INTRODUCTION AND OBJECTIVES: Localized prostate cancer (PCa) is mainly treated with both radical prostatectomy (RP) and radiation therapy. Radiation-induced secondary cancers are possible late-onset adverse events of radiation therapy. The incidence of secondary cancer increases at 10 or more years after completion of the radiation therapy (Figure 1). The secondary cancer varies among the types of radiation therapy, and it has generally been considered that the incidence is lower after brachytherapy alone than that after either external beam radiotherapy (EBRT) alone or brachytherapy combined with EBRT. Our hospital has actively performed high dose rate brachytherapy (HDR-BT) for localized prostate cancer (PCa) since 1998. Recently, we have frequently experienced the incidence of bladder cancer (BCa) in patients treated with HDR-BT. However, secondary BCa was only investigated after low dose rate brachytherapy in previous studies, and no study on secondary BCa after HDR-BT has been reported. We hypothesized that there was an association between BCa risk and HDR-BT. In this study, we retrospectively investigated the risk of BCa in patients treated with HDR-BT with or without EBRT.

METHOD: The subjects were 1,023 patients treated with HDR-BT with or without EBRT for localized PCa between January 1, 1998 and December 31, 2014 at our hospital. The protocol of HDR-BT with or without EBRT was 22-24 Gy/4 fractions of HDR-BT combined with 36.8-41.8 Gy of EBRT to the prostate region until July 2006 and then after August 2006, the protocol was 18-20 Gv/2 fractions of HDR-BT combined with 30 Gy of EBRT (Table 1). Only 83 patients (8.1%) were treated HDR-BT alone. RP (including laparoscopic surgery) was performed during the same period in 283 patients. Not all of the patients could be analyzed because the medical records of patients who did not visit the hospital for a long time were not retained. Therefore, this study was a matched case-control study.

For this study, the outcome was defined as the development of pathologically demonstrated BCa after local treatment. To exclude synchronous cancers, patients with BCa that developed within 2 years after PCa treatment and patients with a past medical history of urothelial cancer before the diagnosis of PCa were excluded. Among the follow-up patients with PCa after local therapy in our institute, 17 cases of newly pathologically diagnosed BCa as of April 2017 and 136 controls (1 matched by both age at the time of PCa treatment and for the follow-up period) were recruited (Figure 2). Logistic regression analysis was performed regarding cigarette smoking (including past smoking history) as a confounding factor.

RESULTS: The median age of the 17 patients in the case group at the onset of BCa was 75 (64-87) years old. Only one (5.9%) of these patients had been treated with RP, and the other 16 patients had received HDR-BT. The median time since prostate treatment was 56 (24-189) months. The clinical and pathological diagnosis was non-muscle-invasive BCa in all patients, and these were treated with transurethral resection. No patient died of BCa (Table 2). In the control group, 41 patients (30.1%) had been treated with RP, and 95 patients had received HDR-BT with or without EBRT. Ten (58.8%) of the 17 patients had a history of smoking in the case group. In the control group, 75 (64.1%) patients smoked cigarettes, 62 did not smoke cigarettes. On logistic regression analysis of local therapy (RP vs. HDR-BT) with the 2 items of history of cigarette smoking and confounding factors, the odds ratio of HDR-BT against surgery was 6.09 (95% CI: 1.35-118.21, p=0.016) and that of the history of cigarette smoking was 1.22 (p=0.703)(Table 3).

CONCLUSIONS: The incidence of secondary BCa after HDR-BT with or without EBRT for localized PCa was about 7 times, and the time to cancer development was about 5 years, which is a relatively short time compared to the previous reported. Although almost cases were treated combined with EBRT, the influence of HDR-BT may have contributed to the cancer, indicating that a prospective observational study may be necessary.

Although none of the patients had advanced BCa, it is necessary to obtain sufficient informed consent when HDR-BT is selected to treat localized PCa.

I. Abstract

II. Objective

To determine the association between exposure to HDR-BT with or without EBRT for the treatment of PCa and subsequent secondary primary bladder cancer.

III. Material and Methods

- **Study Design:** A matched case-control study
- **Subjects:** Patients treated with HDR-BT ± EBRT or RP (including laparoscopic surgery) for localized PCa between January 1998 and December 2014 at Kawasaki Medical School
- **Case Group:** Patients with secondary primary bladder cancer among the follow-up after local therapy
- **Control Group:** Patients without of secondary primary bladder cancer among the follow-up after local therapy
- **Statistical Analysis:** Logistic regression analysis

The ethics committee of Kawasaki Medical School and Hospital approved this study (2259-1)

IV. Results

Table 1: Protocol of HDR-BT ± EBRT in Kawasaki Medical School

<table>
<thead>
<tr>
<th>Year</th>
<th>HDR-BT alone (36.8 Gy)</th>
<th>HDR-BT combined (36.8-41.8 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999-2001</td>
<td>22Gy/4 fractions</td>
<td>36.8 Gy/4 fractions</td>
</tr>
<tr>
<td>2006</td>
<td>18-20Gy/2 fractions</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Patient's characteristics of bladder cancer cases

Table 3: Relationship between HDR-BT and smoking with bladder cancer risk

V. References


Figure 1: Risk of bladder cancer after any radiotherapy compared with no radiation exposure

Figure 2: Distributions of bladder cancer cases and matched controls