ORIGINAL PAPER

Nagoya J. Med. Sci. **84**. 111–119, 2022
doi:10.18999/nagjms.84.1.111

Correlations between intraplan and postplan parameters in I-125 permanent prostate brachytherapy using loose seeds or linked seeds

Fumitaka Ito[1], Hidetoshi Kobayashi[2], Masayuki Ito[1], Ryoichi Shiroki[3] and Shinya Hayashi[1]

[1]*Department of Radiation Oncology, Fujita Health University School of Medicine, Toyoake, Japan*
[2]*Department of Radiation Oncology, Ogaki Municipal Hospital, Ogaki, Japan*
[3]*Department of Urology, Fujita Health University School of Medicine, Toyoake, Japan*

ABSTRACT

The purpose of this study was to determine the most appropriate seed arrangement by comparing two different methods (linked seeds and loose seeds). A total of sixty-one patients (28 linked seed brachytherapy cases and 33 loose seed brachytherapy cases) with clinically localized prostate cancer were treated with I-125 permanent prostate brachytherapy. Modified peripheral loading was the method used for seed placement. The parameters evaluated were as follows: prostate D90, V100, and V150; urethral D90, D10, and D5; and rectal V100 (RV100) and D2 (RD2). Coefficient parameters (r and r^2) were assessed by regression analysis. Prostate V150, urethral D90, urethral D10, urethral D5, and RD2 showed significant correlations between both methods in all patients. Urethral D90, urethral D10, urethral D5, and RD2 showed significant correlations in patients who received linked seed brachytherapy. Prostate V150, urethral D90, urethral D10, urethral D5, RV100, and RD2 showed significant correlations in patients who received loose seed brachytherapy. Urethral D90, urethral D10, urethral D5, and RD2 showed significant correlations in the linked seed and loose seed brachytherapy analyses. In contrast, prostate D90 and prostate V100 showed no correlation. Parameters of normal organ damage showed good correlations between intraplan and postplan parameters. These parameters may be useful to determine normal organ damage during guided brachytherapy with two different methods (linked seeds and loose seeds).

Keywords: prostate cancer, brachytherapy, intraplan, postplan, parameter

Abbreviations:
PI: prostate implantation
CT: computed tomography
TRUS: transrectal ultrasound
PSA: prostate-specific antigen
RV100: Rectal V100
RD2: Rectal D2
GI: gastrointestinal
GU: genitourinary

Received: November 18, 2020; accepted: May 26, 2021
Corresponding Author: Fumitaka Ito, MD, PhD
Department of Radiation Oncology, Fujita Health University School of Medicine, 1-98 Dengakugakubo-Kutsukake, Toyoake 470-1192, Japan
Tel: +81-562-93-9259, Fax: +81-562-95-2253, E-mail: fito@fujita-hu.ac.jp

INTRODUCTION

Transperineal permanent prostate implantation (PI) using I-125 can be an effective treatment modality for low-risk and intermediate-risk prostate cancer.[1,2] The most widely used prognostic parameter in seed treatment is prostate D90, which is the minimum dose received by 90% of the prostate.[3] Prostate D90 is calculated from computed tomography (CT) images performed 4–6 weeks after implantation (postplan).[4] Prostate D90 is not constant after seed brachytherapy because it is affected by changes in prostate volume over time after seed insertion. A previous study showed that the correlations between parameters for intraplan and postplan methods were poor.[5] On the other hand, another study showed excellent correlations.[6] After these studies, Zauls et al first reported intraoperatively built, custom-linked (IBCL) seeds.[5-7] This system was introduced to Japan in 2012.[8] Since 2013, our institute has used linked seeds and loose seeds for each prostate cancer patient. We choose linked seeds and loose seeds at random. When two different methods (linked seeds and loose seeds) are selected, postplan prostate D90 values are difficult to predict precisely at the time of seed insertion. Improvement of calculated prostate D90 using intraplan measurements is not always related to improved postplan prostate D90 calculations. In this study, correlations between parameters for intraplan and postplan methods were evaluated. When seeds are arranged using real-time planning, it is important to know the most reliable parameters.[6]

This study aimed to determine the most appropriate seed arrangement with two different methods (linked seeds and loose seeds) and whether modified peripheral loading is correlated with each index of the postplan when it is used to determine seed arrangement.

MATERIALS AND METHODS

Subjects

Sixty-one patients (Table 1) who underwent PI at Fujita Health University Hospital between March 2013 and April 2014 were analyzed retrospectively (Table 2). All patients gave consent for this study, which was approved by the institutional review board of Fujita Health University (Table 1). Pathological evaluation was conducted by one pathologist at the Fujita Health University Hospital. Patients were divided into three groups based on their Gleason score, clinical stage, and prostate-specific antigen (PSA) level.

Table 1 Patients' background characteristics (n = 61)

		Linked seed brachytherapy 28 cases	**Loose seed brachytherapy 33 cases**
Age (years)		58–74 median 69 years	56–78 median 70 years
FirstPSA (ng/ml)		4.1–22.61 median 6.5	4.6–56.3 median 7.2
Seed numbers	Monotherapy (160Gy)	52–95 median 80	65–100 median 80
	External beam radiotherapy (110Gy)	42–90 median 60	45–60 median 50

Clinical staging	cT1c	13	6
	cT2a	6	14
	cT2b	8	6
	cT2c	1	3
	cT3a	0	4
Gleason score	3 + 3	17	15
	3 + 4	7	8
	4 + 3	3	7
	over 4 + 4	1	3
Risk	Low	13	13
	Intermediate	14	12
	High	1	8
External beam radiotherapy	Yes	11	14
	No	17	19

Table 2 Descriptions of measured parameters

Index parameter	Definition	Units
Prostate D90-PI	the minimum dose received by 90% of the PI using TRUS-based prostate volume	%
Prostate D90-post	the minimum dose received by 90% of the postimplant CT-based prostate volume	%
Prostate V100-PI	the percent of the PI TRUS-based prostate volume receiving at least 100% of the prescription dose	%
Prostate V100-post	the percent of the postimplant CT-based prostate volume receiving at least 100% of the prescription dose	%
Prostate V150-PI	the percent of the PI TRUS-based prostate volume receiving at least 150% of the prescription dose	%
Prostate V150-post	the percent of the postimplant CT-based prostate volume receiving at least 150% of the prescription dose	%
Urethral D90-PI	the urinary catheter dose of the minimum dose received by 90% of the PI using TRUS-based urethral volume	Gy
Urethral D90-post	the urinary catheter dose of the minimum dose received by 90% of the postimplant CT-based urethral volume	Gy
Urethral D10-PI	the urinary catheter dose of the minimum dose received by 10% of the PI using TRUS-based urethral volume	Gy
Urethral D10-post	the urinary catheter dose of the minimum dose received by 10% of the postimplant CT-based urethral volume	Gy
Urethral D5-PI	the urinary catheter dose of the minimum dose received by 5% of the PI using TRUS-based urethral volume	Gy

Urethral D5-post	the urinary catheter dose of the minimum dose received by 5% of the postimplant CT-based urethral volume	Gy
RV100-PI	the PI using TRUS-based rectal volume in cubic centimeters that received at least 100% of the prescribed dose	cm3
RV100-post	the postimplant CT-based rectal volume in cubic centimeters that received at least 100% of the prescribed dose	cm3
RD2-PI	the minimum dose received by 2% of the PI using TRUS-based rectal volume	Gy
RD2-post	the minimum dose received by 2% of the postimplant CT-based rectal volume	Gy

PI: prostate implantation
RV100: Rectal V100
RD2: Rectal D2

Implant Technique

To determine the number of seeds necessary, prostate volumes were measured by transrectal ultrasound (TRUS). The prescription doses of PI were 160 or 110 Gy. Modified peripheral loading using the VariSeed ver.8.0 (Varian Brachytherapy, Charlottesville, VA, USA) treatment planning system was performed to decide intraplan and postplan seed placement. TRUS was used for intraplan images.

Postplan CT was performed 4–6 weeks after seed implantation.

Definitions of Parameters

Calculated dose parameters for intraplan and postplan methods are listed in Table 2.

Prostate D90 was defined as the percentage of the prescribed dose received by 90% of the volume of the prostate. Prostate V100 was defined as the percentage of the prostate volume receiving ≥100% of the prescribed dose. Prostate V150 was defined as the percentage of the prostate volume receiving ≥150% of the prescribed dose. Urethral D90 was defined as the dose received by 90% of the prostatic urethra volume. Urethral D10 was defined as the dose received by 10% of the prostatic urethra. Urethral D5 was defined as the dose received by 5% of the prostatic urethra. Rectal V100 (RV100) was defined as the absolute volume of the rectal wall receiving ≥100% of the prescription dose, and rectal D2 (RD2) was defined as the dose received by 2% of the volume of the rectal wall.

Analysis and Calculations

Coefficient parameters (r and r^2) were assessed by regression analysis [95% confidence interval (CI)]. StatMate version 4.01 statistical software (ATMS, Tokyo, Japan) was used for data analysis.

Evaluation of clinical results

Adverse events for 61 patients were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

PSA failure was evaluated according to the definition of Phoenix.[9]

RESULTS

Tables 3–5 show the correlations between the parameters for the intraplan and postplan methods for all patients (Table 3), linked seed brachytherapy (Table 4), and loose seed brachytherapy (Table 5). Prostate V150, urethral D90, urethral D10, urethral D5, and RD2 showed significant correlations between the two methods in all patients. Urethral D90, urethral D10, urethral D5, and RD2 showed significant correlations in patients who received linked seed brachytherapy. Prostate V150, urethral D90, urethral D10, urethral D5, RV100, and RD2 showed significant correlations in patients who received loose seed brachytherapy.

Table 3 Regression analysis for all cases (n = 61)

	r value	r^2 value	Correlation	(95% CI)	*p* value
Prostate D90-PI, Prostate D90-post	0.09	0.006	None	(–0.26_0.48)	0.54
Prostate V100-PI, Prostate V100-post	0.18	0.034	None	(–0.22_1.35)	0.16
Prostate V150-PI, Prostate V150-post	0.57	0.33	Significant correlation	(0.31_0.69)	<0.001
Urethral D90-PI, Urethral D90-post	0.58	0.33	Significant correlation	(0.34_0.82)	<0.001
Urethral D10-PI, Urethral D10-post	0.69	0.47	Significant correlation	(0.62_1.10)	<0.001
Urethral D5-PI, Urethral D5-post	0.54	0.3	Significant correlation	(0.54_1.16)	<0.001
RV100-PI, RV100-post	0.28	0.08	None	(0.06_0.75)	0.02
RD2-PI, RD2-post	0.54	0.3	Significant correlation	(0.29_0.67)	<0.001

PI: prostate implantation
RV100: Rectal V100
RD2: Rectal D2

Table 4 Regression analysis of linked seed brachytherapy cases (n = 28)

	r value	r^2 value	Correlation	(95% CI)	*p* value
Prostate D90-PI, Prostate D90-post	0.18	0.033	None	(–0.37_1.007)	0.36
Prostate V100-PI, Prostate V100-post	0.28	0.08	None	(–0.37_2.40)	0.14
Prostate V150-PI, Prostate V150-post	0.37	0.14	None	(–0.007_0.76)	0.054
Urethral D90-PI, Urethral D90-post	0.63	0.4	Significant correlation	(0.31_0.91)	0.003

Urethral D10-PI, Urethral D10-post	0.8	0.65	Significant correlation	(0.72_1.34)	<0.001
Urethral D5-PI, Urethral D5-post	0.71	0.3	Significant correlation	(0.71_1.61)	<0.001
RV100-PI, RV100-post	0.02	0.0005	None	(–0.47_0.42)	0.91
RD2-PI, RD2-post	0.54	0.3	Significant correlation	(0.16_0.71)	0.003

PI: prostate implantation
RV100: Rectal V100
RD2: Rectal D2

Table 5 Regression analysis of loose seed brachytherapy cases (n = 33)

	r value	**r^2 value**	**Correlation**	**(95% CI)**	***p* value**
Prostate D90-PI, Prostate D90-post	0.09	0.008	None	(–0.35_0.59)	0.61
Prostate V100-PI, Prostate V100-post	0.09	0.007	None	(–0.79_1.28)	0.62
Prostate V150-PI, Prostate V150-post	0.54	0.3	Significant correlation	(0.17_0.62)	0.001
Urethral D90-PI, Urethral D90-post	0.55	0.3	Significant correlation	(0.27_0.93)	<0.001
Urethral D10-PI, Urethral D10-post	0.56	0.32	Significant correlation	(0.31_1.02)	<0.001
Urethral D5-PI, Urethral D5-post	0.43	0.19	Significant correlation	(0.15_1.07)	0.01
RV100-PI, RV100-post	0.54	0.3	Significant correlation	(0.38_1.36)	0.001
RD2-PI, RD2-post	0.59	0.35	Significant correlation	(0.28_0.86)	<0.001

PI: prostate implantation
RV100: Rectal V100
RD2: Rectal D2

Urethral D90, urethral D10, urethral D5, and RD2 showed significant correlations in both linked seed and loose seed brachytherapy. In contrast, prostate D90 and prostate V100 showed no correlations.

Acute gastrointestinal (GI) adverse events were seen in two patients (grade 1). Late GI adverse events occurred in six patients (5 were grade 1, 1 was grade 2). The acute and late GI complication rate was 13%.

Acute genitourinary (GU) adverse events were seen in seven patients (5 were grade 1, 2 were grade 2). Late GU adverse events occurred in eight patients (4 were grade 1, 4 were grade 2).

The acute and late GU complication rate was 25%.

Grade 3 toxicity was not observed.

PSA failure was seen in one patient (iPSA was 6.1 ng/ml, Gleason score was 3+3, cT1cN0M0 as a low-risk case). The PSA failure patient was given linked seeds as monotherapy. The dose-volume histogram (DVH) of the PSA failure case is shown in Figure 1.

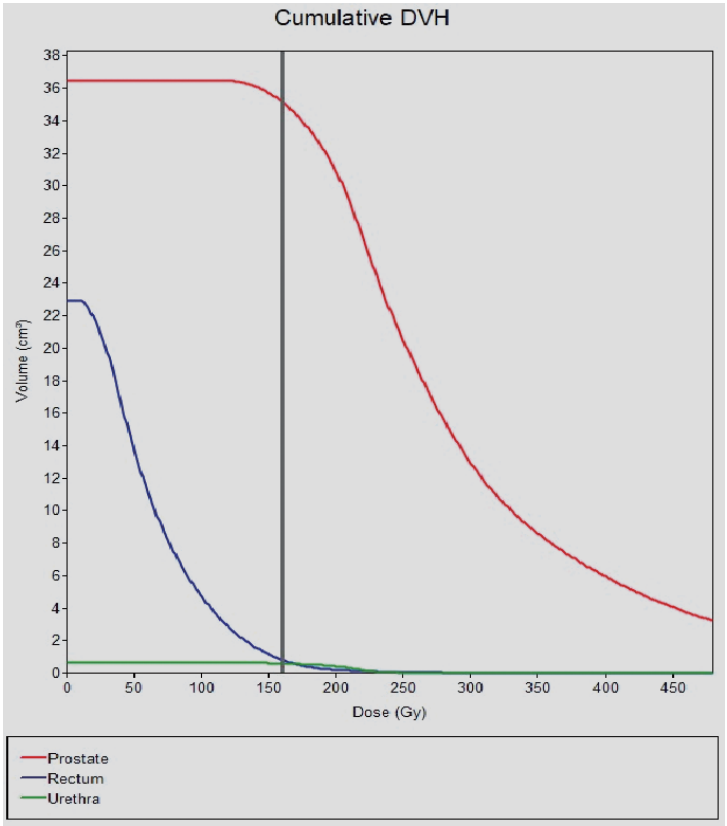

Fig. 1 Dose-volume histogram (DVH) of PSA-failure case
Prescription Dose: 160.0 Gy Prostate D90: 186 Gy, Prostate V100: 96%, Prostate V150: 61% Urethral D90: 161 Gy, Urethral D10: 235 Gy, Urethral D5: 246 Gy Rectal V100 (RV100): 0.81 ml, Rectal D2 (RD2): 175 Gy

DISCUSSION

This study reports the correlations between many prognostic parameters for intraplan and postplan methods. Prostate D90 was poorly correlated; however, urethral D90, D10, D5, and RD2 showed good correlations. The present study also evaluated PSA failure and complications of brachytherapy (loose seeds or linked seeds). Shiraishi et al reported that postplan prostate D90 values were strongly correlated with prognosis.[3] In addition, postplan urethral and rectal parameters were reported to be strongly correlated with urethral and rectal complications.[10,11] These parameters are calculated by means of a postplan CT, which is performed 4 weeks after seed insertion. Potters et al reported that the American Brachytherapy Society recommends that

postimplant CT-based dosimetry be performed for all patients treated with transperineal interstitial permanent prostate brachytherapy (TIPPB).[12] Prostate D90 is not a constant value because it is affected by the size and shape of each prostate, and there are no clear conclusions regarding urethral and rectal parameters.

Permanent seed implantation using I-125 cannot be repeated, and there are no potential correlations between dose distribution and parameters. Furthermore, postplan prostate D90 cannot be calculated using the intraplan method. In the present study, there was a poor correlation between prostate D90 calculated by the intraplan and postplan methods. This means that the attempt to improve the intraplan prostate D90 value did not improve the postplan prostate D90. In addition, the use of linked seeds did not affect the correlation between intraplan and postplan prostate D90 values. This poor correlation is not mainly dependent on seed movement after implantation, but on changes in prostate size and shape after implantation.[4] The present study showed that intraplan prostate D90 is not a good parameter to evaluate prognosis, because it becomes difficult to determine whether to add one more seed or to end seed insertion using the intraplan method.

Postplan images did not include magnetic resonance imaging (MRI) in the present study. Based on the results of the present study, prostate D90 of one PSA-failure patient was good. However, PSA failure was observed. MRI was useful for better prostate definition. As a result, the poor correlation between prostate D90 and prostate V100 in the present study may have been associated with large differences of prostate D90 and prostate V100 between post-implant MRI and CT.[13-15]

There is an approach to solve this difficult situation.

In the present study, GI and GU complications were approximately equal to those reported in preliminary research.[2]

The present results suggest that the most appropriate seed arrangement involves consideration of risk organ protection, such as urethral D90, D10, D5, and RD2 in the two different methods (linked seeds and loose seeds). These parameters are indices for evaluating normal organ damage using the brachytherapy complication-guided method. The present study's limitations include that it was a report from a single institution, and that it included comparatively few subjects.

CONCLUSION

Parameters for normal organ damage showed good correlations between intraplan and postplan values. These parameters may be useful to determine normal organ damage during guided brachytherapy using two different methods (linked seeds and loose seeds).

ACKNOWLEDGMENTS

The authors would like to thank Dr. Takahiro Maruyama and Dr. Hidekazu Hattori for their timely help in achieving the large number of prostate brachytherapies.

CONFLICT OF INTEREST STATEMENT

Dr. Ryoichi Shiroki reports personal fees from Intuitive Surgical Japan, and personal fees from Novartis outside the submitted work. No other authors reported financial interests.

REFERENCES

1 Grimm PD, Blasko JC, Sylvester JE, Meier RM, Cavanagh W. 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. *Int J Radiat Oncol Biol Phys*. 2001;51(1):31–40. doi:10.1016/s0360-3016(01)01601-7.

2 Okamoto K, Okuyama K, Kohno N, Tsugawa T, Clinical outcomes of low-dose-rate brachytherapy based radiotherapy for intermediate risk prostate cancer. *J Contemp Brachytherapy*. 2020;12(1):6–11. doi:10.5114/jcb.2020.92405.

3 Shiraishi Y, Yorozu A, Ohashi T, et al. A dose-response analysis of biochemical control outcomes after (125)I monotherapy for patients with favorable-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2014;90(5):1069–1075. doi:10.1016/j.ijrobp.2014.08.340.

4 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(11):5310–5322. doi:10.1118/1.3246613.

5 Ishiyama H, Kitano M, Satoh T, et al. Difference in rectal dosimetry between pre-plan and post-implant analysis in transperineal interstitial brachytherapy for prostate cancer. *Radiother Oncol*. 2006;78(2):194–198. doi:10.1016/j.radonc.2005.12.008.

6 Al-Qaisieh B, Witteveen T, Carey B, et al. Correlation between pre-and post implant dosimetry for Iodine-125 seed implants for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2009;75(2):626–630. doi:10.1016/j.ijrobp.2009.04.002.

7 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(4):1010–1016. doi:10.1016/j.ijrobp.2010.06.015.

8 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(1):68–74. doi:10.1093/jrr/rrv065.

9 Roach M 3rd, Hanks G, Thames H Jr, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys*. 2006;65(4):965–974. doi:10.1016/j.ijrobp.2006.04.029.

10 Stone NN, Stock RG. Prospective assessment of patient-reported long-term urinary morbidity and associated quality of life changes after 125I prostate brachytherapy. *Brachytherapy*. 2003;2(1):32–39. doi:10.1016/S1538-4721(03)00012-6.

11 Katayama N, Yorozu A, Maruo S, et al. Predictive factors of rectal toxicity after permanent iodine-125 seed implantation: Prospective cohort study in 2339 patients. *Brachytherapy*. 2016;15(6):736–745. doi:10.1016/j.brachy.2016.09.001.

12 Potters L, Cao Y, Calugaru E, Torre T, Fearn P, Wang XH. A comprehensive review of CT-based dosimetry parameters and biochemical control in patients treated with permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys*. 2001;50(3):605–614. doi:10.1016/s0360-3016(01)01473-0.

13 De Brabandere M, Hoskin P, Haustermans K, et al. Prostate post-implant dosimetry: interobserver variability in seed localisation, contouring and fusion. *Radiother Oncol*. 2012;104(2):192–198. doi:10.1016/j.radonc.2012.06.014.

14 Maletz KL, Ennis RD, Ostenson J, et al. Comparison of CT and MR-CT fusion for prostate post-implant dosimetry. *Int J Radiat Oncol Biol Phys*. 2012;82(5):1912–1917. doi:10.1016/j.ijrobp.2011.01.064.

15 Nosrati R, Wronski M, Tseng CL, et al. Postimplant dosimetry of permanent prostate brachytherapy: comparison of MRI-only and CT-MRI fusion-based workflows. *Int J Radiat Oncol Biol Phys*. 2020;106(1):206–215. doi:10.1016/j.ijrobp.2019.10.009.