Observational Study

The curative effect of androgen deprivation therapy alone is insufficient in high-risk prostate cancer

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Abstract

To compare the outcomes of patients with high-risk prostate cancer treated by primary radical prostatectomy (RP) and primary androgen deprivation therapy (ADT).

The study included patients with high-risk or very high-risk prostate cancer. Patients treated with definitive radiation therapy and those with clinical N1 and M1 disease were excluded. The RP group was divided into sub-cohorts of patients treated with ADT and those who received ADT after biochemical recurrence post-RP. Cancer-specific survival (CSS) and overall survival (OS) were analyzed using the Kaplan–Meier method and the Cox proportional hazards model.

The study analyzed 859 patients divided into the RP group (n = 654) and ADT group (n = 205). Castration-resistant prostate cancer was detected in 23 (3.5%) patients in the RP group and 43 (21.0%) patients in the ADT group. Mortality cases included 63 (9.6%) patients in the RP group and 91 (44.4%) patients in the ADT group. CSS ($P = .0002$) and OS ($P < .0001$) were significantly higher in the RP group than in the ADT group. In the sub-cohort, CSS did not differ significantly between the RP and ADT groups, whereas OS was significantly higher in the RP group than in the ADT group ($P < .0001$). In the multivariate analysis, primary ADT increased CSS (hazard ratio, 2.068; $P = .0498$) and OS (hazard ratio, 3.218; $P < .0001$) compared with RP.

In clinically localized high-risk prostate cancer patients, primary RP was associated with better CSS and OS than primary ADT. Comprehensive counseling in this cohort of patients will help the selection of treatment.

Abbreviations: ADT = androgen deprivation therapy, BCR = biochemical recurrence, CRPC = castration-resistant prostate cancer, CSS = cancer-specific survival, OS = overall survival, PSA = prostate specific antigen, RP = radical prostatectomy.

Keywords: androgen deprivation therapy, high-risk, localized, prostate cancer, prostatectomy

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1. Introduction

Androgen deprivation therapy (ADT) is routinely used for the management of prostate cancer of any stage in Asia.[1] ADT is the primary treatment in approximately 50% of Korean and Japanese patients, whereas it is used in approximately 20% of patients in the USA.[2,3] In some patients, surgery is not the primary treatment option because of the potential complications of surgery and anesthesia. ADT is associated with a low rate of bone loss and cardiovascular complications in the Japanese population, and ADT decreases mortality in this cohort compared with its outcomes in Western populations.[4] These differences may be related to ethnicity and geography; however, the mechanism underlying the efficacy of ADT in this cohort remains unclear. To further investigate the efficacy of ADT, studies analyzing a well-defined range of patients are needed.

Risk classification could help predict patient prognosis. There are many risk criteria, including grade, stage, and prostate specific antigen (PSA) level. The National Comprehensive Cancer Network also suggests criteria for the classification of high-risk disease and the criteria were validated in clinically localized prostate cancer.[5,6] High-risk prostate cancer can be treated with radiotherapy combined with ADT or by radical prostatectomy (RP) and lymphadenectomy. Despite these treatment options, the 5-year rate of biochemical recurrence (BCR) in high-risk prostate cancer patients is >50%.[7] In very high-risk localized prostate cancer, the rate of metastasis is 63.1%, that of prostate cancer-related death is 37.8%, and death related to all causes occurs in

42.1% of patients after 10 years.[8] The rate of progressive disease is high in high-risk or very high-risk prostate cancer, suggesting that single treatments are not sufficient to achieve a curative effect. Therefore, multimodal treatment strategies for high-risk prostate cancer need to be developed. However, ADT alone remains a common primary therapy for prostate cancer in Asia. Here, we compared the oncologic outcomes of primary RP and primary ADT in patients with high-risk prostate cancer.

2. Materials and methods

The present study protocol was approved by the ethical review board of our institution. Data of 859 patients with high-risk or very high-risk prostate cancer between January 2008 and December 2013 were retrospectively reviewed. According to National Comprehensive Cancer Network guidelines,[5] the criteria for high-risk prostate cancer were T3a or higher grade or Gleason score 8 or PSA >20 ng/mL. The criteria for very high-risk prostate cancer were T3b and T4 or primary Gleason pattern 5 or more than 4 cores scoring >Gleason 8. Patients who were treated with definitive radiation therapy or had clinical N1 and M1 disease were excluded. All patients were diagnosed as prostate cancer by transrectal biopsy. Clinical data collected included age at diagnosis, body mass index, Charlson comorbidity index, PSA levels, operation type, biopsy Gleason score, clinical stage, and pathological variables. Patients were divided into 2 groups: the RP group comprised patients who underwent primary RP, and the ADT group comprised patients who received primary ADT without RP. RP included robot-assisted laparoscopic prostatectomy and retropubic RP. ADT included leuprolide (7.5 and 22.5 mg), triptorelin (11.25 mg), and goserelin (3.6 and 10.8 mg). Sub-cohort consisted of patients treated with ADT and patients who received ADT after presenting with BCR post-RP. BCR was defined as an increase of PSA >0.2 ng/mL reported twice consecutively. Castration-resistant prostate cancer (CRPC) was defined as an increase in PSA in 3 consecutive measurements taken at least 1 week apart; PSA had to be ≥2 ng/mL above the nadir value despite castrate testosterone (serum testosterone < 50 ng/dL). Cancer-specific

survival (CSS) and overall survival (OS) were calculated from the date of diagnosis of prostate cancer to the date of death in the total cohort. CSS and OS were analyzed from the start of ADT to death in the sub-cohorts. CSS was attributed to progressive metastatic CRPC. The follow-up period was 58.6 months (interquartile range, 38.7–80.0 months).

The baseline clinicopathological characteristics of the patients and tumors were expressed as the mean ± standard deviation or number and percentage. Continuous variables were compared using the Student t test, and categorical variables were analyzed using the chi-square test. Cox proportional hazard regression was used to analyze the survival model. The survival curves were estimated using the Kaplan–Meier method with the log-rank test according to groups. All statistical analyses were performed using R (version 3.5.1; R Project for Statistical Computing, Vienna, Austria). P values < .05 were considered statistically significant.

3. Results

The baseline characteristics of the 859 patients in the RP (n = 654) and ADT (n = 205) groups are presented in Table 1. Significant differences between the 2 groups were observed in all variables. In the RP group versus the ADT group, the mean age was lower (68.2 ± 6.9 vs 75.9 ± 6.9; P < .001) and the mean body mass index was higher (24.8 ± 2.8 vs 23.4 ± 2.8; P < .001). The rate of patients with a comorbidity index ≤1 was higher in the RP group than in the ADT group (96.5% vs 69.3%; P < .001). The mean initial PSA level was lower in the RP group than in the ADT group (16.8 ± 31.6 vs 50.9 ± 156.5; P < .001). Clinical T stage and Gleason score were more favorable in the RP group, and prostate size was smaller in the RP group than in the ADT group (35.7 ± 17.3 vs 39.8 ± 20.7; P < 0.011).

Table 2 lists the post-treatment outcomes. In the RP group, 56.6% of patients had pathologic T3 disease, 6.1% had N1 disease, and 40.4% had pathologic Gleason score 8 or higher. The mean volume of the removed prostate was 31.5 ± 14.9 g. The percent tumor volume was 23.5 ± 22.3%. Robotic surgery was performed in 372 cases (56.9%). The surgical margin was positive in 354 cases (54.1%) and radiotherapy was conducted in

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Table 1			
Baseline characteristics by treatment group.			
	RP (n = 654)	**ADT (n = 205)**	**P**
Age, yr	68.2 ± 6.9 [64.0; 73.0]	75.9 ± 6.9 [73.0; 80.0]	<.001
Body mass index, kg/m²	24.8 ± 2.8 [23.2; 26.4]	23.4 ± 2.8 [21.6; 25.1]	<.001
Charlson comorbidity index			<.001
≤1	631 (96.5%)	142 (69.3%)	
≥2	23 (3.5%)	63 (30.7%)	
Initial PSA value, ng/mL	16.8 ± 31.6 [5.6; 20.1]	50.9 ± 156.5 [9.4; 51.5]	<.001
Clinical T stage			<.001
T2	314 (48.0%)	91 (44.4%)	
T3a	249 (38.1%)	43 (21.0%)	
≥T3b	91 (14.0%)	71 (34.7%)	
Clinical Gleason score			.001
≤7	234 (35.8%)	48 (23.4%)	
≥8	420 (64.2%)	157 (76.6%)	
TRUS volume, cm³	35.7 ± 17.3 [25.0; 42.0]	39.8 ± 20.7 [28.0; 45.0]	.011
NCCN risk group			<.001
High risk	500 (76.5%)	70 (34.1%)	
Very high risk	154 (23.5%)	135 (65.9%)	

[] = interquartile range, ADT = androgen deprivation therapy, NCCN = National Comprehensive Cancer Network, PSA = prostate-specific antigen, RP = radical prostatectomy, TRUS = transrectal ultrasonography.

Table 2

Post-treatment outcomes.

	RP (n = 654)	ADT (n = 205)
Pathology T stage		
T2	284 (43.4%)	
T3a	234 (35.8%)	
≥T3b	136 (20.8%)	
Pathology N1 stage	40 (6.1%)	
Pathology Gleason score		
≤7	390 (59.6%)	
8	113 (17.3%)	
≥9	151 (23.1%)	
Prostate volume, g	31.5±14.9 [21.6; 37.3]	
Tumor volume (%)	23.5±22.3 [8.0; 30.0]	
Operation type		
Open	282 (43.1%)	
Robot	372 (56.9%)	
Positive surgical margin	354 (54.1%)	
Radiation therapy	113 (17.3%)	
Biochemical recurrence	281 (43.0%)	
CRPC	23 (3.5%)	43 (21.0%)
Mortality	63 (9.6%)	91 (44.4%)

[] = interquartile range, ADT = androgen deprivation therapy, CRPC = castration resistant prostate cancer, PSA = prostate-specific antigen, RP = radical prostatectomy.

113 (17.3%). In the RP group, BCR occurred in 281 patients (43.0%) after a median follow-up duration of 21.9 months. CRPC was detected in 23 patients (3.5%) in the RP group and 43 patients (21.0%) in the ADT group. There were 63 mortality cases (9.6%) in the RP group and 91 (44.4%) in the ADT group.

CSS and OS were significantly higher in the RP group than in the ADT group ($P = .0002$ and $P < .0001$, respectively; Fig. 1A and B). The 5-year CSS rate was 99.1% in the RP group and 91.9% in the ADT group, whereas the 5-year OS rate was 97.1% in the RP group and 69.3% in the ADT group. In the sub-cohort, CSS did not differ significantly between the RP and ADT groups

($P = .3630$; Fig. 2A). The 5-year CSS rate was 92.4% in the RP group and 91.9% in the ADT group. The OS of the sub-cohort was significantly higher in the RP group than in the ADT group ($P < .0001$; Fig. 2B). The 5-year OS rate was 92.4% in the RP group and 69.8% in the ADT group.

Table 3 shows the results of univariate and multivariate analyses of CSS and OS. Multivariate analysis of CSS performed after adjusting for all variables showed that ADT was associated with a higher risk of death than RP (hazard ratio, 2.068; 95% confidence interval, 1.001–4.275; $P = .0498$), whereas for OS, the mortality risk was significantly higher in the ADT group than in the RP group (hazard ratio, 3.218; 95% confidence interval, 2.084–4.969; $P < .0001$).

4. Discussion

The identification of a curative treatment for localized high-risk prostate cancer remains challenging. The use of RP for the treatment of high-risk prostate cancer has increased recently.[9] In this study, primary RP was associated with better CSS and OS than primary ADT in the high-risk cohort. The 5-year OS rates in the RP and ADT groups were 97.1% and 69.3%, respectively, which is consistent with the results of previous studies reporting 5-year OS rates of 72.6% to 95.5%.[10] However, to the best of our knowledge, the outcomes of primary ADT in a localized high-risk cohort have not been reported in detail. According to the European Organization for Research and Treatment of Cancer 30,891 trial, T0–4 N0–2 M0 prostate cancer patients who refused local treatment or had a short life expectancy and were treated with primary ADT had 10-year CSS rates of 75% to 77%.[11] In patients with T1–2 disease treated with primary ADT, the 5-year CSS and OS rates are approximately 92% and 62%, respectively, indicating that primary ADT fails to improve survival compared with conservative management.[12] ADT can increase the risk of metabolic, cardiovascular, and bone complications and decrease quality of life.[13] Therefore, in low-risk prostate cancer patients, the dose of ADT needs to be
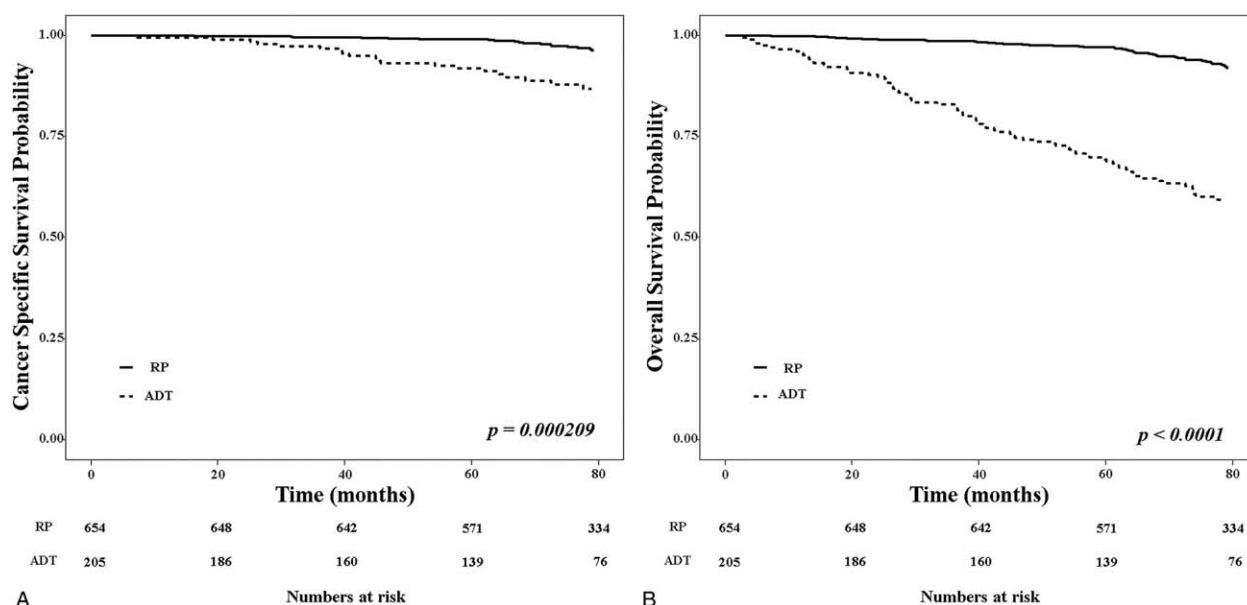
Figure 1. Kaplan–Meier curve of cancer-specific survival (A) and overall survival (B) in the different treatment groups.
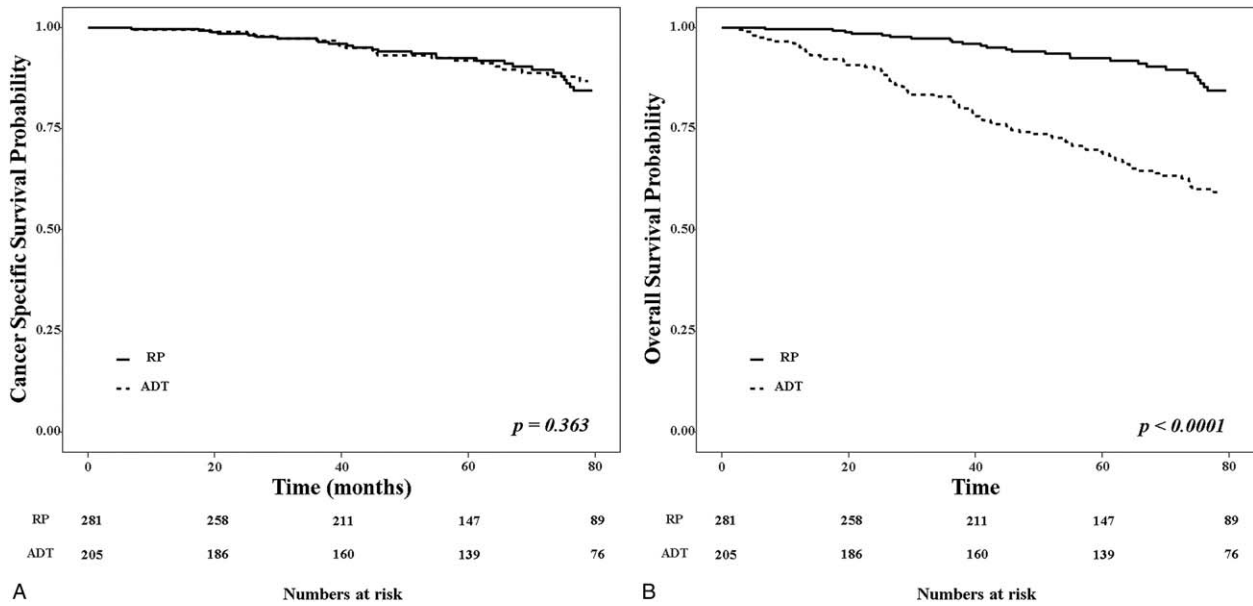
Figure 2. Kaplan–Meier curve of cancer-specific survival (A) and overall survival (B) in the different treatment groups in the sub-cohort.

carefully determined to balance the benefits of treatment against the risk of side effects. In high-risk prostate cancer, the poor antitumor effects of ADT are an issue of concern. In a localized intermediate or high-risk cohort of patients treated with primary ADT, clinical Gleason score 8 or higher and T3a were significant risk factors, and patients who had both factors showed an 8-year OS rate of 16.7%.[14] A high Gleason score is associated with the progression of castration-resistant cells.[15] In this study, a clinical Gleason score of ≥8 was a significant factor for predicting CSS and OS. Patients with risk factors may benefit from more active treatments such as RP or radiotherapy. In our study, radiotherapy was conducted on 113 patients of RP group and in univariate analysis the additional radiotherapy showed improved OS (data not shown). Therefore, active treatments could help to control the disease.

Primary tumors can trigger disease progression and metastasis, which is known as the seed and soil theory.[16] Lindberg et al[17] compared prostatectomy specimens with metastasis samples and confirmed their phylogenetic relationship. Primary tumors contain cancer stem cells, and circulating tumor cells from the primary tumor can have a high metastatic potential.[16] In addition, inflammatory cytokines from the primary tumor can promote cancer progression.[18] The heterogeneity of prostate cancer contributes to its resistance to ADT.[19] ADT is not a radical therapy, whereas RP attempts to eliminate cancer stem cells, cytokines, and the heterogeneity of the primary tumor. In the STAMPEDE trial, radiation therapy to the primary tumor improved OS in low-volume metastatic hormone-sensitive prostate cancer, whereas it had no effect on high-volume disease. This suggests that more active treatment to the primary tumor can be helpful before progression.

ADT can result in castration resistance within 2 to 3 years by triggering androgen receptor mutation, amplification, and the development of variants.[20] In high-risk patients treated with primary ADT, >80% of the cohort progressed to CRPC at 5 years after the initiation of ADT.[21] In the CHAARTED and LATITUDE trials, patients treated with upfront chemotherapy and androgen receptor targeting agents had a better OS than those treated with ADT alone.[22] Combination therapies with ADT affect multiple signaling pathways with antitumor effects,[23] suggesting that ADT alone is insufficient to cure prostate cancer.

In the European Organization for Research and Treatment of Cancer 30,891 randomized trial, deferred ADT showed several

Table 3

Cox hazard analysis of factors affecting cancer-specific and overall survival.

| | Cancer-specific survival | | | | | | | | Overall survival | | | | | | | |
| | Univariate | | | | Multivariate | | | | Univariate | | | | Multivariate | | | |
	HR	95%	CI	P	HR	95%	CI	P	HR	95%	CI	P	HR	95%	CI	P
Age (continuous)	1.060	1.020	1.110	.0040	1.036	0.993	1.081	.1041	1.100	1.070	1.120	<.0001	1.043	1.016	1.071	.0017
Body mass index (continuous)	0.970	0.880	1.060	.4690	0.995	0.903	1.096	.9144	0.900	0.850	0.950	<.0001	0.953	0.899	1.010	.1072
Comorbidity index (≥2 vs 1)	1.410	0.600	3.310	.4250	0.763	0.302	1.925	.5662	3.890	2.710	5.570	<.0001	1.773	1.181	2.719	.0061
PSA (>20 vs ≤20)	1.600	0.930	2.770	.0900	1.153	0.631	2.108	.6427	1.680	1.220	2.310	.0010	1.110	0.781	1.577	.5612
T stage (≥T3 vs ≤T2)	1.070	0.620	1.830	.8110	1.362	0.771	2.406	.2866	0.820	0.600	1.120	.2120	0.903	0.644	1.266	.5532
Gleason score (≥8 vs ≤7)	2.950	1.390	6.250	.0050	3.406	1.500	7.734	.0034	2.240	1.490	3.350	<.0001	1.879	1.209	2.919	.0051
Treatment (ADT vs RP)	2.720	1.570	4.720	<.0001	2.068	1.001	4.275	.0498	5.790	4.200	7.990	<.0001	3.218	2.084	4.969	<.0001

CI = confidence interval, HR = hazard ratio, PSA = prostate-specific antigen.

beneficial effects over immediate ADT regarding quality of life, cost effectiveness, and minimizing the risk of pathologic fractures.[11] RP could delay the initiation of ADT because the use of ADT generally begins after BCR. The Kaplan–Meier curve of CSS in the sub-cohort from the start time of ADT was almost the same in the 2 groups (Fig. 2A), indicating that ADT had no effect on disease progression. However, if RP delays the start of ADT, high-risk patients may benefit from deferred ADT.

Common complications of RP include urinary incontinence and erectile dysfunction. Other complications were bladder neck obstruction, urethral stricture, fistula, deep venous thrombosis, and rectal injury in RP.[24] However, patients treated by RP showed a low risk of urinary obstruction compared with patients in a watchful waiting with ADT group.[25] ADT is associated with side effects that decrease quality of life, such as cardiovascular disease, bone loss, decrease of libido, and depression.[4] In addition, ADT could result in hot flushing, anemia, and fatigue.[24] Johansson et al[25] hypothesized that the psychological score associated with ADT was lower than that of RP because of the immediate consequences of RP, including a positive attitude because of the removed cancer and stronger support from family. In addition, advances in operative techniques including robotic surgery decrease the risk of early urinary incontinence and sexual dysfunction.[26] Among long-term survivors of prostate cancer, including those suffering from complications, patients who undergo RP have a higher quality of life than those receiving other treatments.[27] Good communication regarding tumor biology and the effects of treatment will help patients with high-risk prostate cancer select the most effective treatment.

This study had several limitations. First, this was a retrospective study, which may be associated with selection bias. There were differences in the patient characteristics between groups, and the choice of treatment may be affected by confounders such as patients' or physician's preference. This could limit the generalization of the study results. We therefore adjusted for known risk factors in the multivariate analysis. In addition, to the best of our knowledge, comparison of RP and primary ADT in a high-risk cohort is rare. Second, the next sequencing of systemic therapy after primary ADT was unknown. Although upfront chemotherapy or androgen receptor targeting agent is associated with survival benefits,[22] the identification of new agents could have beneficial effects on the patients. However, this study was performed prior to the publication of recent reports, and the Korean insurance service does not cover new trends; therefore, the effect of next sequencing might be minimal.

5. Conclusion

In clinically localized high-risk prostate cancer patients, primary RP was associated with improved CSS and OS compared with primary ADT. The curative effect of primary ADT is insufficient in high-risk prostate cancer. Indiscriminate use of ADT without considering the benefit for patients should be discouraged even in Asian countries. Comprehensive counseling in this cohort of patients will help the selection of the proper treatment.

Author contributions

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