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Early Experience With Active Surveillance in Low-Risk Prostate Cancer Treated

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Purpose: This study was conducted to describe our early experience with active surveillance (AS).

Materials and Methods: Between January 2008 and December 2012, 35 patients were treated with AS. Selection criteria included the following: Gleason score ≤6 with single positive core, clinical stage ≤T1c, prostate-specific antigen (PSA) ≤10 ng/mL, and unremarkable imaging results. On patient follow-up, we regularly measured PSA (every 3–6 months) and performed prostate biopsies (after 1 and 3 years).

Results: In the first year of follow-up, prostate biopsies were performed in 25 patients (13 patients, negative for cancer; 7 patients, Gleason score of 6 without progression; 5 patients, progression, treated with radical prostatectomy [RP]). In the third year of follow-up, prostate biopsies were performed in five patients (two patients, negative for cancer; one patient, Gleason score of 6 without progression; two patients, progression, treated with RP). Seven patients discontinued AS because of increased anxiety, and three patients were lost to follow-up. Overall, seven patients (28%) who experienced progression had a mean PSA doubling time (DT) of 7.54 years. Six patients had a PSA DT of more than 3 years, whereas one had a PSA DT of less than 3 years. This study was limited by its small sample size and short follow-up period.

Conclusions: PSA kinetics did not correlate with progression, which suggests that regular biopsies should still be performed. AS is an available treatment option for patients with a low risk of prostate cancer but should only be used in carefully selected patients.

Keywords: *Needle biopsy; Prostate-specific antigen; Prostatic neoplasms; Watchful waiting*

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INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer in males worldwide, and the incidence of PCa in Korean men is increasing [1,2]. With the onset of widespread prostate-specific antigen (PSA) testing, resulting in earlier detection of low-risk PCa, the incidence of clinically insignificant PCa has increased proportionately. The changing landscape of PCa has led to concerns regarding overdiagnosis and overtreatment.

Active surveillance (AS) is different from watchful waiting or delayed treatment in that active treatment will be initiated if disease progression becomes apparent at follow-up [3]. In recent years, AS has been more frequently offered as treatment for low-risk PCa [4,5], but this is not the case in Korea.

This study was conducted to describe our early experience with AS.

MATERIALS AND METHODS

1. Patient population

Clinical data were collected retrospectively from 35 patients were placed on AS as a treatment for PCa, between January 2008 and December 2012.

TABLE 1. Comparison of inclusion criteria for active surveillance by institution

Institution	Clinical T stage	PSA (ng/mL)	Gleason score	Positive cores	Single core positivity	Other
Johns Hopkins [3]	≤T1c	-	≤3+3=6	≤2	≤50%	PSAD≤0.15
Toronto University [7]	≤T2a	≤10.0	≤3+3=6	-	-	-
UCSF [10]	≤T2a	≤10.0	≤3+3=6	≤33%	-	-
ERSPC (PRIAS) [8]	≤T2a	≤10.0	≤3+3=6	≤2	-	PSAD≤0.2
MSKCC [11]	≤T2a	≤10.0	≤3+3=6	≤3	≤50%	-
Miami University [12]	≤T2a	≤10.0	≤3+3=6	≤2	≤20%	-
Kagawa University [9]	≤T1c	≤20.0	≤3+3=6	≤2	-	-
Keimyung University	≤T1c	≤10.0	≤3+3=6	1	-	MRI: negative

PSA, prostate-specific antigen; PSAD, PSA density; UCSF, University of California San Francisco; ERSPC, European Randomized Study of Screening for Prostate Cancer; MSKCC, Memorial Sloan Kettering Cancer Center; MRI, magnetic resonance imaging.

2. Criteria for AS

The selection criteria for AS included a biopsy-derived Gleason score ≤6 in a single positive core, clinical stage ≤ T1c, PSA ≤10 ng/mL, and unremarkable magnetic resonance imaging (MRI) results [3,6-12] (Table 1). Biopsy with transrectal ultrasonography was done using the 12-core biopsy scheme.

3. Follow-up

During follow-up, PSA was measured every 3–6 months, and prostate biopsies were performed at 1 and 3 years. The first-year confirmatory biopsy was intended to identify higher-grade cancer that had been missed in the previous biopsy [7].

4. Prediction of disease progression

Patients were reclassified as needing earlier prostate biopsy when the PSA doubling time (DT) was less than 3 years or suspicious clinical progression was observed. The PSA DT was calculated by using the following formula: PSA DT=log2×dT/(log B–log A), where A is the initial PSA measurement, B is the final PSA measurement, and dT is the time difference between the calendar dates of the two PSA measurements [13].

5. Criteria for intervention

Definitive intervention was offered to those patients with Gleason score progression (an increase to 7 or greater) or an increase in the number of positive biopsy cores (to two or more than one lobe).

RESULTS

Overall, the mean age of the patients was 68 years (range, 55–80 years), the mean PSA was 7.38 ng/mL (range, 2.37–10.00 ng/mL), the mean prostate volume was 44.8 mL (range, 20.0–120.0 mL), the mean Gleason score was 4.97 (range, 3–6), the mean PSA density (PSAD) was 0.14 ng/mL (range, 0.05–0.5 ng/mL), and the mean PSA DT was 5.16 years. All of the patients had favorable risk. The mean follow-up duration was 32 months (range, 12–46 months) (Table 2).

TABLE 2. Characteristics of the patients

Variable	Value
No. of patients	35
Age (y)	68 (55–80)
PSA (ng/mL)	7.38 (2.37–10.00)
Prostate volume (mL)	44.8 (20.0–120.0)
Gleason score	4.82 (3.00–6.00)
Follow-up duration (mo)	32 (12–46)

Values are presented as mean (range).
PSA, prostate-specific antigen.

In the first year of follow-up, repeat biopsies were performed in 25 patients (71.4%) (13 patients, negative for cancer; 7 patients, Gleason score of 6 without progression; 5 patients, progression). All five patients with progression had a PSA DT of more than 3 years. Three of the five patients whose cancers progressed underwent radical prostatectomy, whereas the other patients requested a transfer to another hospital of their choice.

In the third year, repeat biopsies were performed in five patients (two patients, negative for cancer; one patient, Gleason score of 6 without progression; two patients, progression, treated with radical prostatectomy). Of the two patients with progression, one had a PSA DT of more than 3 years, whereas the other patient had a PSA DT of less than 3 years.

Before the scheduled first-year follow-up visit, three patients were lost to follow-up, whereas seven patients discontinued AS because of increased anxiety. Of these seven patients, four underwent radical prostatectomy, whereas the remaining three patients were treated with antiandrogens based on their age and/or preference (Fig. 1).

Overall, eight patients had a PSA DT of less than 3 years and underwent prostate biopsy earlier. Only one of these patients had cancer progression. Of the seven patients with progression, six (85.7%) had a PSA DT of more than 3 years. and one (14.3%) had a PSA DT of less than 3 years (Table 3). Seventeen patients (48.6%) discontinued AS, for several reasons (Table 4). The mean PSA DT was 7.54 years in the seven patients (28%) whose cancer progressed. Five pa-

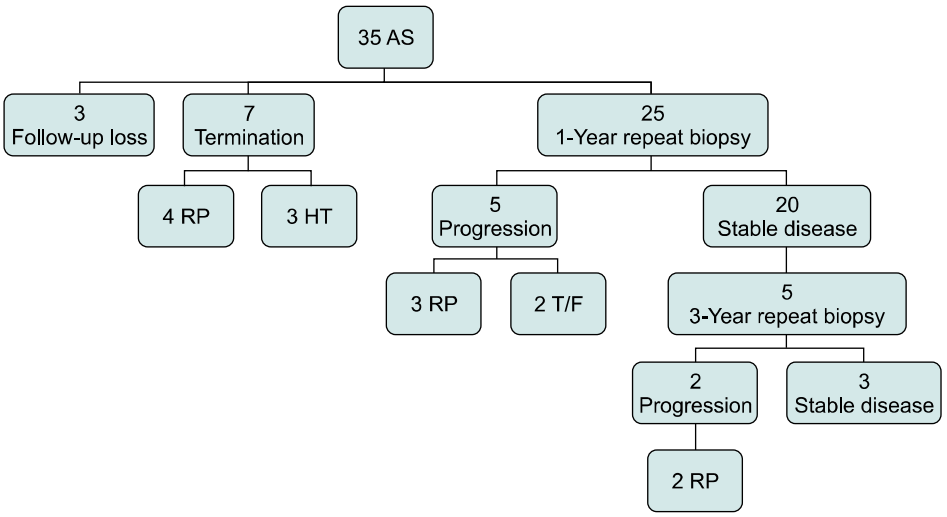

FIG. 1. Flow chart of AS in 35 patients. AS, active surveillance; RP, radical prostatectomy; HT, hormone therapy; T/F, transfer.

TABLE 3. Stratification by baseline Gleason score and PSA doubling time

Variable	No. of patients	Progression	
		1 y	3 y
Gleason score			
3	1	0	0
4	4	1	0
5	2	1	0
6	28	3	2
PSA doubling time (y)			
>3	27	5	1
≤3	8	0	1
Total	35	5	2

PSA, prostate-specific antigen.

TABLE 4. Reasons for termination on surveillance (n=35)

Reason	No. of patients (%)
Radical prostatectomy	9 (25.7)
Progression	5 (14.3)
Patients preference	4 (11.4)
ADT (patients preference)	3 (8.6)
Transferred (progression)	2 (5.7)
Follow-up loss	3 (8.6)
Total	17 (48.6)

ADT, androgen deprivation therapy.

tients with cancer progression underwent radical prostatectomy (Table 5), four of whom had organ-confined disease and one of whom had extracapsular extension.

DISCUSSION

In the current PSA era, most patients with an initial diagnosis of localized PCa are considered to be the most likely to achieve a cure. Current treatment options for patients with localized PCa vary—radical prostatectomy, radiotherapy, cryotherapy, androgen ablation therapy, and AS [14].

Since first being introduced in 2002, AS—the concept of which is to cure clinically significant PCa prior to the development of advanced disease—is now an accepted treatment strategy for patients with PCa [4,6]. However, AS is still underused in the United States and is rarely used in Korea [15]. Patients and/or their physicians appear to want to treat PCa once it is diagnosed [6]. In our study, the 10 patients (28.6%) who discontinued AS did not have cancer progression and had a sufficient understanding of AS before it was initiated.

AS may reduce the risk of overtreatment of clinically insignificant PCa, but the individual risk of disease progression is difficult to determine. The first attempt to identify potentially low-risk PCa was described by Epstein et al. [16,17]. Their description focused on disease with clinical stage T1, a Gleason pattern score ≤3, a PSAD ≤0.1 ng/mL/g, two or fewer positive cores, and no cores with >50% involvement. For contemporary AS protocols, most clinicians incorporate the criteria of a low Gleason score (≤6), a low clinical stage (≤T2a), and low PSA values (≤10 ng/mL) with estimates of tumor volume from the biopsy when selecting patients [18]. We also used a similar but stricter criteria to select patients: clinical stage (≤T1c), one positive core (minimum of 12 cores taken), and negative imaging result. Most patients with low-risk PCa have normal ultrasonographic findings. MRI offers advantages over other imaging techniques for the detection of PCa [10]. Recently, MRI with various imaging techniques has improved tumor detection [19,20]. We think that a tumor undetected by MRI may belong to a more favorable risk group.

PSA kinetics have generally been used to predict disease progression. However, the PSA values over time that can predict disease progression during AS remain unknown [18]. Klotz et al. [7], the Johns Hopkins group [21], and the University of California San Francisco cohort [22] focused on PSA kinetics to determine the triggers indicating that AS should be discontinued. However, no correlations were

TABLE 5. Pathological findings in men with disease progression

Follow-up at progression (y)	Biopsy findings at progression					Radical prostatectomy findings	
	PSA	PSA DT (y)	Positive cores	Glesaon score	Extracapsular extension	Gleason score	Pathologic T stage
1	2.69	12.08	2	3+3=6	Absent	3+3=6	T2c
1	3.31	7.56	2	3+3=6	Absent	3+3=7	T2c
1	6.68	3.85	2	3+3=6	Absent	3+3=6	T2c
3	5.66	−2.77	1	3+4=7	Absent	3+4=7	T2a
3	10.18	1.29	2	4+4=8	Present	4+3=7	T3a

PSA, prostate-specific antigen; PSA DT, prostate-specific antigen doubling time.

found between the PSA DT and adverse pathologic findings from the surveillance biopsy. In our study, the PSA DT was not associated with cancer progression on biopsy. The eight patients (22.8%) who had a PSA DT of <3 years underwent biopsy earlier, but only one patient had cancer progression. Most patients who had a longer PSA DT did not experience cancer progression during AS. Before a patient decides to undergo definitive intervention, we believe that they should first elect to have a repeat biopsy and be reclassified.

The objective endpoint in an AS series is the number of patients remaining on surveillance after a specified time interval [18]. Several studies that have described the incidence of those who received active treatment during AS report that it ranges from 11% to 32% [7,8,11,23-25]. In our study, 17 patients (48.6%) discontinued AS for several reasons. However, only five patients (14.3%) ultimately received radical prostatectomy after progression. This fact is noteworthy. Patients in Korea want to be treated even if, based on the Epstein criteria, they have clinically insignificant PCa [26,27]. This is partly because of the health insurance system.

Kakehi et al. [9] demonstrated that, given the low mortality from PCa in Asian patients compared with Western patients, AS is a more appealing option for Asians. However, in our study, Korean PCa progression rates appear to be higher than those of other western institutions despite our implementation of stricter patient selection criteria. According to another study conducted in Korea, most patients with low-risk PCa detected on multicore prostate biopsy actually had pathologically upgraded or upstaged disease after examination of the radical prostatectomy specimen [28,29]. We think that AS is a reasonable option for low-risk PCa. However, this strategy is difficult to implement in Korea. In order to carry out AS more safely, optimal patient selection and accurate monitoring using new biomarkers and imaging tools are needed.

This study was limited by its small sample size and short follow-up period. Hence, a statistical analysis was not possible. Additional studies are needed to confirm the nature of low-risk PCa in Korea and to define the appropriate criteria for determining patient selection and cancer progression for AS.

CONCLUSIONS

PSA DT did not correlate with the progression of PCa, which suggests that regular biopsies should still be performed while monitoring for cancer progression. Interestingly, progression of PCa during AS resulted in the dissolution of the patient-doctor relationship and resulted in the patients transferring to another hospital. AS is a treatment option for low-risk PCa patients, but is a strategy that is difficult to implement in Korea.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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