

Clinical Outcomes of Patients with Localized and Locally Advanced Prostate Cancer Undergoing High-dose-rate Brachytherapy with External-beam Radiotherapy at our Institute

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Abstract. *Aim: To report the clinical outcomes of localized and locally advanced prostate cancer patients undergoing high-dose-rate brachytherapy (HDR-BT) with external-beam radiotherapy (HDR-BT+EBRT) at the Kanazawa University Hospital. Patients and Methods: From 1999 until 2012, we examined 327 patients with T1c-T3bN0M0 prostate cancer that underwent HDR-BT+EBRT and were followed-up for ≥ 1 year. Before 2005, treatment consisted of HDR-BT at 18 Gy/3 fractions and EBRT to the prostate at 44 Gy/22 fractions, whereas after 2006, treatment consisted of HDR-BT at 19 Gy/2 fractions and EBRT to the prostate at 46 Gy/23 fractions. Results: Median age was 68 years (range=45-84 years), median follow-up duration was 57 months (range=12-148 months), and median prostate-specific antigen (PSA) level at diagnosis was 9.2 ng/ml (range=2.6-458.6 ng/ml). The patients' clinical stages were T1c:82, T2a:112, T2b:70, T2c:5, T3a:29, T3b:29, and their Gleason score was ≤ 6 :120, 7:108, ≥ 8 :99, respectively. The 5-year overall survival, and biochemical recurrence-free survival (bRFS) was 97.5% and 95.3%, respectively. Recurrence was reported in 20 cases (6.1%), and 11 patients died during follow-up, but only 1 patient died of prostate cancer. The 5-year recurrence-free survival bRFS for the patients in low-risk, intermediate-risk, and high-risk groups according to the D'Amico risk classification criteria were 100%, 95.6%, and 90.7%, respectively. Regarding adverse events genitourinary toxicity was major, and thus, 8.8% patients had urethral stricture and 4.3% patients were classified as grade 3. Conclusion: HDR-BT+EBRT is*

considered a suitable treatment modality for localized and locally advanced prostate cancer, including high-risk cases. However, genitourinary toxicity is observed frequently, and therefore, it may be necessary to modify the therapeutic planning of the HDR-BT+EBRT modality.

Current strategies for localized prostate cancer (PCa) are radical prostatectomy (RP), hormonal therapy (HT), and radiotherapy (RT). Although treatment outcomes of RP for localized early-stage PCa are good, the procedure has several disadvantages. This therapy is more invasive than other forms of therapies, biochemical recurrence-free survival (bRFS) decreases in high-risk patients (1, 2), and there is a high incidence of adverse effects, such as urinary incontinence and erectile dysfunction (3, 4). In contrast, HT is well-tolerated, and many patients of advanced age can undergo this therapy. However, HT is also associated with a number of adverse effects, such as erectile dysfunction, hot flashes, and osteoporosis (5-7). In addition, outcomes of HT are poorer than those of RP and RT (8). High-dose-rate brachytherapy (HDR-BT) is an effective treatment modality that can be utilized either alone or in combination with external-beam RT (EBRT) for patients with localized PCa in all risk groups (9-12). Combined use of EBRT and HDR-BT allows for considerable dose escalations while decreasing the dose administered to organs at risk, thereby improving PCa treatment outcomes (13). Furthermore, it has been reported that the combination of androgen deprivation therapy (ADT) with EBRT and HDR-BT improved treatment results of high-risk PCa cases (14).

We have previously reported the usefulness of HDR-BT with EBRT (15). We have treated 446 patients between February 1999 and December 2012 at the Kanazawa University Hospital. We could accumulate a number of cases, and conduct a long follow-up schedule. In the present study, we performed an updated analysis of the outcomes of the HDR-BT with EBRT treatment to examine its usefulness. In

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addition, we examined a utility of the combination of ADT with HDR-BT and EBRT.

Patients and Methods

In our institution, HDR-BT was indicated for non-metastasized PCa cases of any T stage. The present study population consisted of 327 patients diagnosed with T1c-T3bN0M0 PCa who were followed up for ≥ 1 year. In this study, we described T1c-T3bN0M0 PCa as localized and locally advanced PCa. Lesions were categorized according to the tumor-node-metastasis classification by the International Union Against Cancer (2009). Risk classification was based on that developed by D'Amico (16), by which patients were classified as having low risk (PSA ≤ 10 ng/ml, Gleason score ≤ 6 , and clinical stage $\leq T2a$), intermediate risk (PSA 10-20 ng/ml and/or Gleason score=7 and/or clinical stage T2b), and high risk (PSA ≥ 20 ng/ml and/or Gleason score ≥ 8 and/or clinical stage $\geq T2c$). Neoadjuvant HT (NAHT) was administered to decrease the prostate volume (<30 ml) and prevent disease progression while awaiting treatment. Adjuvant HT (AHT) for 2-3 years was recommended for high-risk patients. HT consisted basically of luteinizing hormone-releasing hormone agonist with or without bicalutamide. The HDR-BT treatment strategy consisted of using an 192Ir microelectron (Nucletron, BV, Leersum, Holland) at 18 Gy/3 fractions and EBRT to the prostate at 44 Gy/22 fractions between 1999 and 2005, whereas HDR-BT at 19 Gy/2 fractions and EBRT to the prostate at 46 Gy/23 fractions was used after 2006. In this study, biochemical recurrence was determined according to the Phoenix criteria (17). The survival curves were calculated by the Kaplan-Meier method. Adverse effects were recorded according to the Common Terminology Criteria for Adverse Events v4.0.

Results

Patients' characteristics are shown in Table I. The mean patient age was 67.6 years (range=45-84 years) and the median follow-up duration was 57.5 months (range, 12-148 months). Of the 327 patients included in this study, 82 (25.1%) were in clinical stage T1c, 112 (34.2%) in T2a, 70 (21.4%) in T2b, 5 (1.5%) in T2c, 29 (8.9%) in T3a, and 29 (8.9%) in T3b. The median initial PSA level was 9.2 ng/ml (range=2.6-458.6 ng/ml) and the Gleason score was ≤ 6 (120, 36.7%), 7 (108, 33%), ≥ 8 (99, 30.3%). According to the D'Amico risk classification criteria, 69 patients were at low risk, 118 were at intermediate risk, and 140 were at high risk. A total of 286 patients (87.5%) underwent NAHT for a median of 6 months. Seventy-eight patients (23.9%) received AHT for a mean of 2.4 years. Patients in the AHT group were mainly high-risk subjects (69, 88.5%).

Figure 1 shows the various survival curves calculated by the Kaplan-Meier method. The 5-year and 8-year overall survival (OS) was 97.5% and 93.1%, respectively (Figure 1A). The 5-year and 8-year bRFS rates were 95.3% and 89.6%, respectively. The 5-year bRFS for the patients in low-risk, intermediate-risk, and high-risk group was 100%, 95.6%, and 90.7%, respectively (Figure 1B). When limited to the non-AHT group, the 5-year bRFS for patients in the

Table I. Characteristics of the patients (T1c-T3b, N0, M0).

Mean age (years)	67.6 (45-84)	N=327
Follow-up (months)	Median 57.5 (12-148)	Mean 61.2
Clinical stage	T1c	82
	T2a	112
	T2b	70
	T2c	5
	T3a	29
	T3b	29
Gleason score	≤ 6	120
	7	108
	≥ 8	99
PSA at diagnosis	Median	9.2 (2.6-458.6) ng/ml
	Mean	17.5 ng/ml
	≤ 10	178
	10-20	90
	≥ 20	59
Neoadjuvant hormone therapy	+	286
	-	41
Adjuvant hormone therapy	+	78
	-	249
D'Amico risk classification*	Low	69
	Intermediate	118
	High	140

*Low risk: PSA ≤ 10 and Gleason score ≤ 6 and clinical stage $\leq T2a$. Intermediate risk: PSA 10-20 and/or Gleason score=7 and/or clinical stage T2b. High risk: PSA ≥ 20 and/or Gleason score ≥ 8 and/or clinical stage $\geq T2c$.

low-risk, intermediate-risk, and high-risk groups was 100%, 95.4%, and 87.6%, respectively (Figure 1C). One patient died of prostate cancer.

Table II shows the characteristics of patient recurrence. Eight out of 140 patients (5.7%) presented recurrence in the high-risk group and 12 out of 187 patients (6.4%) in the low-risk/intermediate-risk groups (low: 5 patients, intermediate: 7 patients).

Table III shows the characteristics of high-risk patients. AHT was administered in approximately half of the cases. Biochemical recurrence was observed in 5 patients (7.0%) in the non-AHT group and in 3 patients (4.3%) in the AHT group. Figure 2 shows bRFS curves for high-risk patients. The 5-year bRFS was 93.6% and 87.6% in the AHT and the non-AHT groups, respectively. Although there was no significant difference in the recurrence rate between non-AHT and AHT groups, there were more patients with 2-3 risk factors according to the D'Amico risk classification in the AHT group than in the non-AHT group.

Adverse events were observed in 73 patients (Table IV). The most frequent genitourinary complications were pollakiuria or urgency (10.4%) without \geq grade 3 toxicity. Urethral stricture was found in 8.8% cases and 4.3% of them were grade 3, which were observed in the late phases (median=638 days; range=73-2451 days) and managed

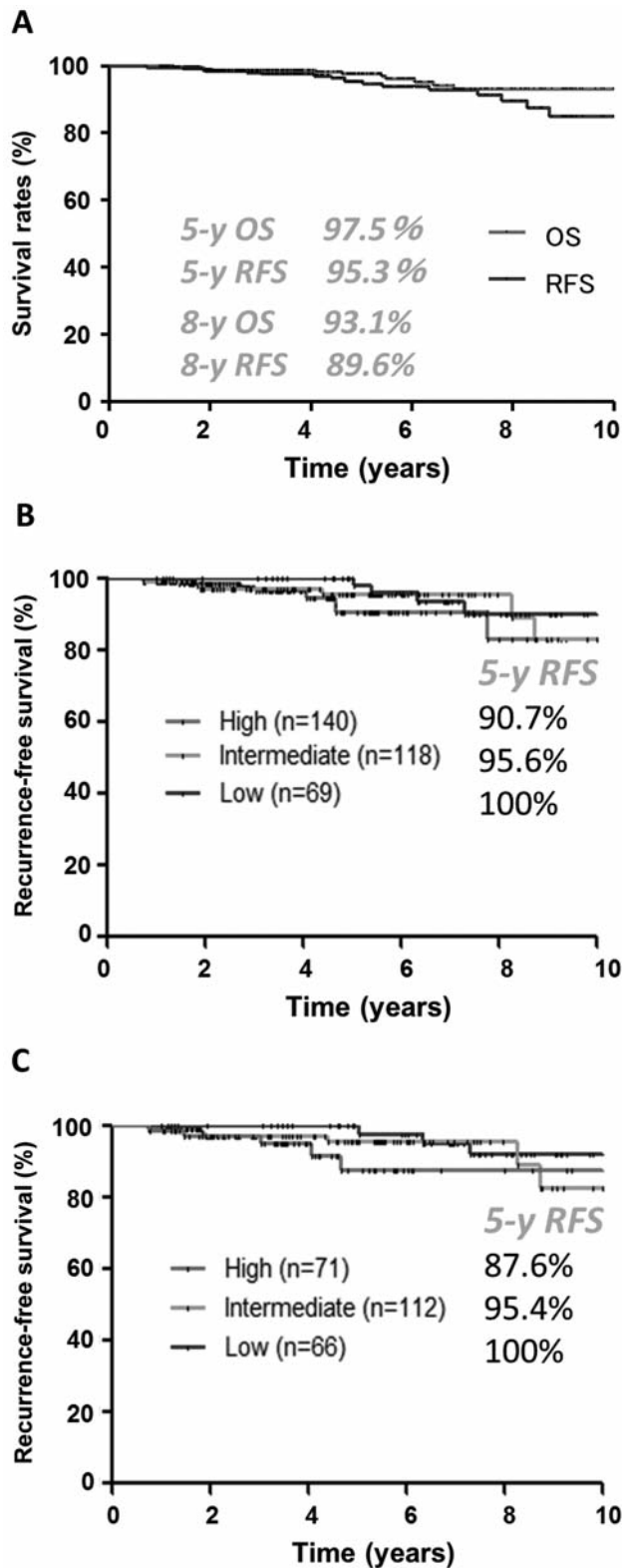


Figure 1. A. Overall survival and recurrence-free survival rates for all patients. B. Recurrence-free survival rates for all patients stratified by the risk group. C. Recurrence-free survival rate for non-AHT group stratified by the risk group.

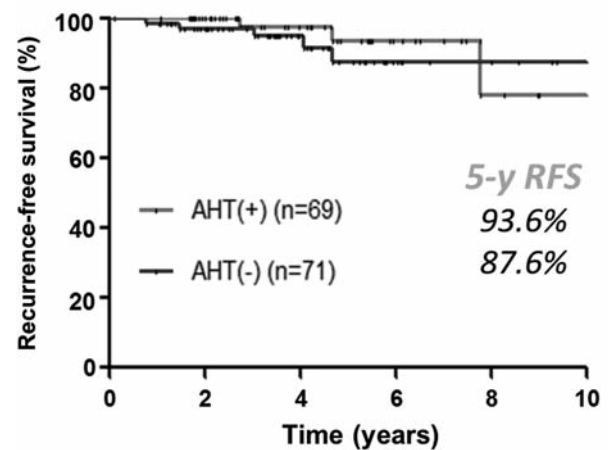


Figure 2. Recurrence-free survival rate of 140 high-risk patients stratified by whether AHT was performed or not.

successfully by urethral dilatation or internal urethrotomy. In contrast, rectal toxicity, such as proctitis, diarrhea, and rectal hemorrhage, was rare. Most of them were \leq grade 2 at a rate of $<1\%$, but only 1 patient experienced grade 3 rectal hemorrhage.

Discussion

Over the past years, many institutions have reported on treatment outcomes of HDR-BT for patients with PCa. The 5-year bRFS for patients in the low-risk, intermediate-risk, and high-risk groups in most reports was $\geq 90\%$, $80\%-90\%$, $60\%-70\%$, respectively (14). According to our study, the 5-year bRFS for patients in the low-risk, intermediate-risk, and high-risk groups was 100% , 95.6% , and 90.7% , respectively. These promising results can be explained by the combined use of HT, although the irradiation dose employed was lower than in previous studies. In the present work, NAHT was administered in 286 patients (87%) and AHT was administered in 78 patients (24%). AHT was administered in 69 patients of the high-risk group, which corresponded to approximately half of the patients in this group. The 5-year bRFS of the high-risk non-AHT and AHT groups was 87.6% and 93.6% ($p = 0.49$). When we compared the non-AHT groups with the AHT groups in the high-risk group, the mean PSA level was 13.6 ng/ml and 45.5 ng/ml, respectively. Furthermore, there were more patients with ≥ 2 risk factors according to the D'Amico risk classification, and with higher T stages, such as cT3, in the AHT group. In other words, the patients at higher risk became part of the AHT groups. The dosing period of AHT had a mean of 2.4 years, which corresponds to the recommended dosing period according to the NCCN guidelines (2-3 years). After all, HT is considered

Table II. *Characteristics of patients' recurrence.*

Subgroup (No. of patients' recurrence)	Mean age	T-stage	Gleason score	PSA	Number of high risk factor
High group 8(/140: 5.7%)	65.5	T1c: 1 T2a: 3 T2b: 2 T3a: 2	≤6:1 7:1 ≥8:6	Mean: 16.3 ≤10:4 10-20:3 ≥20:1	1 factor: 7 (/85: 8.2%) 2 factors: 1 (/29: 3.4%) 3 factors: 0 (/26: 0%)
Low/Intermediate group 12(/187: 6.4%)	69.4	T1c: 6 T2a: 1 T2b: 5	≤6:7 7:5	Mean: 6.3/11.3	Classification: Low 5(/69:7.2%) Intermediate 7(/118: 5.9%)

Table III. *Characteristics of high risk patients.*

Subgroup (No. of patients)	Mean age	T-stage	Gleason score	PSA	Number of high risk factor	PSA recurrence
AHT(−) group (n=71)	67.4	T1c: 15 T2a: 27 T2b: 13 T2c: 3 T3a: 10 T3b: 3	≤6:6 7:16 ≥8:49	Mean: 13.6 ≤10:41 10-20:16 ≥20:14	1 factor: 63 2 factors: 8 3 factors: 0	5 (7.0%) 1 factor: 5 2 factors: 0
AHT(+) group (n=69)	68.5	T1c:1 T2a: 5 T2b: 16 T2c: 2 T3a: 19 T3b: 26	≤6:4 7:15 ≥8:50	Mean: 45.5 ≤10:11 10-20:13 ≥20:45	1 factor: 22 2 factors: 21 3 factors: 26	3 (4.3%) 1 factor: 2 2 factors: 1

more effective in cases in which distant micrometastasis are thought to be present by the time of primary therapy. The Radiation Therapy Oncology Group Protocol 92-02 (RTOG 92-02) was a randomized trial comparing the use of short-term vs. long-term AHT combined with EBRT for patients with T2c-T4 locally advanced (18). Statistically significant improvement in biochemically disease control, distant metastasis failure, local control, and disease-free survival were observed for patients receiving long-term HT. Thus, these results suggest that long-term AHT is at least effective for higher-risk patients. However, we have to consider the possibility that AHT will maintain serum testosterone levels low for extended periods of time, even after discontinuing HT because of testicular atrophy. A persistent low testosterone level may prevent PCa recurrence. Likewise, the incidence of recurrence may increase after serum testosterone level increases. Therefore, we need to observe patients, who underwent AHT, carefully for a long term.

In our study, the adverse events were mainly genitourinary toxicities, such as urethral stricture and pollakiuria or urgency. Several studies have reported cases of urethral stricture following HDR-BT with EBRT, with a urethral stricture rate of 5%-10%. Strictures were located at the

Table IV. *Adverse events.*

	All grades (n=73)	Grade 3
Urethral stricture	29 (8.8%)	14 (4.3%)
Pollakisuria, urgency	34 (10.4%)	
Urinary retention	2 (0.6%)	
Hematuria	3 (0.9%)	
Acute prostatitis	2 (0.6%)	
Diarrhea	3 (0.9%)	
Proctitis	3 (0.9%)	
Rectal hemorrhage	2 (0.6%)	1 (0.3%)

bulbo-membranous urethra in 92.1% cases, with a median time to diagnosis of 22 months (19-24 months). Urethral stricture in our study occurred at similar rates as those described in previous studies. Therefore, surgical management, such as dilatation and internal urethrotomy, was necessary for approximately half of the patients.

The HDR-BT modality dose has certain limitations. For instance, the patients require complete bed resting during the treatment period to avoid the accidental removal of the

catheter from the perineum. Therefore, this aspect is less convenient for patients. In addition, this method is associated with an increased risk of deep vein thrombosis. In contrast, it has been reported that the administration of a single-fraction HDR protocol resulted in a high disease control rate and low toxicity (25). Therefore, this modality may contribute to a short treatment time and improve of the quality of life of patients during the treatment course. We recently began administering the single-fraction HDR protocol, but a longer follow-up is required to assess the effect of this dose escalation protocol on long-term biological control.

There has been no randomized trial of the combination of ADT and HDR-BT. Further study is required to explore whether ADT really improves OS when it is combined with HDR-BT.

Conclusion

Herein, we report an updated analysis of the outcomes of PCa patients treated with HDR-BT+EBRT. We obtained good results, even in the high-risk cases. Especially, long-term AHT for patients at very high-risk might be appropriate. However, urethral stricture seems an unavoidable reaction. Thus, the HDR protocol still offers some room for improvement. HDR-BT+EBRT was considered a good strategy for localized and locally advanced PCa. In addition, tri-modality treatment of the combination of ADT may contribute to improvement of OS. Although further studies with longer follow-up are necessary.

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