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Original Article

Prostate Biopsy May Not Be Indicated Early after Bacillus Calmette Guérin Treatment

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Bacillus Calmette-Guérin (BCG) treatment for non-muscle-invasive bladder cancer frequently causes an intraprostatic BCG granuloma. We investigated the optimal timing for a prostate biopsy after BCG treatment by retrospectively analyzing the cases of 22 patients with non-muscle-invasive bladder cancer who underwent a prostate biopsy after BCG treatment at our institute (2013-2017). Biopsies were indicated for a rising prostate-specific antigen (PSA) level, positive digital rectal examination findings, or the appearance of de novo low apparent diffusion coefficient lesions on MRI. The control group was comprised of 28 age- and PSA-matched patients. The relationships among the cancer detection rate and the patients' PSA levels and MRI findings were analyzed. Prostate cancer was detected by biopsy in only 13.9% (3/22) of the patients in the BCG group but in 78.5% (22/28) of the control patients ($p = 0.0001$). The three patients in the BCG group in whom prostate cancer was detected had all undergone the biopsy > 1 year after their BCG treatment. The remaining biopsies were performed within 1 year after BCG treatment and resulted in no diagnoses of prostate cancer. We suggest that performing a prostate biopsy early after BCG treatment is not informative or useful.

Key words: bacillus Calmette-Guérin, prostate granuloma, prostate cancer, bladder cancer, prostate biopsy

Bladder and prostate cancer are common in older men, and prostate cancer frequently develops in patients with bladder cancer [1]. Prostate cancer screening is thus recommended for older men with bladder cancer [2]. Bacillus Calmette-Guérin (BCG) treatment is a standard adjunctive treatment that is administered after a transurethral resection of bladder tumors (TURBT) for non-muscle-invasive bladder cancer [3]. Both an elevated level of prostate-specific antigen (PSA) and digital rectal examination (DRE) findings suspicious of prostate cancer have been reported after BCG treatment, and these are related to the formation of intraprostatic BCG granulomas [4]. BCG granulomas also mimic prostate cancer in multiparametric magnetic resonance imaging (MRI), making this imaging modality an unreliable tool for cancer detection [5,6]. It has thus been proposed that instead of undergoing a prostate biopsy, patients after BCG treatment should be monitored for alterations in PSA levels [5].

However, it has also been suggested that since the development of asymptomatic granulomatous prostatitis after BCG treatment is common, and since it is difficult to distinguish asymptomatic granulomatous prostatitis from prostate cancer on MRI, a biopsy is the only way to establish the diagnosis [6,7]. To investigate the usefulness and the optimal timing of performing a biopsy after BCG treatment, we retrospectively analyzed the clinical findings of patients who underwent a prostate biopsy after receiving BCG treatment at our institute, with an emphasis on temporal changes in the

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patients' clinical findings.

Patients and Methods

Study design. This was a retrospective study of patients who underwent a prostate biopsy at our institute. This study was approved by the Ethics Committee of Hyogo Medical University (Institutional Review Board approval no. 3131). Informed consent was obtained in the form of an opt-out option, which was available on our institution's website.

Patients and data collection. Prostate biopsies were performed on 965 patients at our institute between 2013 and 2017. Among them, 22 patients with non-muscle-invasive bladder cancer who underwent BCG treatment before the prostate biopsy were included as the study group. The patients' initial bladder cancer stages were Ta (n = 5), Tis (n = 5), Ta + Tis (n = 9), and T1 (n = 3). The biopsied patients were noted to have high PSA levels at an annual PSA checkup by their family physicians. Before the biopsy, all 22 patients had undergone MRI, the findings of which were re-interpreted by an independent radiologist using standard criteria. A biopsy was indicated for an elevated PSA level, positive DRE findings, or the appearance of one or more *de novo* low apparent diffusion coefficient (ADC) lesions on MRI.

We analyzed the clinical courses of the BCG group (n = 22) in a comparison with a control group consisting of 28 age- and PSA-matched patients. The relationships among the cancer detection rate and the temporal changes in the patients' PSA levels and MRI findings were analyzed. The statistical analyses were conducted using Student's *t*-test and the χ^2-test with GraphPad Prism software (GraphPad, San Diego, CA, USA).

Results

Table 1 summarizes the background and clinical characteristics of the BCG and control groups. In the BCG group and control group, the median (range) ages of the patients were 74 (58-86) versus 71 (54-89) years; the median PSA levels were 5.75 (1.21-26) and 6.34 (2.14-20.75) ng/mL, and the median prostate volumes were 22.5 (15-47) and 28.5 (12-60) mL, respectively, with no significant between-group differences in any of these variables.

The DRE-positive rate in the BCG and control groups were 45% versus 39%, and the rates of the presence of low-ADC lesions were 81.8% and 96.0%, respectively, with no significant between-group difference. However, prostate cancer was detected by biopsy in only 13.9% (3/22) of the patients in the BCG group but in 78.5% (22/28) of the patients in the control group ($p = 0.0001$ by χ^2-test).

De novo ADC lesions observed on MRI that appeared within 1 year after the completion of BCG treatment were all diagnosed as BCG granulomas based on biopsy findings (Figs. 1, 2). In contrast, the biopsies of the three patients in the BCG group with prostate cancer were all conducted > 1 year after the completion of BCG treatment (Fig. 2).

When we focused on the 17 patients in the BCG group whose biopsy had been conducted within 1 year post-BCG treatment, we observed that two of 15 patients (13%) had low-ADC lesions on MRI before BCG treatment; this rate increased significantly to 13 of the 17 (76%), within one year after they had undergone BCG treatment. Six patients had undergone a cystectomy for bladder cancer, and prostate cancer was not detected pathologically in any of these patients. Among the remaining 11 patients, nine underwent a post-treatment follow-up MRI examination at a median interval of 2.5 years; low-ADC lesions were detected in

Table 1 Background of 22 patients in BCG group and 28 patients in control

	BCG group (n = 22)	Control (n = 28)	*P*-value
Age (Y)	74 (58–86)	71 (54–89)	0.1528
Positive digital rectal examination	10 (45%)	11 (39%)	0.061
PSA (ng/mL)	5.75 (1.21–26)	6.34 (2.14–20.75)	0.6991
Prostate volume (mL)	22.5 (15–47)	28.5 (12–60)	0.2894
Low ADC lesion in MRI	18 (81.8%)	27 (96%)	0.08
Positive biopsy	3 (13.9%)	22 (78.5%)	0.0001

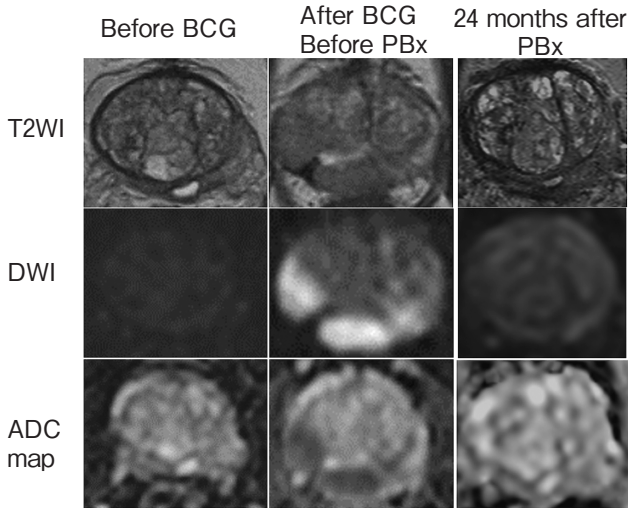

Fig. 1 MRI of a representative case showing temporal changes. A *de novo* low-ADC lesion, which was not detected before BCG treatment, appeared 3 months after the completion of the BCG treatment. A subsequent biopsy detected a BCG granuloma, with no malignant findings. These lesions had disappeared 24 months later.

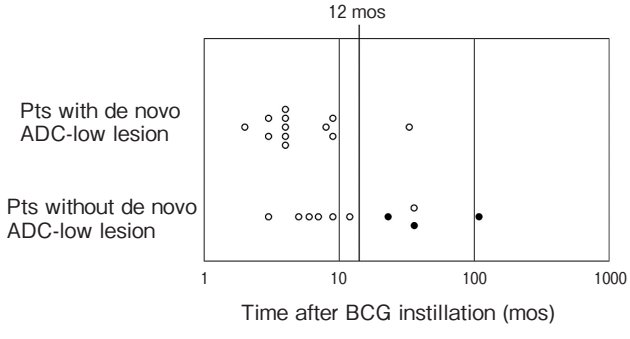

Fig. 2 The post-biopsy timepoints for the patients with and without *de novo* low-ADC lesions after BCG treatment. Twenty-two patients underwent an MRI examination before and after BCG treatment. *Open circles*: the cases in which no malignancy was detected by a biopsy. *Closed circles*: the cases with biopsy-confirmed prostate cancer.

only two of the nine patients (22%) (Fig. 2). The serum PSA levels of BCG group were 3.2 ± 1.8 ng/mL before BCG treatment but increased significantly to 5.8 ± 2.7 ng/mL at the timepoint of the biopsy after BCG treatment. The PSA levels of these patients at follow-up were 4.0 ± 3.1 ng/mL, which was no longer significantly different from the pre-BCG treatment levels (Table 2).

The patients who had undergone a prostate biopsy within 1 year of the completion of BCG treatment had a median observation period of 7 years (5-9 years) with no clinical prostate cancer.

Table 2 PSA levels and MRI findings in 17 patients who underwent prostate biopsy within 1 year after prostate biopsy

	Before BCG	At Prostate Biopsy	At latest follow-up
N	17	17	11**
PSA (ng/mL)	3.2 ± 1.8	5.8 ± 2.7*	4.0 ± 3.1
Low ADC lesion in prostate MRI	2/15	13/17*	2/9

*, $P<0.01$ vs Before BCG therapy; **, Excluding six cases undergoing cystectomy.

Discussion

The results of our analyses revealed that a prostate biopsy performed early after BCG treatment, if indicated only by a one-point elevation in PSA, suspicious DRE findings and/or a low ADC on MRI, rarely detects prostate cancer, and this underscores the importance of closely monitoring the patients' clinical course over laboratory tests or imaging in such a context.

The development of a prostatic granuloma after intravesical BCG treatment is considered fairly common. For example, Lafontaine *et al.* identified granulomatous prostatitis in 9 of 12 patients (75%) who had undergone a radical cystectomy after BCG treatment [8]. However, Kim *et al.* reported that they identified post-BCG treatment prostatitis in only 50 of 194 patients (25.8%) after 3 months of BCG treatment while the patients' PSA levels were < 4 ng/mL, even though elevated PSA values are not uncommon after BCG treatment [9].

The differentiation of BCG granuloma and prostate cancer on MRI is considered difficult [6, 7, 10]. Indeed, patients with granulomatous prostatitis frequently have MRI findings with moderate-to-high levels of suspicion for the presence of prostate cancer [11]. Several studies have attempted to identify MRI features that could be used for differentiating BCG granuloma and prostate cancer with the use of multi-parametric features or contrast-enhancement patterns, but a definitive consensus remains to be reached [6, 7, 12-15]. Moreover, lesions suspicious for prostate granuloma or prostate cancer can be a potential cause of benign F-18 fluorodeoxyglu-

cose uptake in positron emission tomography [16].

In the present series of patients, the presence of low-ADC lesions did not differ significantly between the BCG and control groups (81.8% vs. 96%) and therefore cannot explain the substantial difference in the biopsy-positive rate (13.9% vs. 73.5%, respectively). BCG granulomas were detected in all of the cases with *de novo* low-ADC lesions appearing within 1 year after BCG treatment. In contrast, the biopsies of the three patients in whom prostate cancer was detected were performed more than 1 year after their BCG treatment. When we focused on the patients whose biopsy was performed within 1 year post-BCG treatment, we observed that the PSA levels and the percentage of patients with low-ADC lesions on MRI that appeared after BCG treatment both returned to pre-biopsy levels within the follow-up period (Table 2).

These findings suggest that the timing of a biopsy after BCG treatment is more important than the one-point change in the PSA level or the MRI findings, as reported by some authors [17-19]. Neither PSA values nor MRI findings may be indicative of prostate cancer in this scenario. In the present study, the DRE positivity rate was not significantly different between the patients and controls, and DRE positivity was not indicative of cancer in most cases. PSA measurement, a DRE, and an MRI examination may therefore be useful before TURBT but not within one year after BCG treatment [19].

Patients undergoing treatment for bladder cancer who are suspected of having prostate malignancy are best diagnosed by a histopathologic examination. However, the potential morbidities and complications of a prostate biopsy mandate the identification of patients for whom an unnecessary prostate biopsy can be avoided. Our present findings demonstrate that the patient's clinical course should be prioritized over laboratory values or MRI findings. However, if more than 1 year has passed since a patient's BCG treatment, an elevation of the patient's PSA level (particularly if it is rising rapidly) should be considered a strong indicator for a prostate biopsy.

A limitation of this study is the small number of total cases, and further validation in a larger number of cases may be helpful. Additionally, if a patient's original bladder cancer is extensive high-grade carcinoma, a prostate biopsy may occasionally be necessary to rule out intraprostatic extension of urothelial carcinoma, in which case measurement of the patient's PSA is not helpful.

We propose that a prostate biopsy may not be indicated for de novo ADC lesions early after BCG treatment. Neither PSA measurement nor a DRE are useful adjuncts in this scenario. Our findings provide a basis for avoiding unnecessary biopsies in these patients.

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