate D_{90}, V_{150}, and RV_{100} decreased in the linked seed group compared with that in the loose seed group. However, although the post-operative D_{90} decreased in the linked seed group compared to the loose seed group, the prescription dose was maintained (D_{90} > 100%). Thus, as the irradiation dose of the prostate is maintained, this difference may have little clinical impact. Further, reduction of the post-operative V_{150} leads to a reduction over the high-dose region of the prostate. As the rectal dose also shows downward trends, a reduction of adverse events can be expected as a result. Placing linked seeds on or adjacent to the prostate capsule can cover a dose from the extracapsular area. Since linked seeds are more spaced apart, the seed-to-seed distance is greater in the prostate compared with loose seeds; therefore, the high-dose region (V_{150}) in the prostate may be reduced. Additionally, as linked seeds can be customized intraoperatively compared with suture-embedded seeds, the high-dose regions of the rectum may also be reduced.

Table 4 shows the previous studies comparing the dose parameters between linked and loose seeds. Regarding the D_{90} and the rectal dose for the linked seed group, five previous reports showed no significant differences,

Table 4. Literature survey of dosimetric comparisons between linked and loose seeds

Study [ref]	*n* (linked/loose)*	Parameter	Linked seeds	Loose seeds	*p*
Zauls *et al*. [17]	91 (48/43)	D_{90}	165.1%	164.5%	NS
		ΔD_{90}	–8.3%	–5.5%	NS
		% of RV_{100} > 1.3 cc	27.6%	16.7%	NS
Jarusevicius *et al*. [22]	230 (124/106)	D_{90}	177.9 Gy	184.7 Gy	0.002
		V_{100}	94.9%	95.5%	NS
		V_{150}	53.2%	65.3%	< 0.001
		RV_{100}	0.3 ml	0.6 ml	< 0.001
Ishiyama *et al*. [31]	140 (74/66)	D_{90}	174.4 Gy	170.7 Gy	NS
		V_{100}	96.60%	95.70%	NS
		V_{150}	60.40%	62.10%	NS
		RV_{100}	0.47 ml	0.51 ml	NS
Ishiyama *et al*. [24]	630 (314/316)	D_{90}	118.1%	119.3%	NS
		ΔD_{90}	–3.82%	–3.14%	NS
		V_{100}	95.5%	95.5%	NS
		V_{150}	60.2%	67.6%	< 0.001
Katayama *et al*. [23]	64 (32/32)	D_{90}	180.7 Gy	178.1 Gy	NS
		V_{100}	98.2%	97.0%	NS
		RV_{100}	0.97 ml	1.00 ml	NS
Inada *et al*. [25]	74 (37/37)	D_{90}	119.8%	115.5%	NS
		V_{100}	96.9%	95.2%	0.02
		V_{150}	57.1%	64.5%	0.005
		RD_{2cc}	61.0%	64.1%	NS
Present study	76 (39/37)	D_{90}	118.8%	127.2%	< 0.01
		ΔD_{90}	–0.41%	6.95%	< 0.01
		V_{100}	98.0%	98.7%	0.061
		V_{150}	51.7%	66.7%	< 0.001
		RV_{100}	0.44 ml	0.61 ml	0.030

Values are presented as the means based on the one-month computed tomography analyses. Bold figures represent significantly higher values.
**The number of patients in linked/loose seed group was indicated in parentheses.*
NS – not significant, D_{90} – the minimum dose received by 90% of the prostate volume, V_{100} – the percent volume of the prostate receiving 100% of the prescribed dose, V_{150} – the percent volume of the prostate receiving 150% of the prescribed dose, ΔD_{90} – the post-operative D_{90} minus intraoperative D_{90}, RV_{100} – the rectal volume receiving > 100% of the prescribed dose, RD_{2cc} – the minimum dose received by 2 cc of the rectum

while one report showed significantly lower doses in the linked seed group.

Lastly, our study showed no significant difference in migration between the two groups, although a declining trend was noted in the linked seed group. We hypothesize that this finding is due to the fact that it may be difficult for the seeds to migrate out of the prostate because each linked seed is connected. Accordingly, previous studies have also shown significant reductions in the seed migration rate. Tapen *et al*. reported lower lung migration for stranded seeds compared to loose seeds (0.7% vs. 11%, p = 0.002) [12], and Ishiyama *et al*. reported lower migration in linked compared to loose seeds (0% vs. 52%, $p < 0.001$), and lower lung migration (0% vs. 30%) [31]. However, the impact on the dose distribution by migration is debatable. Wang *et al*. [32] reported that the prostate post-implant V_{100}, D_{90}, and rectal wall RV_{100} for patients without seed loss were 94.6%, 113.9%, and 0.98 cm^3, respectively, as compared to 95.0%, 114.8%, and 0.95 cm^3 for the group with seed loss; there were no correlations between seed loss due to migration and post-plan dosimetry. Miyazawa *et al*. reported that the D_{90} was 150.0 ± 19.6 Gy in patients without seed migration and 149.5 ± 19.4 Gy in patients with seed migration, and also found no significant difference in the post-planning dose delivered to the prostate between patients that did and did not display seed migration [33]. Of note, there are several reports on adverse events due to seed migration. Several studies have reported radiation pneumonitis, acute myocardial infarction, and secondary carcinoma due to migration [34,35,36]. Reducing migration using linked seeds may decrease these concerns.

Our study has some limitations. Most importantly, this study was a retrospective analysis, and further prospective studies are needed to confirm our findings. As urinary catheters were not used for the post-implant dosimetry, there were uncertainties of urethral delineation and dosimetry. Therefore, we did not evaluate the urethral dose for post-operative planning. However, because all patients were treated by the same radiation oncologist and urologist, inter-observer variability in dosimetry should be limited in our study.

Conclusions

Linked seeds showed reduced differences in terms of the prostate D90 between intraoperative and post-operative planning compared to loose seeds. Thus, the post-operative plan was reproduced intraoperatively. In addition, the high-dose region in the prostate, and the rectal dose was decreased using linked seeds, as was the lung migration.

Acknowledgments

We would like to thank Editage (www.editage.jp) for English language editing.

Disclosure

The authors report no conflict of interest.

References

1. Yorozu A, Kuroiwa N, Takahashi A et al. Permanent prostate brachytherapy with or without supplemental external beam radiotherapy as practiced in Japan: outcomes of 1300 patients. *Brachytherapy* 2015; 14: 111-117.
2. Grimm P, Billiet I, Bostwick D et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU Int* 2012; 109 Suppl 1: 22-29.
3. Morris WJ, Keyes M, Spadinger I et al. Population-based 10-year oncologic outcomes after low-dose-rate brachytherapy for low-risk and intermediate-risk prostate cancer. *Cancer* 2013; 119: 1537-1546.
4. Okamoto K, Wada A, Kohno N. High biologically effective dose radiation therapy using brachytherapy in combination with external beam radiotherapy for high-risk prostate cancer. *J Contemp Brachytherapy* 2017; 9: 1-6.
5. Merrick GS, Galbreath RW, Butler WM et al. Prostate cancer-specific death in brachytherapy treated high-risk patients stratified by pre-treatment PSA. *J Contemp Brachytherapy* 2017; 9: 297-303.
6. Merrick GS, Butler WM, Galbreath RW et al. Stratification of brachytherapy-treated intermediate-risk prostate cancer patients into favorable and unfavorable cohorts. *J Contemp Brachytherapy* 2015; 7: 430-436.
7. Sekiguchi A, Ishiyama H, Satoh T et al. 125Iodine monotherapy for Japanese men with low- and intermediate-risk prostate cancer: outcomes after 5 years of follow-up. *J Radiat Res* 2014; 55: 328-333.
8. Ohashi T, Yorozu A, Saito S et al. Combined brachytherapy and external beam radiotherapy without adjuvant androgen deprivation therapy for high-risk prostate cancer. *Radiat Oncol* 2014; 9: 13.
9. Reed DR, Wallner KE, Merrick GS et al. A prospective randomized comparison of stranded vs. loose 125I seeds for prostate brachytherapy. *Brachytherapy* 2007; 6: 129-134.
10. Fuller DB, Koziol JA, Feng AC. Prostate brachytherapy seed migration and dosimetry: analysis of stranded sources and other potential predictive factors. *Brachytherapy* 2004; 3: 10-19.
11. Lee WR, deGuzman AF, Tomlinson SK et al. Radioactive sources embedded in suture are associated with improved postimplant dosimetry in men treated with prostate brachytherapy. *Radiother Oncol* 2002; 65: 123-127.
12. Tapen EM, Blasko JC, Grimm PD et al. Reduction of radioactive seed embolization to the lung following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1998; 42: 1063-1067.
13. Fagundes HM, Keys RJ, Wojcik MF et al. Transperineal TRUS-guided prostate brachytherapy using loose seeds versus RAPIDStrand: a dosimetric analysis. *Brachytherapy* 2004; 3: 136-140.
14. Heysek RV, Gwede CK, Torres-Roca J et al. A dosimetric analysis of unstranded seeds versus customized stranded seeds in transperineal interstitial permanent prostate seed brachytherapy. *Brachytherapy* 2006; 5: 244-250.
15. Lin K, Lee SP, Cho JS et al. Improvements in prostate brachytherapy dosimetry due to seed stranding. *Brachytherapy* 2007; 6: 44-48.
16. Saibishkumar EP, Borg J, Yeung I et al. Loose seeds vs. stranded seeds: a comparison of critical organ dosimetry and acute toxicity in (125) I permanent implant for low-risk prostate cancer. *Brachytherapy* 2008; 7: 200-205.
17. Zauls AJ, Ashenafi MS, Onicescu G et al. Comparison of intraoperatively built custom linked seeds versus loose seed gun applicator technique using real-time intraoperative planning for permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2011; 81: 1010-1016.

18. Guinot JL, Ricos JV, Tortajada MI et al. Comparison of permanent (125) I seed implants with two different techniques in 500 cases of prostate cancer. *J Contemp Brachytherapy* 2015; 7: 258-264.
19. Saibishkumar EP, Borg J, Yeung I et al. Sequential comparison of seed loss and prostate dosimetry of stranded seeds with loose seeds in 125I permanent implant for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2009; 73: 61-68.
20. Langley SE, Laing RW. 4D Brachytherapy, a novel real-time prostate brachytherapy technique using stranded and loose seeds. *BJU Int* 2012; 109 Suppl 1: 1-6.
21. Hinnen KA, Moerland MA, Battermann JJ et al. Loose seeds versus stranded seeds in I-125 prostate brachytherapy: differences in clinical outcome. *Radiother Oncol* 2010; 96: 30-33.
22. Jarusevicius L, Inciura A, Juozaityte E et al. Comparison of implant quality between loose and intra-operatively linked iodine-125 seeds in prostate cancer brachytherapy. *J Radiat Res* 2012; 53: 439-446.
23. Katayama N, Takemoto M, Takamoto A et al. Comparison of implant quality between intraoperatively built custom-linked seeds and loose seeds in permanent prostate brachytherapy using sector analysis. *J Radiat Res* 2016; 57: 393-399.
24. Ishiyama H, Satoh T, Yorozu A et al. Multi-institutional retrospective analysis of learning curves on dosimetry and operation time before and after introduction of intraoperatively built custom-linked seeds in prostate brachytherapy. *J Radiat Res* 2016; 57: 68-74.
25. Inada M, Yokokawa M, Minami T et al. Dosimetry advantages of intraoperatively built custom-linked seeds compared with loose seeds in permanent prostate brachytherapy. *J Contemp Brachytherapy* 2017; 9: 410-417.
26. Taussky D, Igidbashian L, Donath D et al. Is intraoperative real-time dosimetry in prostate seed brachytherapy predictive of biochemical outcome? *J Contemp Brachytherapy* 2017; 9: 304-308.
27. Stone NN, Potters L, Davis BJ et al. Customized dose prescription for permanent prostate brachytherapy: insights from a multicenter analysis of dosimetry outcomes. *Int J Radiat Oncol Biol Phys* 2007; 69: 1472-1477.
28. Abel S, Renz P, Gayou O et al. Evaluation of intraoperative magnetic resonance imaging/ultrasound fusion optimization for low-dose-rate prostate brachytherapy. *J Contemp Brachytherapy* 2017; 9: 309-315.
29. Ohashi T, Yorozu A, Toya K et al. Comparison of intraoperative ultrasound with postimplant computed tomography – dosimetric values at Day 1 and Day 30 after prostate brachytherapy. *Brachytherapy* 2007; 6: 246-253.
30. Nath R, Bice WS, Butler WM et al. AAPM recommendations on dose prescription and reporting methods for permanent interstitial brachytherapy for prostate cancer: report of Task Group 137. *Med Phys* 2009; 36: 5310-5322.
31. Ishiyama H, Satoh T, Kawakami S et al. A prospective quasi-randomized comparison of intraoperatively built custom-linked seeds versus loose seeds for prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2014; 90: 134-139.
32. Wang Y, Nasser NJ, Borg J et al. Evaluation of the dosimetric impact of loss and displacement of seeds in prostate low-dose-rate brachytherapy. *J Contemp Brachytherapy* 2015; 7: 203-210.
33. Miyazawa K, Matoba M, Minato H et al. Seed migration after transperineal interstitial prostate brachytherapy with I-125 free seeds: analysis of its incidence and risk factors. *Jpn J Radiol* 2012; 30: 635-641.
34. Miura N, Kusuhara Y, Numata K et al. Radiation pneumonitis caused by a migrated brachytherapy seed lodged in the lung. *Jpn J Clin Oncol* 2008; 38: 623-625.
35. Zhu AX, Wallner KE, Frivold GP et al. Prostate brachytherapy seed migration to the right coronary artery associated with an acute myocardial infarction. *Brachytherapy* 2006; 5: 262-265.
36. Chen WC, Katcher J, Nunez C et al. Radioactive seed migration after transperineal interstitial prostate brachytherapy and associated development of small-cell lung cancer. *Brachytherapy* 2012; 11: 354-358.