Predictors of Secondary Bladder Cancer in Patients with Prostate Cancer Treated with Brachytherapy: A Single-institution Study of a Japanese Cohort

Kiyoshi Takahara[1], Makoto Sumitomo[1], Masayuki Ito[2], Fumitaka Ito[2], Masashi Nishino[1], Takuhisa Nukaya[1], Masashi Takenaka[1], Kenji Zennami[1], Kosuke Fukaya[1], Manabu Ichino[1], Naohiko Fukami[4], Hitomi Sasaki[1], Mamoru Kusaka[4], Shinya Hayashi[2], Hiroshi Toyama[3], Ryoichi Shiroki[1]

Purpose: The incidence of secondary bladder cancer after treatment for localized prostate cancer (PCa) remains unclear. In this study, PCa cases treated with brachytherapy (BT) were evaluated to assess the incidence of a second malignancy of bladder cancer in a Japanese cohort.

Materials and Methods: Overall, 969 patients treated with BT at our hospital between July 2006 and January 2019 were included in the study cohort. The incidence and predictors of secondary bladder cancer were also assessed.

Results: The incidence of secondary bladder cancer was 1.5% (n = 14). Of the seven factors (age, pretreatment PSA, Gleason score, cTNM stage, prostate volume, total activity, and combined external beam), prostate volume and total activity showed significant differences between the cohorts with and without secondary bladder cancer (P = .03 and P = .001, respectively). Upon comparison of the seven parameters for the 969 patients treated with BT, we found that only the total activity factor was affected by the incidence of secondary bladder cancer in the multivariate analysis (P = .007).

Conclusion: The incidence of secondary bladder cancer was evaluated after BT for PCa. Total activity was associated with the incidence of secondary bladder cancer in Japanese patients who received BT.

Keywords: brachytherapy; prostate cancer; secondary bladder cancer

INTRODUCTION

Prostate cancer (PCa) ranking is the second most frequent cancer and the fifth leading cause of cancer death in men[(1)]. PCa has recently become a common type of cancer globally. However, owing to widespread PSA detection, PCa has often been discovered at a localized stage[(2,3)]. Many management strategies are available for localized PCa, including active surveillance, radical prostatectomy (RP), robot-assisted radical prostatectomy, and radiation therapy. A systematic review showed that external beam radiation therapy (EBRT), brachytherapy (BT), and RP are effective monotherapies for localized PCa; BT has a similar biochemical progression-free survival rate as RP in patients with a low to moderate risk of PCa[(4)]. Multiple prospective studies have assessed patient-reported toxicity differences among the three major definitive therapy options: RP, EBRT, and BT[(5,6)]. With high survival rates associated with each of these therapies, men and their partners often make treatment decisions based on their understanding of quality of life differences between each treatment modality[(7)].

As mentioned above, BT is a valid treatment option for localized PCa. BT has been found to be a highly effective and safe treatment, providing a good alternative to the surgical removal of the prostate, breast, and cervix, while reducing the risks of some long-term side effects[(8)]. However, the long-term risk of secondary malignancy, especially the risk of bladder cancer, is a potential late effect of BT.

This study aimed to evaluate localized PCa patients treated with BT at our hospital to assess the incidence and predictors of secondary bladder cancer in a Japanese cohort.

MATERIALS AND METHODS

Study Design

In the current study, we retrospectively reviewed the clinicopathological data of 969 patients treated with BT at our hospital between July 2006 and January 2019. For all patients, serum PSA levels were checked; cTNM stage was assigned by computed tomography, magnetic resonance imaging, and whole-body bone scan. Prostate volume was assessed using transrectal ultrasound at the time of the prostate biopsy.

The study design was approved by the ethics commit-

[1]Department of Urology, Fujita Health University School of Medicine, Toyoake, Aichi, Japan.
[2]Department of Radiation Oncology, Fujita Health University School of Medicine, Toyoake, Aichi, Japan.
[3]Department of Radiology, Fujita Health University School of Medicine, Toyoake, Aichi, Japan.
[4]Department of Urology, Okazaki Medical Center, Fujita Health University, Okazaki, Japan.
*Correspondence to: Kiyoshi Takahara, M.D., Ph.D., Department of Urology, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukakecho, Toyoake, Aichi 470-1192, Japan.
Tel: 81-562-93-2600, Fax: 81-562-93-4593, e-mail: takahara@fujita-hu.ac.jp.
Received February 2021 & Accepted October 2021

Table 1. Patient characteristics.

Baseline Patient Characteristics	Brachy therapy (n=969)
Age, y/o, Median (range)	70 (48 - 84)
Serum PSA level, ng/ml, Median (range)	7.1 (3.2-89)
cTNM stage, (%)	cT1N0M0 288 (29.7) cT2N0M0 546 (56.3) cT3N0M0 64 (6.6) others 71 (7.3)
Gleason score, (%)	~ 6 468 (48.3) 7 370 (38.2) 8 ~ 10 98 (10.1) unknown 33 (3.4)
D'Amico Risk classification, (%)	Low 389 (40.1) Intermediate 372 (38.4) High 137 (14.1) unknown 71 (7.3)
Follow up, Median (range)	81 (0 - 151)

tee of our hospital (Approval number of Fujita Health University School of Medicine: HM18-089). The need for informed consent from all patients included in this study was waived because of the retrospective design.

Treatment Classification

The D'Amico Risk classification[9] was used to determine the BT treatment. As a general rule, BT alone was performed for low-risk, combination of BT and EBRT for intermediate-risk, and trimodality treatment consisting of hormonal therapy, EBRT, and BT for high-risk PCa patients.

Patient Selection

Among the 969 localized PCa patients who received BT, 581 were treated with a 160 Gy permanent interstitial iodine-125 (I-125) implant alone by real-time intraoperative planning; 388 were treated with a 110 Gy permanent seed implantation, followed by a 45 Gy supplemental intensity-modulated radiation therapy to the prostate and seminal vesicles 2 months later. The current approach for BT dose calculation is based on the AAPM TG-43 dosimetry formalism, with recent advances in acquiring single-source dose distributions [10].

Follow-up Evaluations

Follow-up evaluations were performed at 3- to 6-month intervals for 5 years and yearly thereafter. The clinical data of each patient were collected from medical records. Secondary bladder cancer was diagnosed by transurethral resection of the bladder. Pathological findings, including grade and pT stage, were also obtained.

Statistical Analysis

For statistical analysis, the comparison between two groups was performed using Mann-Whitney's U test, chi-square test, or Fisher's exact test. The prognostic

Table 2. Incidence of secondary bladder cancer and patient characteristics.

	Brachy therapy (n=969)
Incidence of secondary bladder cancer, (%)	14 (1.5%)
Grade, (%)	G1 2 (14.3) G2 10 (71.4) G3 2 (14.3)
pT stage, (%)	pTa 9 (64.3) pT1 5 (35.7)
Time to secondary bladder cancer, months, Median (range)	48 (9-87)

Table 3. Patients' characteristics with and without secondary bladder cancer.

	Secondary bladder cancer (Yes: n=14)	Secondary bladder cancer (No: n=955)	p value
Age, y/o, Median (range)	70 (55-77)	70 (48-84)	NS
Serum PSA level, ng/ml, Median (range)	6.7 (4.8-9.1)	7.1 (3.2-89)	NS
Gleason score, (%)	~ 6 8 (57.1) 7 6 (42.9) 8 ~ 10 0 (0) unknown 0 (0)	~ 6 462 (48.4) 7 363 (38.0) 8 ~ 10 98 (10.3) unknown 32 (3.4)	NS
cTNM stage, (%)	cT1N0M0 6 (42.9) cT2N0M0 8 (57.1) cT3N0M0 0 (0) others 0 (0)	cT1N0M0 283 (29.6) cT2N0M0 538 (56.3) cT3N0M0 64 (6.7) others 70 (7.3)	NS
Prostate volume, ml, Median (range)	28.6 (16.9-41.9)	22.7 (5.5-51.4)	0.03
Total activity, MBq, Median (range)	1179 (589.5-1310)	851.5 (262-1427.9)	0.001
Combined external beam, (%)	3 (21.4)	385 (40.3)	NS

significance of certain factors was assessed using univariate and multivariate analyses. All data were analyzed using IBM SPSS Statistics version 23 (SPSS Japan Inc., Tokyo, Japan), and a p-value < 0.05, which was considered significant in all statistical analyses.

RESULTS

The clinical characteristics of 969 Japanese patients with localized PCa treated with BT included in this study are summarized in **Table 1**. The median age was 70 years; the median serum PSA level was 7.1. Regarding the cTNM stage and Gleason score, cT2N0M0 and

Table 4. Univariate and multivariate analyses of seven factors.

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p value	HR (95%CI)	p value
Age	0.927-1.114	0.73		
Serum PSA level	0.697-1.091	0.231		
Gleason score	0.576-2.290	0.693		
cTNM stage	0.659-1.807	0.733		
Prostate volume	1.017-1.155	0.014	0.905-1.134	0.821
Total activity	1.001-1.006	0.006	1.001-1.006	0.007
Combined external beam	0.145-1.865	0.315		

Gleason score < 6 were observed in 56.3% and 48.3% of patients, respectively. In the context of D'Amico risk classification, the low-risk group was most frequently observed in 40.1%.

We then evaluated the incidence of secondary bladder cancer in 969 PCa patients treated with BT, which was observed in 14/969 (1.5%) patients. Upon histological grading, G2 was observed most frequently in 71.4% of cases; all cases of pT stage were under pT1 (**Table 2**).

To investigate the effect on the incidence of secondary bladder cancer, we focused on seven factors (age, pretreatment PSA, Gleason score, cTNM stage, prostate volume, total activity, and combined external beam) related to PCa and BT in the 969 patients treated with BT. Prostate volume and total activity showed significant differences between cohorts with and without secondary bladder cancer (P = .03 and P = .001, respectively) (**Table 3**).

Among these seven factors, we evaluated which factor was associated with the incidence of secondary bladder cancer in 969 PCa patients treated with BT. Univariate analysis showed that prostate volume and total activity were independent factors for the incidence of secondary bladder cancer (P = .014 and .006, respectively). In the multivariate analysis, total activity was the only factor directly associated with the incidence of secondary bladder cancer (P = .007) (**Table 4**).

DISCUSSION

The potential side effects and long-term toxicities of treatment for PCa are important considerations in selecting the best therapy for patients[11-14]. A second primary cancer is generally considered to be radiation-induced if (i) it is diagnosed after a latency period (usually considered to be 5 years or more) following irradiation; (ii) it occurs within the radiation field (for prostate radiotherapy, this includes the rectum, bladder, anus, prostate, soft tissues, bones, or joints of the pelvis and pelvic lymphoma); (iii) it is a different histological type from the original cancer; and (iv) the second tumor was not evident at the time of radiotherapy[15,16]. Rather than using this definition, we opted for a more inclusive strategy, as suggested by others[17]. Several recent studies have reported the incidence of secondary bladder cancer among PCa treatments, including RP, EBRT, and BT. A previous study using the Surveillance, Epidemiology, and End Results database from 1973 to 2011 showed that the relative risk of developing bladder cancer after 10 years was significantly higher following BT than after EBRT or EBRT and BT[18]. Another study showed that PCa patients treated with any radiation therapy were 1.70 times more likely to develop secondary bladder cancer compared with RP alone[19]. However, Zelefsky et al. reported that the 10-year likelihood of bladder cancer that developed after treatment in the RP, BT, and EBRT cohorts was 1.4%, 1.0%, and 1.2%, respectively, with no significant differences[20]. Collectively, these findings suggest that the prognostication of each PCa treatment for secondary bladder cancer should be conducted. Accordingly, in the current study, we focused on localized PCa patients treated with BT to investigate the incidence and predictors of secondary bladder cancer in a Japanese cohort. In this study, 969 Japanese patients who underwent BT for localized PCa treatment were evaluated. The incidence of secondary bladder cancer was observed in 14/969 (1.5%) patients. In the context of histological findings of secondary bladder cancer after BT treatment, G2 and G3 were observed in 85.7% of cases; pT stage in all cases was under pT1. Our histological results were consistent with a previous report that the majority of bladder cancers following BT were of high grade and low stage at diagnosis, most of which demonstrated luminal immunophenotype[21].

To evaluate which factors influenced the incidence of secondary bladder cancer after BT therapy in Japanese patients with localized PCa, several analyses were performed with the seven factors (age, pretreatment PSA, Gleason score, cTNM stage, prostate volume, total activity, and combined external beam). Between cohorts with and without secondary bladder cancer, prostate volume and total activity showed significant differences. Since the total activity was dependent on the prostate volume in order to deliver 160 Gy, except combining extra beam, our analysis between cohorts with and without secondary bladder cancer was acceptable. Interestingly, in the multivariate analysis, total activity was the only factor directly associated with the incidence of secondary bladder cancer. In this study, BT was not performed for PCa with a large prostate volume; total activity was decreased when the extra beam was combined. Furthermore, only total activity remains an important factor for the incidence of secondary bladder cancer. Moreover, the combination of BT and external beam therapy was not associated with the incidence of secondary bladder cancer in our Japanese cohort.

In the current study, we reported that the incidence of secondary bladder cancer after BT for localized PCa patients was 1.5%, within a median follow-up of 81 months. Total activity was an important predictor of the incidence of secondary bladder cancer in Japanese patients who received BT.

This study has some limitations. First, this was a retrospective, single-institution study. In addition, since patient characteristics were not fully obtained, well-designed analyses were lacking. In particular, the population of patients who had a history of smoking should be selected, considering that tobacco smoking is the best-established risk factor for bladder cancer in both men and women[22]. Further studies are needed to validate our assessment of the predictors of secondary bladder cancer in patients with PCa and BT.

CONCLUSIONS

In conclusion, the incidence of secondary bladder cancer after BT for localized PCa treatment was evaluated. Total activity was the only significant independent predictive factor for the incidence of secondary bladder cancer in Japanese patients who received BT.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare regarding this study.

REFERENCES

1. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of

Disease Study. JAMA Oncol. 2017;3:524-48.
2. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360:1310-9.
3. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009;360:1320-8.
4. Wolff RF, Ryder S, Bossi A, et al. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. Eur J Cancer. 2015;51:2345-67.
5. Chen RC, Basak R, Meyer AM, et al. Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer. JAMA. 2017;317:1141-50.
6. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med. 2008;358:1250-61.
7. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375:1415-24.
8. Skowronek J. Current status of brachytherapy in cancer treatment - short overview. J Contemp Brachytherapy. 2017;9:581-9.
9. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998;280:969-74.
10. Nath R, Anderson LL, Luxton G, Weaver KA, Williamson JF, Meigooni AS. Dosimetry of interstitial brachytherapy sources: recommendations of the AAPM Radiation Therapy Committee Task Group No. 43. American Association of Physicists in Medicine. Med Phys. 1995;22:209-34.
11. Laing R, Uribe J, Uribe-Lewis S, et al. Low-dose-rate brachytherapy for the treatment of localised prostate cancer in men with a high risk of disease relapse. BJU Int. 2018;122:610-7.
12. Liauw SL, Sylvester JE, Morris CG, Blasko JC, Grimm PD. Second malignancies after prostate brachytherapy: incidence of bladder and colorectal cancers in patients with 15 years of potential follow-up. Int J Radiat Oncol Biol Phys. 2006;66:669-73.
13. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7-30.
14. Suriano F, Altobelli E, Sergi F, Buscarini M. Bladder cancer after radiotherapy for prostate cancer. Rev Urol. 2013;15:108-12.
15. Cohen WG. Sarcoma arising in irradiated bone; report of 11 cases. Cancer. 1948;1:3-29.
16. Sale KA, Wallace DI, Girod DA, Tsue TT. Radiation-induced malignancy of the head and neck. Otolaryngol Head Neck Surg. 2004;131:643-5.
17. Boorjian S, Cowan JE, Konety BR, et al. Bladder cancer incidence and risk factors in men with prostate cancer: results from Cancer of the Prostate Strategic Urologic Research Endeavor. J Urol. 2007;177:883-7; discussion 7-8.
18. Keehn A, Ludmir E, Taylor J, Rabbani F. Incidence of bladder cancer after radiation for prostate cancer as a function of time and radiation modality. World J Urol. 2017;35:713-20.
19. Abern MR, Dude AM, Tsivian M, Coogan CL. The characteristics of bladder cancer after radiotherapy for prostate cancer. Urol Oncol. 2013;31:1628-34.
20. Zelefsky MJ, Pei X, Teslova T, et al. Secondary cancers after intensity-modulated radiotherapy, brachytherapy and radical prostatectomy for the treatment of prostate cancer: incidence and cause-specific survival outcomes according to the initial treatment intervention. BJU Int. 2012;110:1696-701.
21. Au S, Keyes M, Black P, Villamil CF, Tavassoli P. Clinical and pathological characteristics of bladder cancer in post brachytherapy patients. Pathol Res Pract. 2020;216:152822.
22. Humans IWGotEoCRt. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum. 2004;83:1-1438.