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

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Keywords : brachytherapy, lower urinary tract symptoms, prostate cancer

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Short running title : Predictor of LUTS after brachytherapy

Number of pages of text : 9

Number of figures : 1

Number of tables : 4

Abstract

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

Materials and Methods : 42 patients with localized prostate cancer treated with ^{125}I 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 ^{125}I brachytherapy in prostate cancer patients.

目的：前立腺癌に対する密封小線源永久挿入療法における，急性期下部尿路症状(lower urinary tract symptoms, LUTS)の増悪予測因子を検討する。

対象と方法：2013 年 1 月から 2014 年 10 月の間に ^{125}I 小線源単独療法が行われた限局性前立腺癌患者 42 例を対象とした。処方線量は全患者において 160 Gy であった。小線源療法前および 3 か月後に国際前立腺症状スコア(International Prostate Symptom Score, IPSS)を用いて LUTS を調査した。IPSS の 12 以上の増加を明らかな LUTS の増悪(obvious deterioration of LUTS, ODL)と定義し，ODL と以下に挙げる因子との関係を解析した；年齢，線源の総放射能，前立腺体積，線量体積ヒストグラム(dose – volume histogram, DVH)におけるパラメータである前立腺 V150 (cc, %)および尿道 D30 (Gy) (尿道の 30%の体積が照射される線量)。

結果：17 例(40.5%)において ODL が発生していた。単変量解析では V150 (%)および V150 (cc)において ODL 発生との間に有意な相関関係を認めた。多変量解析では V150 (cc)のみにおいて ODL 発生との間に有意な相関関係を認めた($P = 0.039$)。

結論：V150 (cc)は，^{125}I 小線源療法が行われた限局性前立腺癌患者における LUTS 増悪の予測因子であると考えられる。

Ⅰ Introduction

Permanent low-dose-rate brachytherapy is a common treatment option for localized prostate cancer. This treatment method shows excellent long-term disease control [1) -8)], especially for low-risk prostate cancer [1)]. 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 dysfunction [9) 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 EBRT [11)]. 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 degree [12)]. The symptoms are usually manageable, but they sometimes progress and therefore careful observation is required [13) 14)]. This study was performed to identify predictive factors for deterioration of acute LUTS after iodine-125 (^{125}I) brachytherapy for prostate cancer patients.

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 ≤ 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 ≥ 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 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), prostate 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 ($P = 0.039$). 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.* reported that 85.4% of patients receiving ^{125}I brachytherapy developed some degree of LUTS, with urinary frequency and retention being relatively common [14].

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 mean 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 deterioration 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 studies [16) 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 studies [20) 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 ^{125}I 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 studies [16) 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 ^{125}I 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.

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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.

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

Factors	Group with ODL	Group without ODL	*P*-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

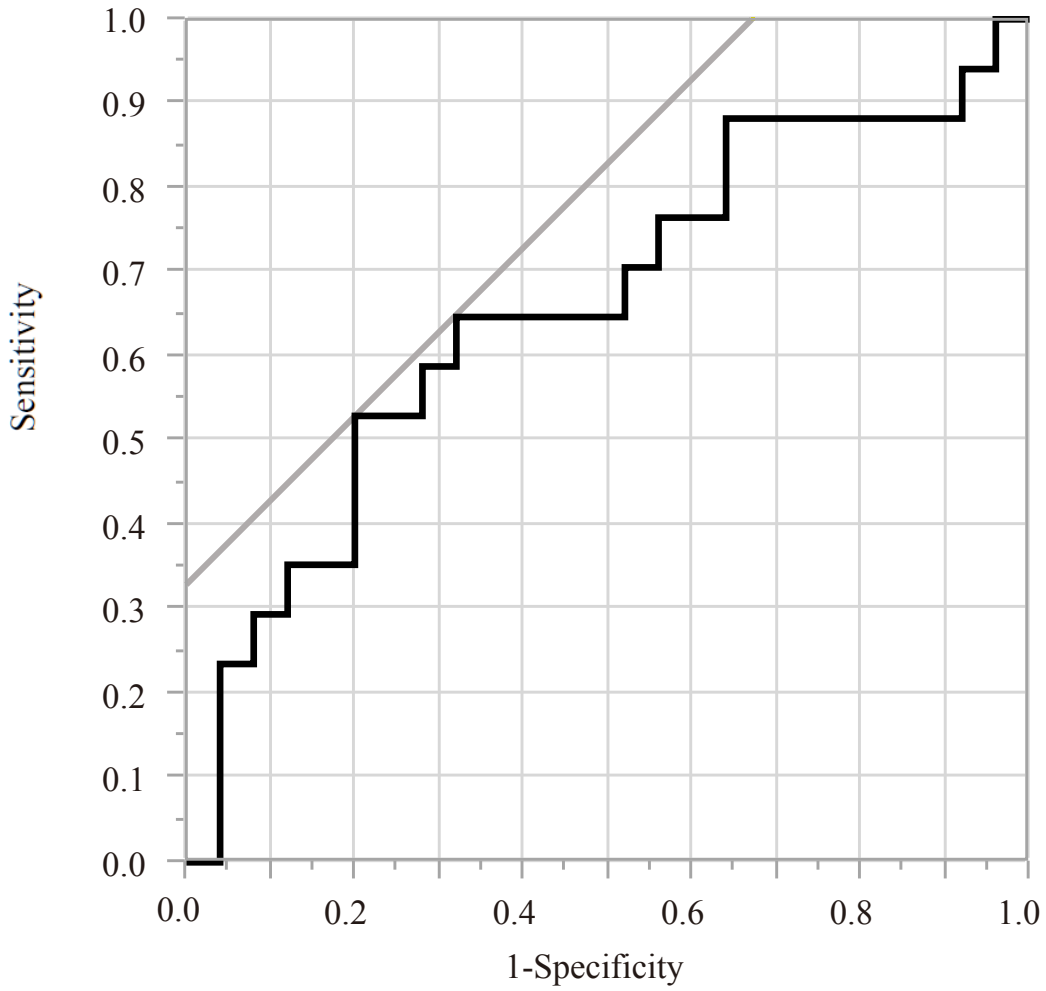
Factors	Group with ODL	Group without ODL	*P*-value	Odds ratio (95 % CI)
Total activity of sources (mCi)†	26.6 ± 4.8	25.3 ± 4.7	0.86	1.04 (0.684 – 1.592)
Prostate volume (cc)†	25.7 ± 6.2	25.5 ± 7.7	0.059	0.58 (0.309 – 0.978)
Prostate V150 (%)†	55.1 ± 12.7	47.6 ± 15.5	0.139	0.82 (0.616 – 1.045)
Prostate 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.

Figure legend

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

Fig. 1


Sensitivity
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