MP22-18 : Risk of second bladder cancer after high dose rate brachytherapy for prostate cancer

Yoshiyuki Miyaji*, Tota Nakatsuka, Hiroyasu Takasaki, Seitetsu Sugiyama, Shin Ohira, Masaichiro Fujita, Shinjiro **Shimizu**,
Shohei Tsukimori, Mikako Kaifu, Ryoei Hara, Tomohiro Fujii and Atsushi Nagai, Kawasaki Medical School, Kurashiki, Japan

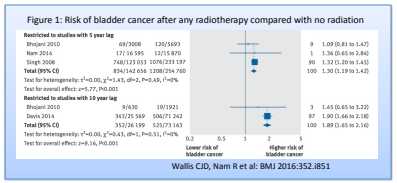
I. Abstract

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)[1]. The secondary cancer varies among the types of radiation therapy, and it has been generally 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) following PCa patients after HDR-BT. However, secondary BCa was only investigated after low dose rate brachytherapy in previous studies[2], 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 who received 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 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 Gy/2 fractions of HDR-BT combined with 39 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 285 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 (1:8 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 PR, 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, 73(54.1%) 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 as confounding factors, the odds ratio of HDR-BT against surgery was 6.99 (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.

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



Wallis CJD, Nam R et al: BMJ 2016:352.i851

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

	1998-2001	2001-2006	HDR-BT alone (2003-2006) only Low risk group	2006-
HDR-BT	22Gy/4fr.	24Gy/4fr.	37.5Gy/5fr.	18-20Gy/2fr.
EBRT	41.8Gy/19fr.	36.8Gy/16fr.	-	39Gy/13fr.
BED	82Gy	82Gy	78Gy	92-98Gy

BED: biological effective dose fr.: fraction

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 cancers.

III. MATERIAL & 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

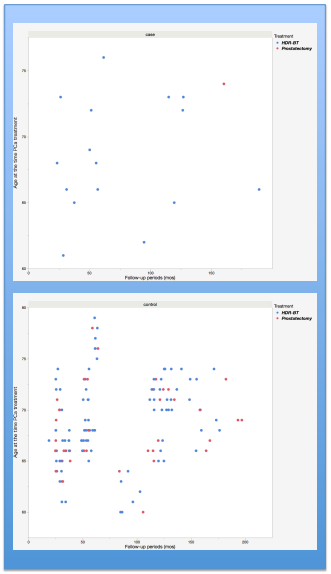
•Case Group:
Patients with secondary primary bladder cancer among the follow-up after local therapy

•Control Group:
Patients without of secondary primary bladder cancer among the follow-up after local therapy
Patients were recruited 1:8 matched by both age at the time of treatment and for the follow-up period

•Statistical Analysis:
Logistic regression analysis
Covariates: Treatment (HDR-BT/RP) and cigarette smoking

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

Figure 2: Distributions of bladder cancer cases and matched controls



IV. RESULTS

Table 2: Patient's characteristics of bladder cancer cases

No.	Age	Treatment	Periods after Treatment(mo)	Symptom	Tumor number	Site	Pathology	Adjuvant therapy	Outcome
1	71	HDR-BT+EBRT	38	hematuria	solitary	trigone	High, pTa&pTis	BCG	30mos, rec-
2	84	HDR-BT+EBRT	126	hematuria	multiple	trigone, rt.lateral	Low, pTa	-	22mos, rec-
3	76	HDR-BT+EBRT	51	hematuria	multiple	trigone, posterior	High, pTa	BCG	4mos, rec+
4	70	HDR-BT+EBRT	95	hematuria	multiple	neck-posterior	High, pTa&pTis	BCG	6mos, rec+
5	73	HDR-BT+EBRT	50	hematuria	solitary	posterior (lt.)	Low, pTa	-	6mos, rec+
6	71	HDR-BT+EBRT	57	hematuria	solitary	posterior (lt.)	Low, pTa	-	6mos, rec+
7	73	HDR-BT+EBRT	56	hematuria	solitary	posterior (rt.)	Low, pTa	-	49mos, rec-
8	83	HDR-BT alone	115	hematuria	solitary	posterior	High, pTa&pTis	BCG	8mos, rec-
9	64	HDR-BT alone	29	hematuria	solitary	lt.lateral	Low, pTa	-	44mos, rec+
10	81	HDR-BT+EBRT	62	hematuria	solitary	rt.lateral	Low, pTa	-	8mos, rec-
11	75	HDR-BT+EBRT	26	hematuria	solitary	lt.lateral	Low, pTa	-	17mos, rec+
12	70	HDR-BT+EBRT	25	hematuria	solitary	dome	Low, pTa	-	21mos, rec-
13	68	HDR-BT+EBRT	31	hematuria	multiple	postrior-lt.lateral	High, pT1	BCG	6mos, rec+
14	87	Prostatectomy	160	hematuria	multiple	trigone, posterior	High, pTa&pTis	BCG	24mos, rec-
15	82	HDR-BT+EBRT	127	hematuria	solitary	trigone	Low, pTa	-	25mos, rec-
16	76	HDR-BT+EBRT	120	hematuria	multiple	postrior-rt.lateral	High, pTa&pTis	-	7mos, rec+
17	81	HDR-BT+EBRT	189	hematuria	solitary	lt.lateral	Low, pTa	-	3mos, rec-

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

		Cases(N=17) N(%)	Controls(N=136) N(%)	Odds Ratio (95% CI)	P value
Treatment	RP	1(5.9)	41(30.1)	1.00 (reference)	
	HDR-BT± EBRT	16(94.1)	95(69.9)	6.99 (1.35-128.21)	0.016
Smoking	Never	7(41.2)	62(45.6)	1.00 (reference)	
	Former or current	10(58.8)	73(54.1)	1.22 (0.44-3.60)	0.703

V. REFERENCES

1.Wallis CDJ and Nam R, et al; Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. BMJ 2016:352.i851

2.Hamilton SN et al; Incidence of second malignancies in prostate cancer patients treated with low-dose-rate brachytherapy and radical prostatectomy. Int J Radiation Oncol Biol Phys 2014: 1-8