

Predictive Factors for Deterioration of Lower Urinary Tract Symptoms After Iodine-125 Brachytherapy in Prostate Cancer Patients

Ayumu FUKAZAWA^{1)*}, Keiichiro KOIWA¹⁾, Takesumi OZAWA¹⁾
Hirohide MATSUSHITA²⁾ and Masumi KADOYA¹⁾

1) *Department of Radiology, Shinshu University, School of Medicine*

2) *Department of Comprehensive Cancer Therapy, Shinshu University, School of Medicine*

Purpose : To identify predictive factors for deterioration of lower urinary tract symptoms (LUTS) after iodine-125 (¹²⁵I) brachytherapy for prostate cancer.

Materials and Methods : 42 patients with localized prostate cancer treated with ¹²⁵I brachytherapy as monotherapy between January 2013 and October 2014 were reviewed. In all patients, the prescribed dose was 160 Gy. Patients were asked to complete the International Prostate Symptom Score (IPSS) questionnaire just before and 3 months after the treatment. With an increase in IPSS \geq 12 points defined as indicating obvious deterioration of LUTS (ODL), we analyzed the association between ODL and the following factors : age ; total activity of the sources ; prostate volume ; and dose-volume histogram (DVH) parameters, including V150 (%) of the prostate, V150 (cc) of the prostate, and D30 (Gy) of the urethra (minimal dose received by 30 % of the urethral volume).

Results : Seventeen (40.5%) patients developed ODL. On univariate analyses, V150 (%) and V150 (cc) were found to be significantly associated with ODL. On multivariate analysis, only V150 (cc) was shown to have a significant relationship with ODL ($P=0.039$).

Conclusion : V150 (cc) could be a predictive factor for deterioration of LUTS after ¹²⁵I brachytherapy in prostate cancer patients. *Shinshu Med J 66 : 131—137, 2018*

(Received for publication October 30, 2017 ; accepted in revised form December 26, 2017)

Key words : brachytherapy, lower urinary tract symptoms, prostate cancer

I Introduction

Permanent low-dose-rate brachytherapy is a common treatment option for localized prostate cancer. This treatment method shows excellent long-term disease control¹⁾⁻⁸⁾, especially for low-risk prostate cancer¹⁾. Although surgical treatment and external beam radiation therapy (EBRT) are also common treatment options, they have a number of drawbacks. One side effect of surgical treatment is sexual dysfunction⁹⁾¹⁰⁾. Brachytherapy is advantageous in this regard, because it usually does not adversely

affect sexual function. It is sometimes problematic that EBRT requires several weeks. Brachytherapy is more convenient because it takes a much shorter time than EBRT¹¹⁾. However, lower urinary tract symptoms (LUTS) occur more frequently after brachytherapy than after any other form of treatment. Previous studies indicated that a large proportion of patients experienced acute LUTS after brachytherapy, with 78% of patients in one study developing acute genitourinary symptoms to some degree¹²⁾. The symptoms are usually manageable, but they sometimes progress and therefore careful observation is required¹³⁾¹⁴⁾. This study was performed to identify predictive factors for deterioration of acute LUTS after iodine-125 (¹²⁵I) brachytherapy for prostate cancer patients.

* Corresponding author : Ayumu Fukazawa
Department of Radiology Shinshu University School of
Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621,
Japan
E-mail : afukazawa@shinshu-u.ac.jp

II Materials and Methods

Our Institutional Review Board approved this retrospective study and waived the need for informed consent from the patients. We usually perform ^{125}I brachytherapy as monotherapy in prostate cancer patients who fulfil the following criteria: localized disease (T1c-T2c), Gleason score $\leq 3+4$, and PSA < 10 ng/mL. The therapy is not applied in patients with at least one of the following conditions: expected not to survive > 5 years, those with a history of pelvic irradiation or transurethral prostatectomy, and prostate volume ≥ 40 mL. Between January 2013 and October 2014, 42 consecutive patients selected in accordance with the above rules were treated with ^{125}I brachytherapy alone and were included in this study. The patient characteristics are shown in **Table 1**. No patients received neoadjuvant hormonal therapy.

In brachytherapy, we employed a transperineal approach with transrectal ultrasound guidance for patients under spinal anaesthesia in the lithotomy position. The prescribed dose was 160 Gy to cover $\geq 95\%$ of the prostate volume. We used peripheral loading technique with a VariSeed version 8.0 planning system (Varian Medical Systems, Palo Alto, CA, USA) for permanently implanting the ^{125}I radioactive sources in the prostate. The median number of sources was 77 (range, 48–95), and the median total radioactivity of the implanted sources was 27.2 mCi (range, 16.3–32.3). Alpha-1 blockers were prescribed for all patients for at least 3 months after implantation.

Computed tomography (CT) and magnetic resonance imaging (MRI) were performed 1 month after implantation. The imaging data were sent to the same planning system as used in the implantation and registered to implement dosimetric analysis. The dose-volume histogram (DVH) parameters utilized in this study were obtained from the analysis. Representative data of dosimetric analysis are shown in **Table 2**.

Just before and 3 months after implantation, the patients were requested to complete the International

Table 1 Patient characteristics

Age (years) †	56–78 (65)
ECOG-PS ‡	
0	41
1	1
T stage ‡	
T1c	29
T2a	11
T2b	1
T2c	1
Gleason score ‡	
3+3=6	24
3+4=7	18
PSA level at diagnosis (ng/mL) †	4.01–9.50 (5.73)
Prostate volume (cc) †	11.4–39.7 (25.6)

† Range of value (median). ‡ Number of patients. PSA, prostate-specific antigen; ECOG-PS, the Eastern Cooperative Oncology Group performance status.

Table 2 Representative data of dosimetric analysis

Prostate V150 % (as %) †	19.4–74.6 (49.9)
Prostate V150 % (as cc) †	5.4–22.2 (12.6)
Urethra D30 % (as %) †	82.1–183.3 (126.4)
Urethra D30 % (as Gy) †	131.4–293.3 (202.3)

† Range of value (median). Prostate V150 %, percentage of the prostate volume receiving 150 % of prescribed dose; Urethra D30 %, minimal dose received by 30 % of the urethral volume.

Prostate Symptom Score (IPSS) questionnaire according to their LUTS. This questionnaire consists of seven questions related to obstructive LUTS, with the score per question ranging from 0 to 5; an IPSS score of 0 indicates no symptoms, while a score of 35 indicates maximal severity of symptoms. The score was divided into three levels: mild (0–7 points), intermediate (8–19 points), and severe (20–35 points).¹⁵⁾ We defined an increase in IPSS ≥ 12 points as obvious deterioration of LUTS (ODL) based on the rationale that an increase ≥ 12 points at 3 months brings patients with mild and intermediate levels just before implantation into a higher level.

We divided the patients into two groups, i.e., those with ODL and those without ODL. The associations between ODL and the following factors were analyzed: age (dichotomized into < 70 and ≥ 70), pros-

Table 3 Univariate analysis of the associations between ODL and various factors

Factors	Group with ODL	Group without ODL	<i>P</i> -value
Age (< 70 yrs. vs. ≥ 70 yrs.) †	13 vs. 4	18 vs. 7	0.75
Total activity of sources (mCi) ‡	26.6 ± 4.8	25.3 ± 4.7	0.195
Prostate volume (cc) ‡	25.7 ± 6.2	25.5 ± 7.7	0.46
Prostate V150 (%) ‡	55.1 ± 12.7	47.6 ± 15.5	0.047*
Prostate V150 (cc) ‡	14.3 ± 4.9	11.6 ± 4.3	0.037*
Urethra D30 (Gy) ‡	208.2 ± 20.5	204.3 ± 34.1	0.32

**P*<0.05. † Number of patients. ‡ Mean ± standard deviation. ODL, obvious deterioration of lower urinary tract symptoms; Prostate V150 %, percentage of the prostate volume receiving 150 % of prescribed dose; Urethra D30 %, minimal dose received by 30 % of the urethral volume.

Table 4 Multivariate analysis of the associations between ODL and selected factors

Factors	Group with ODL	Group without ODL	<i>P</i> -value	Odds ratio (95 % CI)
Total activity of sources (mCi) †	26.6 ± 4.8	25.3 ± 4.7	0.86	1.04 (0.684 – 1.592)
Prostate volume (cc) †	25.7 ± 6.2	25.5 ± 7.7	0.059	0.58 (0.309 – 0.978)
Prostate V150 (%) †	55.1 ± 12.7	47.6 ± 15.5	0.139	0.82 (0.616 – 1.045)
Prostate V150 (cc) †	14.3 ± 4.9	11.6 ± 4.3	0.039*	2.99 (1.194 – 10.068)
Urethra D30 (Gy) †	208.2 ± 20.5	204.3 ± 34.1	0.122	0.96 (0.906 – 1.004)

**P*<0.05. † Mean ± standard deviation. ODL, obvious deterioration of lower urinary tract symptoms; Prostate V150 %, percentage of the prostate volume receiving 150 % of prescribed dose; Urethra D30 %, minimal dose received by 30 % of the urethral volume.

tate volume (cc), total activity of implanted sources (mCi), prostate V150 (%), (cc) (volume receiving 100% of the prescription dose), and urethra D30 (Gy) (minimal dose received by 30 % of the urethral volume). All statistical analyses were performed with JMP version 11.2.0 (SAS Institute Inc., Cary, NC, USA). Paired *t* tests were performed on univariate analyses for all factors other than age (Chi-square test). We performed multivariate analysis for the factors selected according to the results of univariate analysis. On multivariate analysis, logistic regression analysis was performed. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive capability for ODL of each factor that showed a significant difference on multivariate analysis. In all analyses, *P* < 0.05 was taken to indicate statistical significance.

III Results

The median IPSS just before implantation was 4 points (range, 0–22), while that at 3 months after implantation was 14 points (range, 0–33). The median increase in IPSS during the 3-month period was 10 points. IPSS increased in 41 patients, and decreased in one patient. Seventeen (40.5%) patients developed ODL. The median increase in IPSS in the patients with ODL was 18 points (range, 12–25).

The results of univariate and multivariate analyses of the association between ODL and the factors outlined above are shown in **Table 3** and **Table 4**. On univariate analysis, prostate V150 (%) (*P* = 0.047) and prostate V150 (cc) (*P* = 0.037) were significantly higher in the group with than without ODL. On multivariate analysis, only prostate V150 (cc) was significantly associated with ODL (*P* = 0.039).

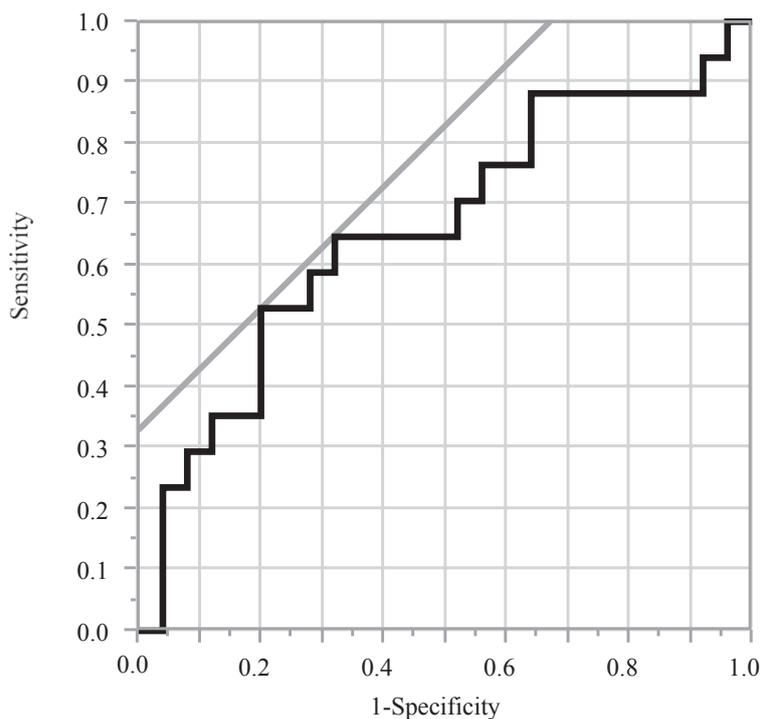


Fig. 1 ROC curve to evaluate the predictive capability of prostate V150 (cc) for ODL

The ROC curve to evaluate the predictive capability of prostate V150 (cc) for ODL is shown in **Fig. 1**. The accuracy of the prediction was moderate (area under the curve [AUC]=0.66). A cut-off value of 14.7 cc yielded 52.9% sensitivity and 80.0% specificity to predict the occurrence of ODL.

IV Discussion

^{125}I brachytherapy is accepted as a common therapeutic option for localized prostate cancer due to its advantages over other options. However, it has the drawback that some patients experience acute LUTS after treatment. Ohashi et al.¹⁴⁾ reported that 85.4% of patients receiving ^{125}I brachytherapy developed some degree of LUTS, with urinary frequency and retention being relatively common.

IPSS, proposed by the American Urological Association to evaluate benign prostate hyperplasia symptoms, is a useful tool to quantify LUTS and it has been adopted in many studies to evaluate LUTS after permanent implantation of radioactive sources into the prostate. Previous reports indicated that IPSS showed an increase after implantation with a peak at 1–6 months^{16)–21)}. We evaluated IPSS 3 months

after implantation, which seems appropriate considering the results of previous studies.

In the present study, prostate V150 (cc) was a predictive factor for deterioration of acute LUTS. Predictive factors for acute LUTS deterioration after implantation have been explored in various studies. Steggerda et al.²²⁾ reported that a dose to 0.5 cc of the bladder neck was correlated with acute LUTS. Thomas et al.²³⁾ reported that parameters of urethral base (D50 and V100) were predictive of higher maximum increase in IPSS. These results could be related to our findings. High V150 (cc) indicates that the volume of the high-dose region in the prostate is large. This means that the high-dose region in the bladder neck and the urethral base may also be large. Calculation of the doses to the bladder neck and urethral base may not be impossible, but it is complicated and not reproducible. On the other hand, calculating prostate V150 (cc) is simpler and more reproducible. Therefore, prostate V150 (cc) could be a convenient and useful predictive factor for deterioration of acute LUTS. Patients with high prostate V150 (cc) should be followed up more frequently and carefully in order to prevent the deteri-

oration of acute LUTS appropriately.

In the present study, both V 150 (%) and V 150 (cc) were significantly associated with deterioration of acute LUTS in univariate analysis, but only V 150 (cc) was significant in multivariate analysis. There was no significant difference in the prostate volume between patients with and without ODL, so the absolute V 150 might have represented almost the same implication as the relative V150 did in each group of the patients. A plausible explanation for the result of the multivariate analysis is that susceptibility of the regions at risk described above is independent from the prostate volume. The prostate volume itself was found to be a predictive factor of acute LUTS deterioration in several previous studies¹⁶⁾²⁰⁾²²⁾²⁴⁾⁻²⁶⁾, but this was not the case in the present study. This may have been because there were no patients with a large prostate volume (> 40 mL) in the present cohort.

Neoadjuvant hormonal therapy was also found to be a predictive factor of acute LUTS deterioration in some other studies²⁰⁾²⁴⁾²⁷⁾. The therapy causes the prostate to shrink and deform, and there may be some difficulty in implanting radioactive sources uniformly into a shrunken, deformed prostate. This may lead to an increase in prostate V150, and eventually deterioration of acute LUTS.

There were some limitations in the present study. First, this was a retrospective study, and the population size was not large enough to yield rigorous evidence. Second, we analyzed only patients that underwent ¹²⁵I brachytherapy as monotherapy, and therefore the results of this study cannot be applied to patients receiving brachytherapy in combination with external beam radiation therapy. Third, the definition of ODL is arbitrary. In fact, the definition of the deterioration of LUTS varied among previous studies¹⁶⁾¹⁹⁾²²⁾²³⁾²⁵⁾. This makes it impossible to compare the results of these studies with each other. Therefore, a widely accepted consensus regarding the definition of deterioration of LUTS is required for future studies.

V Conclusion

V150 (cc) could be a predictive factor for deterioration of acute LUTS after ¹²⁵I brachytherapy in prostate cancer patients. Keeping prostate V150 (cc) as low as possible should be considered in treatment planning.

VI Acknowledgements

The authors are grateful to Mrs. I. Koiwai and Mrs. Y. Ogawa for technical assistance.

References

- 1) Sylvester JE, Grimm PD, Wong J, Galbreath RW, Merrick G, Blasko JC: Fifteen-year biochemical relapse-free survival, cause-specific survival, and overall survival following I(125) prostate brachytherapy in clinically localized prostate cancer: Seattle experience. *Int J Radiat Oncol Biol Phys* 81: 376-381, 2011
- 2) Crook J, Borg J, Evans A, Toi A, Saibishkumar EP, Fung S, Ma C: 10-year experience with I-125 prostate brachytherapy at the Princess Margaret Hospital: results for 1,100 patients. *Int J Radiat Oncol Biol Phys* 80: 1323-1329, 2011
- 3) Zelefsky MJ, Yamada Y, Pei X, Hunt M, Cohen G, Zhang Z, Zaider M: Comparison of tumor control and toxicity outcomes of high-dose intensity-modulated radiotherapy and brachytherapy for patients with favorable risk prostate cancer. *Urology* 77: 986-990, 2011
- 4) Bittner N, Merrick GS, Galbreath RW, Butler WM, Wallner KE, Allen ZA, Brammer SG, Moyad M: Primary causes of death after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 72: 433-440, 2008
- 5) Kao J, Stone NN, Lavaf A, Dumane V, Cesaretti JA, Stock RG: (125)I monotherapy using D90 implant doses of 180 Gy or greater. *Int J Radiat Oncol Biol Phys* 70: 96-101, 2008
- 6) Morris WJ, Keyes M, Palma D, Spadinger I, McKenzie MR, Agranovich A, Pickles T, Liu M, Kwan W, Wu J, Berthelet E, Pai H: Population-based study of biochemical and survival outcomes after permanent ¹²⁵I brachytherapy

- for low- and intermediate-risk prostate cancer. *Urology* 73:860-865; discussion 865-867, 2009
- 7) Pickles T, Keyes M, Morris WJ: Brachytherapy or conformal external radiotherapy for prostate cancer: a single-institution matched-pair analysis. *Int J Radiat Oncol Biol Phys* 76:43-49, 2010
 - 8) Kupelian PA, Potters L, Khuntia D, Ciezki JP, Reddy CA, Reuther AM, Carlson TP, Klein EA: Radical prostatectomy, external beam radiotherapy < 72 Gy, external beam radiotherapy > or = 72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int J Radiat Oncol Biol Phys* 58:25-33, 2004
 - 9) Yarbrow CH, Ferrans CE: Quality of life of patients with prostate cancer treated with surgery or radiation therapy. *Oncol Nurs Forum* 25:685-693, 1998
 - 10) Potosky AL, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF, Harlan LC: Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. *J Natl Cancer Inst* 96:1358-1367, 2004
 - 11) Holmboe ES, Concato J: Treatment decisions for localized prostate cancer: asking men what's important. *J Gen Intern Med* 15:694-701, 2000
 - 12) Tanaka N, Asakawa I, Anai S, Hirayama A, Hasegawa M, Konishi N, Fujimoto K: Periodical assessment of genitourinary and gastrointestinal toxicity in patients who underwent prostate low-dose-rate brachytherapy. *Radiat Oncol* 8:25, 2013
 - 13) Han BH, Demel KC, Wallner K, Ellis W, Young L, Russell K: Patient reported complications after prostate brachytherapy. *J Urol* 166:953-957, 2001
 - 14) Ohashi T, Yorozu A, Toya K, Saito S, Momma T: Acute urinary morbidity following I-125 prostate brachytherapy. *Int J Clin Oncol* 10:262-268, 2005
 - 15) Gutman S, Merrick GS, Butler WM, Wallner KE, Allen Z, Galbreath RW, Adamovich E: Severity categories of the International Prostate Symptom Score before, and urinary morbidity after, permanent prostate brachytherapy. *BJU Int* 97:62-68, 2006
 - 16) Meyer A, Wassermann J, Warszawski-Baumann A, Baumann R, Machtens S, Karstens JH, Christiansen H, Merseburger A, Kuczyk MA, von Klot C: Segmental dosimetry, toxicity and long-term outcome in patients with prostate cancer treated with permanent seed implants. *BJU Int* 111:897-904, 2013
 - 17) Takeda K, Jingu K, Koto M, Fujimoto K, Narazaki K, Kubozono M, Saito H, Yamada S, Mitsuduka K, Ishidoya S, Ariga H, Arai Y, Yamada S: Predicting the severity of acute urinary toxicity after brachytherapy with iodine-125 for localized prostate cancer. *Tohoku J Exp Med* 223:55-60, 2011
 - 18) Li X, Fang D, Cooperberg MR, Whitson JM, Lue TF, Zhou L, Shinohara K: Long-term follow-up of International Prostate Symptom Score (IPSS) in men following prostate brachytherapy. *World J Urol* 32:1061-1066, 2014
 - 19) Murakami N, Itami J, Okuma K, Marino H, Nakagawa K, Ban T, Nakazato M, Kanai K, Naoi K, Fuse M: Urethral dose and increment of international prostate symptom score (IPSS) in transperineal permanent interstitial implant (TPI) of prostate cancer. *Strahlenther Onkol* 184:515-519, 2008
 - 20) Keyes M, Miller S, Moravan V, Pickles T, McKenzie M, Pai H, Liu M, Kwan W, Agranovich A, Spadinger I, Lapointe V, Halperin R, Morris WJ: Predictive factors for acute and late urinary toxicity after permanent prostate brachytherapy: long-term outcome in 712 consecutive patients. *Int J Radiat Oncol Biol Phys* 73:1023-1032, 2009
 - 21) Ohashi T, Yorozu A, Saito S, Tanaka N, Katayama N, Kojima S, Maruo S, Kikuchi T, Dokiya T, Fukushima M, Yamanaka H: Urinary and Rectal Toxicity Profiles After Permanent Iodine-125 Implant Brachytherapy in Japanese Men: Nationwide J-POPS Multi-institutional Prospective Cohort Study. *Int J Radiat Oncol Biol Phys* 93:141-149, 2015
 - 22) Steggerda MJ, Witteveen T, van den Boom F, Moonen LM: Is there a relation between the radiation dose to the different sub-segments of the lower urinary tract and urinary morbidity after brachytherapy of the prostate with

I-125 seeds ? *Radiother Oncol* 109 : 251-255, 2013

- 23) Thomas C, Keyes M, Liu M, Moravan V : Segmental urethral dosimetry and urinary toxicity in patients with no urinary symptoms before permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 72 : 447-455, 2008
- 24) Roeloffzen EM, van Vulpen M, Battermann JJ, van Roermund JG, Saibishkumar EP, Monninkhof EM : Pretreatment nomogram to predict the risk of acute urinary retention after I-125 prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 81 : 737-744, 2011
- 25) Pal RP, Bhatt JR, Khan MA, Duggleby S, Camilleri P, Bell CR, Elwell C, Kunkler RB : Prostatic length predicts functional outcomes after iodine-125 prostate brachytherapy. *Brachytherapy* 10 : 107-116, 2011
- 26) Steggerda MJ, van der Poel HG, Moonen LM : An analysis of the relation between physical characteristics of prostate I-125 seed implants and lower urinary tract symptoms : bladder hotspot dose and prostate size are significant predictors. *Radiother Oncol* 88 : 108-114, 2008
- 27) Ohashi T, Yorozu A, Toya K, Saito S, Momma T : Predictive factors of acute urinary retention requiring catheterization following 125I prostate brachytherapy. *Jpn J Clin Oncol* 36 : 285-289, 2006

(2017. 10. 30 received ; 2017. 12. 26 accepted)
