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A single-center long-term experience of active surveillance for prostate cancer: 15 years of follow-up

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Purpose: To describe a single-center 15-year experience of active surveillance (AS) for prostate cancer (PCa).

Materials and Methods: We retrospectively reviewed patients who underwent AS between 2003 and 2018. One hundred fifty-three patients were selected according to the following criteria: (1) biopsy Gleason pattern ≤3+4 with (2) ≤two positive core(s) and (3) ≤50% core involvement, clinical-stage ≤T2a, and prostate-specific antigen (PSA) ≤20 ng/mL. Follow-up included PSA measurement every six months, prostate biopsies at one year and then every 2–3 years, and MRI every year. Intervention was triggered by (1) Gleason score (GS) upgrading, (2) >two positive cores, or (3) PSA doubling-time in <3 years.

Results: Mean (±standard deviation) follow-up was 36.4 (±31.9) months. Ninety-three (60.8%) and 20 (13.1%) patients received second and third biopsies, respectively. Seventy-two patients (47.1%) discontinued AS for various reasons (59, intervention; 13, follow-up loss). Reasons for intervention consisted of GS upgrading (42.4%), >two positive cores (8.5%), abnormal PSA kinetics (11.9%), and patient preference (37.3%). Notably, 12 (25.5%) patients had pathologic GS ≥4+3 (unfavorable disease) and 3 (6.4%) patients had pathologic stage ≥T3a at radical prostatectomy. Median time to treatment-free survival was 19.5 months. Of the 59 patients who switched to intervention, biochemical recurrence was reported in only one (0.7%) patient.

Conclusions: AS is an available option for low-risk PCa in carefully selected patients. Further larger prospective studies are needed to determine the optimal criteria for AS, especially in Korean PCa patients.

Keywords: Patient selection; Prostatic neoplasms; Watchful waiting

INTRODUCTION

Active surveillance (AS) for low-risk localized prostate cancer (PCa) has long been accepted as an option that can defer radical treatment without sacrificing prognosis, with the recent literature indicating high cancer-specific and overall survival rates [1-3]. However, while the focus of AS is to prevent overtreatment, the criteria for patients eligible for AS, as well as the definition of triggers for intervention, are still controversial and lack comprehensive prospective validation. This is further complicated by the ethnic differences of PCa aggressiveness suggested in Asian populations, where Jeong et al. [4] (2016) found that Korean males had a higher incidence of high-grade (Gleason score ≥8) and

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advanced-stage (pathologic T3 or higher) PCa compared to Western (Caucasian and African-American) populations. In this study, Korean males had statistically significant odds ratios (ORs) of high-grade PCa of 3.48 and 3.14, as well as ORs of 2.40 and 1.59 for advanced-stage PCa compared to Caucasian and African-American males, respectively. A multi-center study further supported this finding. A retrospective analysis of radical prostatectomy (RP) patients revealed an overall 47.5% postoperative upgrading or upstaging in 324 males classified as low-risk [5].

The current criteria for AS are based on Western studies, and validations using Korean populations must be made to identify the optimal criteria for patient selection. However, previous studies conducted in Korea have mainly used only the strictest criteria, and while they produced promising results in terms of outcome, it is questionable whether such stringent selection is feasible in actual clinical practice or accurately represents patient needs and wants to defer active treatment [6,7]. A broader enrollment further offers the chance to avoid overtreatment in low-risk PCa, but further validation is required in long-term cohorts. In this study, we aimed to apply the reported Western AS protocols to patients undergoing AS at a single institution and review a 15-year experience with AS.

MATERIALS AND METHODS

1. Study population

This study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (approval number: B-2004/608-110). It was a retrospective single-institution study comprised of 153 patients undergoing AS from April 2003 to March 2018. The candidates eligible for AS were selected based on (1) Gleason score ≤3+4 (Gleason Group 2), (2) clinical stage ≤T2a, (3) PSA ≤20 (ng/mL), and (4) ≤2 positive cores, with maximum involvement rate in any core ≤50% on a 12-core biopsy, which were less stringent criteria than in foreign studies [1,8]. Standard 12-core transrectal ultrasound (TRUS) were performed for initial biopsies, and magnetic resonance imaging (MRI) fusion biopsies were done based on the clinician's discretion and/or if suspicious lesions were identified on MRI. Computed tomography or MRI findings were not included as selection criteria to reflect clinical practice in the early years. Clinicopathological data included the age at diagnosis, the follow-up duration, PSA and PSA density, Gleason scores, the number of positive cores, and pathological outcomes for those who underwent radical prostatectomies. A regular outpatient follow-up included PSA measurements every six months, prostate biopsies at one year and then every 2 to 3 years, and MRI every year. An intervention was triggered in cases of (1) Gleason score upgrading, (2) >two positive cores, or (3) a PSA doubling-time of <3 years.

All data were collected from our prospectively maintained database, and pathological specimens were reviewed in detail by our uropathologist according to standard pathological procedures using the modified definition of the 2005 International Society of Urological Pathology Consensus conference [9]. Tumor stage and grading were evaluated according to the 2002 American Joint Committee on Cancer (AJCC)/Union Internationale Contre le Cancer (UICC) TNM classification.

2. Statistical analyses

The statistical analyses of the clinicopathological variables were performed by the Chi-squared test for the categorical variables and an independent t-test for the continuous variables. A treatment-free (intervention-free) survival curve was generated by Kaplan–Meier analysis. Statistical analyses were performed with IBM SPSS software package version 21.0 (Statistical Package for Social Sciences™; IBM Corp., Armonk, NY, USA). A 2-tailed p-value <0.05 was considered significant for all analyses.

RESULTS

A total of 153 patients were selected for analysis, and the mean and median ages at diagnosis were 66.1 years and 68.0 years, respectively (range, 41–77 years) (Table 1). The mean and median follow-up periods were 36.4 months and 26.0 months, respectively (interquartile range, 13.5–49.0 months). The average PSA levels at diagnosis were 6.36 ng/mL and 126 (82.4%) patients had a PSA of less than 10 ng/mL. Mean and median cores biopsied were 12.3 and 12.0 cores, respectively. One hundred forty-two (92.8%) patients had a Gleason score of 6 (GG1) and 11 (7.2%) patients had a Gleason score of 7 (3+4) (GG2). The patients had a mean of 1.3 positive cores. One hundred twelve patients (73.2%) had a single positive core at biopsy, and all GG2 patients had one positive core. One hundred twenty-two (79.7%) patients had a maximal core tumor involvement rate of less than 20%. The mean PSA density (PSAD) was 0.18 ng/mL/cc, and 106 (69.3%) patients had less than 0.2 ng/mL/cc. Mean and median TRUS volume was 37.6 and 34.8 mL, respectively. One hundred one (66.0%) and 52 (34.0%) patients had a clinical T stage of T1 and T2a, respectively.

Out of the 153 patients, a total of 13 (8.5%) patients were lost to follow-up or converted to watchful-waiting, 59 (38.6%)

patients underwent intervention, with 81 patients were currently enrolled in AS (Fig. 1, Table 2). A repeat biopsy at one year and every 2–3 years on follow-up was done in 93 (60.8%) and 20 (13.1%) patients, respectively. Intervention was triggered due to either GS upgrading (25 patients, 42.4%), >2 positive cores on follow-up biopsy (5 patients, 8.5%), elevated PSA (7 patients, 11.9%), or patient preference (22 patients, 37.3%).

Ten patients underwent additional hormonal therapy (HT) and one patient underwent radiation therapy (RT). Out of the 10 patients who underwent HT, 3 patients were due to GS upgrade, 3 patients due to >2 positive cores, and 4 due to patient preference (Fig. 1). Forty-eight patients underwent RPs, either robotic, laparoscopic, or open. Twelve (25.5%) RP patients had a pathologic upgrading of GS ≥7 (4+3), and three (6.4%) patients were upstaged to ≥T3a. Biochemical recurrence (BCR), defined as PSA progression after intervention, was observed in one patient. The mean and median time to treatment-free survival was 19.5 months (95% confidence interval [CI], 15.971–23.012) and 14.0 months (95% CI, 11.950–16.050), respectively (Fig. 2). In logistic regression analysis, maximal percentage of core involvement was significantly associated with risk of intervention (HR, 1.145; 95% CI, 1.045–1.255; p=0.004). A subanalysis for patients with the strictest criteria (Gleason score ≤3+3, clinical stage ≤T2a, PSA ≤10 ng/mL, and ≤2 positive cores with maximum involvement rate in any core ≤20%) found no difference in

Table 1. Baseline characteristics among 153 patients undergoing AS

Characteristic	Value
Total number of patients	153
Age at diagnosis (y)	66.1±8.2
Follow-up periods (mo)	36.4±31.9
PSA at diagnosis (ng/mL)	6.36±3.45
PSA at diagnosis (ng/mL), ≤ 10	126 (82.4)
Gleason score	
6	142 (92.8)
7 (3+4)	11 (7.2)
Positive cores, 1	112 (73.2)
Maximum % cancer, ≤ 20	122 (79.7)
PSAD, <0.2	106 (69.3)
Clinical T stage	
T1	101 (66.0)
T2a	52 (34.0)
Total number of biopsy, 1st/2nd/3rd	153 (100)/93 (60.8)/20 (13.1)

Values are presented as number only, mean±standard deviation, or number (%).
AS, active surveillance; PSA, prostate-specific antigen; PSAD, PSA density.

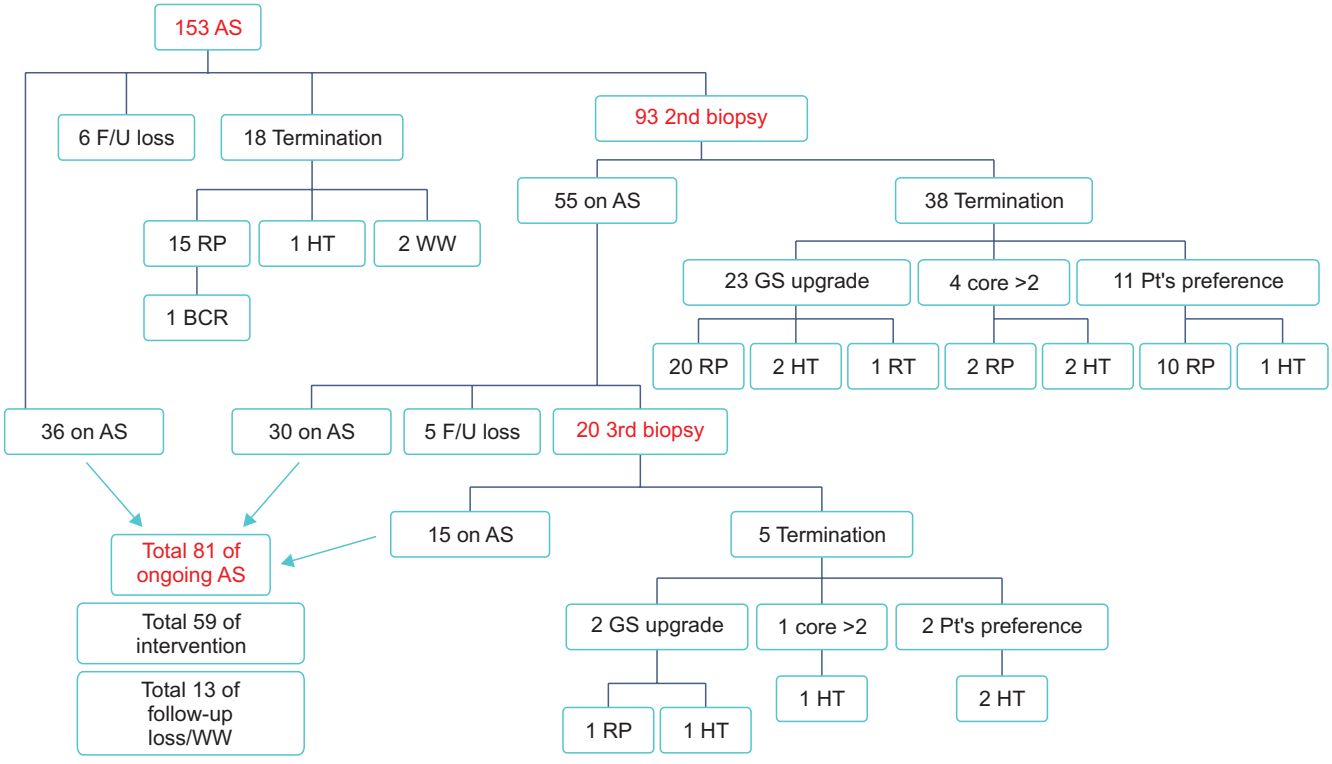

Fig. 1. Flow chart for active surveillance (AS). Of the 153 males on AS, 93 and 20 males underwent 2nd and 3rd follow-up biopsies. Eighteen patients discontinued AS before the 2nd biopsy, 38 patients prior to 3rd biopsy, and 5 patients after 3rd biopsy. Total of 81 patients are currently under ongoing AS. F/U, follow-up; RP, radical prostatectomy; HT, hormone therapy; RT, radiation therapy; WW, watchful waiting; BCR, biochemical recurrence; GS, Gleason score; Pt, patient.

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Table 2. Outcomes of intervention

Outcomes	Value
Interventions	59 (38.6)
HT	10 (16.9)
RT	1 (1.7)
RP	48 (81.4)
Time to intervention, months	19.5±13.8
Triggers for intervention	
GS upgrading	25 (42.4)
Positive cores, >2	5 (8.5)
PSA elevation	7 (11.9)
Patient preference	22 (37.3)
RP pathology (n=48, missing=1)	
Pathologic GS, ≥7 (4+3)	12 (25.5)
Pathologic GS, ≥8	0 (0.0)
Pathologic T stage, ≥ T3a	3 (6.4)
BCR, yes	1 (0.7)

Values are presented as number (%) or mean±standard deviation.
HT, hormonal therapy; RT, radiation therapy; RP, radical prostatectomy; GS, Gleason score; PSA, prostate specific antigen; BCR, biochemical recurrence.

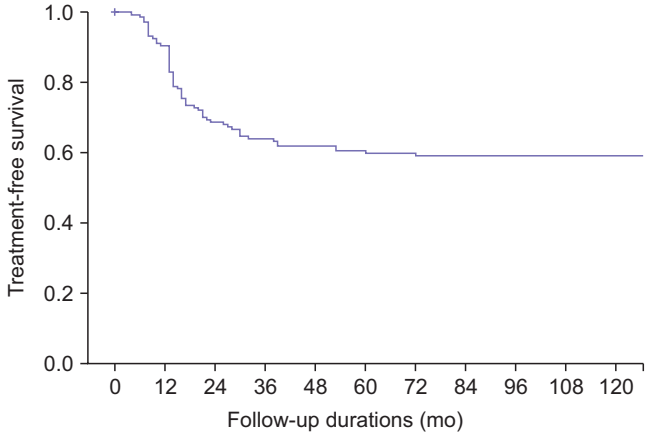

Fig. 2. Kaplan–Meier curve for treatment-free survival. Mean time-to-treatment was 19.5 months (95% CI, 15.971–23.012), and median was 14.0 months (95% CI, 11.950–16.050). Thirteen (8.5%) patients underwent intervention by 12 months, 45 (29.4%) patients by 24 months, and 55 (35.9%) males by 48 months follow-up. CI, confidence interval.

rate of intervention and BCR between the two groups (37.5% vs. 33.3%, p=0.684 for rate of intervention and 8.9% vs. 2.8%, p=0.244 for rate of BCR, respectively).

DISCUSSION

AS has long been suggested for low-risk tumors in select patients where careful monitoring is possible and immediate treatment is unnecessary. The critical challenge is where to draw the line between maximizing the number of patients who can avoid active treatment and the associated side effects, and at the same time minimizing the probability of missing aggressive or high-risk cancer. This is perhaps most relevant in Korea, where the prevalence of PCa increased from 9,881 to 86,435 between 2000 to 2017, making it the fourth most frequently diagnosed cancer in males, causing a steep increase in medical costs and economic burdens [10-12]. However, previous reports have suggested that Korean patients are more likely to harbor more aggressive PCa features than Western males, with implications that more stringent criteria must be applied to safely select patients for AS [13]. Reasons described in previous literature for such disparities include not only dietary and socioeconomic factors that led to an earlier diagnosis in Caucasian males, but also multiple genetic polymorphisms identified more frequently in Asian subpopulations compared to their Caucasian or African-American counterparts [14,15]. In a multi-institutional analysis using the Korean Prostate Cancer Database, Koo et al. [13] (2017) found that Korean patients who were eligible for AS based on conventional Western criteria had a lower rate of organ-confined GS ≤ 6 disease (56.1% in Korean males vs. 69.2% in a similar representative Western group), as well as higher rates of extracapsular extension and pathological upgrading (12.9% vs. 4.1%, 42.3% vs. 27.8%, respectively) [16]. This racial disparity, as well as a relatively low economic burden for active treatment, has caused a general preference for early intervention and the underuse of AS in the Korean population [11], as represented in the high intervention rate (38.6%) and early time to intervention (mean 19.5 months) in our study.

Taking these factors into consideration, there is a clear need to establish inclusion criteria for AS in Korea that can produce comparable results to our Western counterparts. Previous literature produced at Johns Hopkins, the University of Toronto, Memorial Sloan Kettering Cancer Center (MSKCC), and Prostate Cancer Research International (PRIAS) used slightly varying criteria for patient selection, but commonly included biopsy GS ≤6, clinical-stage ≤T1c–T2a, PSA ≤10–15, ≤2 biopsy cores, and a maximal cancer involvement rate in any core of ≤20%–50% [1,17-19]. The Royal Marsden and University of Toronto extended the entry criteria to GS 7 (3+4) for ages ≥65 and 70 years in their follow-up reports, and currently, the AUA and NCCN guidelines support this decision, listing AS as an option for favorable intermediate-risk PCa, further including PSA values ≤10–20 ng/mL [20,21]. Meanwhile, guidelines for Korean populations have not yet been established and differ between institutions. Ha et al. [6] (2017) published an 8-year follow-up report with the most stringent criteria of biopsy GS ≤6, clinical-

stage ≤T1c, PSA ≤10 ng/mL, one bipsy core, and negative MRI findings, whereas Jeong et al. [7] (2018) developed new selection criteria to include the clinical T2a stage, as well as a PSA density of <0.15 ng/mL/mL, and ≤2 positive cores among 10 or more total biopsy cores, with maximal core involvement in any core ≤20% [6]. Both criteria were stricter than contemporary Western studies, with relatively better outcomes in the rate of unfavorable disease and recurrence-free survival. However, applying an excessively strict protocol will unavoidably lead to the overtreatment of low-risk PCa, as shown in an epidemiological study in 2015 where mortality increased only by 3.3 deaths per 100,000 people (2.3 to 5.6) while the prevalence increased 6-fold (3.3 to 20.4) from 2000 to 2011 [22]. Thus, further assessment must be made to determine whether broader eligibility criteria can be applied to produce optimal outcomes.

Our study attempted to review a 15-year single-institution experience with AS based on well-established, Western multi-center reports, with broader selection criteria to include GS ≤3+4, ≤ two positive core(s) with ≤50% core involvement, clinical-stage ≤2a, and PSA ≤20 ng/mL. Contrary to the expected drawbacks of a liberal enrollment as suggested in previous literature, the results showed a relatively low rate of unfavorable disease [pathologic GS ≥7 (4+3), 25.5%] and ≥pathologic T3a (6.4%) at RP, with a single incidence of BCR (0.7%). These results are consistent with previous RP pathology in Western AS cohorts, where the percentage of unfavorable disease and ≥T3a pathologic staging were 29% and 18.0%, respectively, in the PRIAS protocol, and 25.3% and 36.5%, respectively, in a multi-institutional European cohort [23,24]. While previous literature on AS have cited clinicopathologic factors such as number of positive cores, percent core involvement, and PSA density as predictors of increased risk of intervention [1,25,26], only maximal percentage of core involvement was significantly associated with risk of intervention in our results (HR, 1.145; 95% CI, 1.045–1.255; p=0.004), which may be due to a relatively small sample size. While ≤50% maximal percentage of single core involvement was included to reflect the most liberal enrollment criteria in reported Western cohorts [27], previous report on Korean males by Jeong et al. [4] have also reported significant similar association with a hazard ratio of 1.02 (95% CI, 1.01–1.03; p<0.001). While these results may suggest a stricter application of single core positivity, patients with over 20% core involvement constituted only 3 (2.0%) males in our cohort, and would not have significantly affected our results. However, a future analysis with more patients at our institution is certainly indicated.

Our study had several limitations. First, the mean and median follow-up duration was 36.4 and 26.0 months, respectively, which is comparable to early reports (median range 1.8 to 3.9 years) [27] but still relatively shorter than the latest literature with a median follow-up of 68 to 102 months. This was due to a change in our institutional practice whereby AS enrollment was less preferred in the early 2000s when only seven patients were selected for AS from 2003 to 2005. However, the numbers dramatically increased in the 2010s when 69 patients were enrolled from 2015 to 2017. These trends also explain the low rate of BCR in the study, as the total span of this study was too short to fully estimate cancer-related or overall survival. More clinical value can be expected in later years as more patients are collected. Also, the MRI findings and PSA density were omitted in the entry criteria as to reflect early practices, despite recent 11 (7.2%) patients having underwent initial MRI fusion biopsies. However, literature supporting the necessity of including such factors are limited and did not accurately represent early practices. As more patients recently enrolled are being offered MRI fusion biopsies rather than the standard 12-core TRUS biopsy, further analysis of whether biopsy modalities affect AS outcome may be worthwhile in future analyses. In addition, while GS 7 (3+4) was included in our analysis, these patients constituted only 7.2% of the total cohort, so the actual mature effect of its incorporation may be questioned. However, of the 11 (7.2%) males who were intermediate risk, 5 patients underwent intervention, with 4 males undergoing RP and 1 HT. Treatment-free patients was similar to the overall population and did not significantly affect our results (mean time to treatment-free survival 19.8 months and median 14.0 months). As retrospective studies of intermediate-risk RP patients displayed higher rates of adverse pathology, further reassessment limiting the criteria to GS ≤6 (3+3) is warranted [26].

Despite these limitations, our study showed that Western criteria for AS can be applied to Korean populations without risking early BCR or adverse pathology on RP. These results suggest that AS can be safely implemented in Korea, especially if optimal protocols and criteria are established. Future prospective trials and large scale studies are required to further refine enrollment guidelines.

CONCLUSIONS

As the incidence of clinically significant PCa continuously increases in the Asian population, selection for individualized approaches, including AS, becomes more and more crucial. Outcomes from our single institution AS cohort showed broad criteria based on Western guidelines to be a feasible

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option in a Korean population, despite previous literature describing more aggressive PCa in Asian males. AS can be a practical treatment option in carefully selected males. However, further prospective trials are required to refine the current guidelines and establish the optimal criteria.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Jung Kwon Kim and Seok-Soo Byun. Data acquisition: Jung Kwon Kim, Hakmin Lee, Sangchul Lee, Sung Kyu Hong, and Seok-Soo Byun. Statistical analysis: Jung Kwon Kim. Data analysis and interpretation: Sang Hun Song and Jung Kwon Kim. Drafting of the manuscript: Sang Hun Song and Jung Kwon Kim. Critical revision of the manuscript: Jung Kwon Kim and Seok-Soo Byun. Administrative, technical, or material support: Hakmin Lee, Sangchul Lee, Sung Kyu Hong, and Seok-Soo Byun. Supervision: Seok-Soo Byun. Approval of the final manuscript: Jung Kwon Kim and Seok-Soo Byun.

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