



Research Article

Clinical experience with active surveillance protocol using regular magnetic resonance imaging instead of regular repeat biopsy for monitoring: A study at a high-volume center in Korea



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ARTICLE INFO

Article history:

Received 10 March 2020

Received in revised form

3 November 2020

Accepted 9 November 2020

Available online 5 December 2020

Keywords:

Active surveillance

Magnetic resonance imaging

Prostatectomy

Prostatic neoplasms

ABSTRACT

Background: Here, we report the experience of a multiparameter magnetic resonance imaging (MRI)–based active surveillance (AS) protocol that did not include performing a repeat biopsy after the diagnosis of prostate cancer by prostate biopsy or transurethral resection of prostate.

Methods: From January 2010 to December 2017, we reviewed 193 patients with newly diagnosed prostate cancer who were eligible for AS. The patients were divided into AS group (n = 122) and definitive treatment group (n = 71) based on initial treatment. Disease progression was defined as a remarkable change in MRI findings. To confirm the stability of protocol, we compared the clinicopathological characteristics of patients who initially underwent radical prostatectomy (RP) (n = 58) and RP after termination of AS (n = 20).

Results: Among patients who initially selected AS (median adherence duration = 31.4 months), 70 (57.3%) subsequently changed their treatment options. Disease progression (n = 30) was the main cause for termination. No significant differences were found in the clinicopathologic characteristics at initial diagnosis and pathologic outcomes between patients who initially underwent RP and those who chose RP after termination of AS. In a comparative analysis of diagnostic methods, the patients with incidental prostate cancer by transurethral resection of prostate had higher age, lower prostate-specific antigen level and density, as well as longer AS adherence duration and follow-up duration compared with those diagnosed by prostate biopsy.

Conclusions: Our AS monitoring protocol, which depends on MRI instead of regular repeat biopsy, was feasible. Patients with incidental prostate cancer continued AS more compared with patients diagnosed by prostate biopsy.

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1. Introduction

The treatment options for localized prostate cancer are varied, ranging from definitive therapies, such as radical prostatectomy (RP) and radiotherapy, to conservative follow-up strategies, such as active surveillance (AS) and watchful waiting of localized prostate cancer patients.^{1–3} So far, RP is the most widely chosen treatment option.⁴ Recently, owing to concerns of over-diagnosis and over-treatment of prostate cancer, AS is increasingly being offered as an alternative treatment option for low-risk prostate cancer patients. However, patients who would benefit from different

treatment regimens must be selected. To select suitable patients and monitor their disease status, several standard protocols using prostate-specific antigen (PSA) levels, Gleason score, clinical stage, tumor involvement, number of positive biopsy cores, and PSA density have been suggested.^{5–8} However, various criteria, including clinical and pathological characteristics, have been proposed based on several protocols.

Our institution investigated how an existing AS protocol, the Prostate Cancer Research International: Active Surveillance protocol,⁹ could be modified for Korean patients. The usefulness of multiparametric magnetic resonance imaging (MRI) for the selection, monitoring, and management of patients on AS was investigated. Low-risk prostate cancer patients with no visible tumor on MRI qualified for AS.¹⁰ Moreover, the presence of a suspected tumor lesion of ≤ 1.0 cm in diameter on MRI improved the prediction of

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insignificant prostate cancer.¹¹ In cases of incidental prostate cancer diagnosed by transurethral resection of prostate (TURP), clinical outcomes were satisfactory regardless of the initial treatment, such as AS, RP, or androgen deprivation therapy.¹² Based on these preliminary analyses, we relied on regular follow-up MRI and PSA testing for clinical decision-making regarding intervention during follow-up instead of regular repeat biopsy. The primary end points of this report were to establish a protocol and clinical features of regular follow-up MRI and PSA testing. The secondary end points were to compare the AS outcomes according to diagnostic methods (biopsy vs. TURP).

2. Materials and methods

2.1. Patient cohort

The present study was approved by our institutional review board. We reviewed the data of all patients newly diagnosed with prostate cancer who were eligible for AS and presented at our institution between January 2010 and December 2017. The patients' clinicopathologic data, including age, body mass index, Charlson comorbidity index, PSA level, prostate volume, disease staging according to the 7th edition of the American Joint Committee on Cancer, and initial treatment options were obtained.

2.2. Criteria for AS in our institution

The criteria for AS included patients diagnosed with prostate cancer by prostate biopsy using the 12-core biopsy scheme, PSA level ≤ 10 ng/mL, PSA density < 0.15 ng/ml/g, Gleason grade group ≤ 2 within two positive cores, and a clinical stage of cT1–cT2 (a suspected tumor lesion ≤ 1.0 cm in diameter). For patients diagnosed with incidental prostate cancer with TURP, the AS enrollment criteria were clinical stage of cT1a, cT1b (enrollment with $< 16.7\%$ of positive chips, considering % of positive core (2/12) for patients diagnosed with prostate biopsy), or cT2 (a suspected tumor lesion ≤ 1.0 cm in diameter), as well as Gleason grade group ≤ 2 , PSA level ≤ 10 ng/ml, and PSA density < 0.15 ng/ml/g.

2.3. Follow-up and outcomes

All patients eligible for AS received an explanation of the treatment options available for their particular cases, including AS, radiotherapy, RP, and androgen deprivation therapy. To promote understanding of the characteristics of each treatment option, we provided a guidebook written by our urology department, which contained information on prostate cancer treatment options and monitoring methods.

For the patients enrolled in the AS registry, PSA levels were measured every 3–6 months, and MRI was performed every year or if PSA levels increased more than two times consecutively. A definitive intervention was offered in cases of remarkable changes in MRI findings, which we assumed to represent disease progression, or when the patient indicated their desire to discontinue AS. All patients were provided sufficient explanations of their disease status and the detection rate of prostate cancer with MRI, after which they were offered treatment options of maintenance of AS with PSA follow-up, repeat biopsy, and termination of AS. A prostate biopsy for confirmation was not mandatory during the follow-up duration.

2.4. Assessment of variables

For clinical staging, all patients underwent MRI using a 3.0-T MRI system (Intera Achieva 3.0 T, Phillips Medical System, Best,

the Netherlands) equipped with a phased array coil (6-channel). The MRI protocol used at our institution was as follows: (1) two b values (0 and 1,000) in diffusion weighted-MRI (DW-MRI) were used, and diffusion restriction was quantified by apparent diffusion coefficient (ADC) mapping; (2) dynamic contrast-enhanced MRI was also performed. MRI data were interpreted by urologists in our institution.

Remarkable changes in MRI findings were defined as (1) a newly visible lesion in patients with no visible mass at the initial prostate cancer diagnosis, or (2) a lesion that increased in size by > 1.0 cm in patients with an existing mass. Although our institution currently evaluates suspected tumor lesions using the Prostate Imaging Reporting and Data System (PI-RADS),¹³ we did not evaluate MRI readings using PI-RADS in patients with MRI data before the implementation of PI-RADS.

2.5. Statistical analysis

In comparing the pathologic outcomes of patients who underwent RP (initially underwent RP vs. RP after the termination of AS), we defined upstaging as prostate cancer with extracapsular extension and/or seminal vesicle invasion upon pathologic examination. Upgrading was defined as a higher-grade group in the final pathological evaluation than in the biopsy. Significant prostate cancer was defined when one or more of the following conditions were met: Gleason grade group ≥ 2 , pathologic upstaging, or tumor volume > 0.5 cc.

Continuous variables are expressed as the mean \pm standard deviation. Categorical variables were reported as the number of occurrences and frequency. The Pearson Chi-square test and paired samples *t* tests were used to determine the significance of the differences observed between the rates of categorical variables. Review of charts and death certificates were used to assess the cause of death until July 2019. All statistical comparisons were conducted using the IBM SPSS Statistics, version 25 (IBM Corporation, Armonk, NY, USA). A *P* value < 0.05 was considered to be statistically significant.

3. Results

Table 1 presents the baseline characteristics of the patients eligible for AS. In total, 193 patients (mean age = 69.0 years, mean PSA = 5.6 ng/mL) were included in the study. The median duration of prostate cancer follow-up was 48.0 months. A total of 122 patients (63.2%) chose to undergo AS (mean AS adherence duration = 41.7 months). Among these patients, the proportion of those with Charlson comorbidity index ≥ 2 was lower; they had lower PSA density and number of positive biopsy cores; and the proportion of those with incidental prostate cancer after TURP was higher than that among those in the definitive treatment group ($P = 0.014$, $P = 0.006$, $P < 0.001$, and $P < 0.001$, respectively). No differences were found in age, PSA, prostate volume, Gleason grade group, clinical stage, percentage of maximum core involvement (≤ 50), risk stratification according to NCCN guideline, and follow-up duration between the AS and the definitive treatment groups.

The 5-year overall survival (OS) and cancer-specific survival (CSS) rates were 93% and 100%, respectively. There were no significant differences in OS and CSS between the patients who did and did not undergo AS (93% vs. 100%, log-rank $P = 0.157$; 100% vs. 100%, not evaluable, respectively).

Of the patients who were enrolled in the AS registry, 70 (57.4%) subsequently changed their treatment options. The principal cause for terminating AS was disease progression ($n = 30$, 42.9%), followed by follow-up loss ($n = 18$, 25.7%) and change of treatment options to definite treatment ($n = 9$, 12.9%). The median duration of

Table 1
Comparison of baseline characteristics of patients with prostate cancer who chose definitive treatment and those who underwent active surveillance.

	Total	Definitive Treatment	Active Surveillance	P
No. patients	193	71 (36.8)	122 (63.2)	
Age (y)	69.8 ± 7.5	68.6 ± 6.4	70.5 ± 8.0	0.082
Charlson comorbidity index (≥2)	22 (11.4)	14 (19.7)	8 (6.6)	0.014
Family history	7 (3.6)	4 (5.6)	3 (2.5)	0.307
PSA (ng/mL)	5.6 ± 3.0	5.9 ± 2.7	5.4 ± 3.1	0.212
Prostate volume (cc)	44.9 ± 18.3	41.5 ± 16.7	46.9 ± 19.0	0.051
PSA density (ng/mL/cc)	0.14 ± 0.08	0.16 ± 0.08	0.12 ± 0.08	0.006
Gleason Grade group				0.184
1	164 (85.0)	56 (78.9)	108 (84.4)	
2	29 (15.0)	15 (21.1)	14 (15.6)	
Clinical stage				0.886
cT1	147 (76.2)	54 (76.1)	93 (76.2)	
cT2	46 (23.8)	17 (23.9)	29 (23.8)	
No. of positive biopsy cores				<0.001
1	117 (75.0)	39 (56.5)	78 (89.7)	
2	39 (25.0)	30 (43.4)	9 (10.3)	
Maximum percentage involvement				0.423
≤20%	113 (73.3)	50 (72.5)	63 (74.1)	
20%–50%	37 (24.1)	18 (26.1)	19 (22.4)	
>50%	4 (2.6)	1 (1.4)	3 (3.5)	
Incidental PCa after TURP	42 (21.8)	3 (4.2)	39 (32.0)	<0.001
% of positive biopsy chips	4.3 ± 6.6	1.5 ± 0.3	4.5 ± 6.9	0.459
Risk stratification				0.083
Very low	7 (3.6)	7 (9.9)	0 (0.0)	
Low	146 (75.6)	53 (74.6)	73 (76.2)	
Favorable intermediate	37 (19.2)	11 (15.5)	26 (21.3)	
Unfavorable intermediate	3 (1.6)	0 (0.0)	3 (2.5)	
Follow-up duration (mo)	42.7 (25.2–64.2)	47.8 (18.8–70.0)	41.8 (27.9–63.6)	0.746
AS adherence duration (mo)			31.4 (19.2–56.7)	

Data are n (%), mean ± standard deviation or median (interquartile range).

AS, active surveillance; PCa, prostate cancer; PSA, prostate-specific antigen; TURP, transurethral resection of prostate.

AS for patients with termination because of follow-up loss, change to definitive treatment, and anxiety was 29.2 months (Table 2).

To evaluate the safety of AS selection criteria, we compared the clinicopathologic characteristics of patients who underwent RP (initially underwent RP [n = 58] vs. RP after termination of AS [n = 20]). The higher proportion of risk stratification according to NCCN guideline (favorable intermediate) in RP after termination of AS showed. No significant differences were found in the incidence of adverse pathologic events, including Gleason Grade group upgrading, upstaging, or both, between the two groups (Table 3).

In subanalysis for the comparison of patient characteristics according to diagnostic methods, the patients with incidental prostate cancer had higher age, lower PSA level and PSA density, as well as longer AS adherence duration and follow-up duration (Table 4).

4. Discussion

The problem of accurately evaluating disease progression has been a major obstacle for AS programs. In terms of clinical practice, there remain uncertainties around AS, with no clear evidence as to which aspects of the many different monitoring protocols are most important for long-term outcomes. Regular repeat biopsy has been

the most effective monitoring tool for disease progression of prostate cancer. As such, many studies seek to enroll only men with the lowest risk of disease, and include aggressive monitoring strategies that require regular PSA testing and repeat biopsy.¹⁴ However, it could be considered as over-treatment for a large proportion of patients who will not experience disease progression during the AS regime.¹⁵ The goal of AS is to defer treatment and avoid its potential side-effects while maintaining quality of life and normal activities. Therefore, we developed our monitoring protocol that depended on MRI instead of regular repeat biopsy based on our previous results, as it allows for more precise evaluation of disease progression.^{9–12}

Prior studies of AS cohorts have reported OS and CSS rates of 82–98% and 97–100%, respectively. These results were consistent with those in the present study (93% and 100%, respectively).^{8,16,17} Van As *et al.* showed that 44% of patients (median follow-up = 22 months) who opted to defer radical treatment for localized prostate cancer in lieu of AS subsequently experienced pathologic upgrading.¹⁸ In our study (median follow-up duration = 48.0 months), the rate of pathologic upgrading was 50.0%, which was similar to that in the previous study. In addition, we compared the pathologic outcomes between patients who initially underwent RP and those who did so after terminating AS. No significant differences were found in the proportion of upstaging, tumor volume, or incidence of significant prostate cancer. Therefore, our AS protocol using MRI not only confirmed the stability, but also could help maintain the patient's quality of life and normal activities, which is the fundamental purpose of AS.

Several studies have investigated the monitoring criteria and variables of AS to avoid unnecessary repeat biopsy. Olivier *et al.* suggested that repeat biopsy at 1 year can be avoided when there is no suspicious lesion on MRI considering PSA kinetics, including PSA velocity and PSA doubling time.¹⁹ Another study reported that PSA

Table 2
Reasons for termination of active surveillance

	Termination of AS (n = 70)
Disease progression	30 (42.9)
Anxiety for active surveillance strategy	6 (8.6)
Follow-up loss	18 (25.7)
Expired due to other disease	7 (10.0)

Data are n (%).

AS, active surveillance.

Table 3

Comparison of clinical characteristics of patients who initially underwent RP versus those who underwent RP after termination of AS.

	Initially underwent RP	RP after termination of AS	<i>P</i>
No. of patients	58	20	
Age (y)	67.0 ± 5.7	66.0 ± 4.5	0.571
Charlson comorbidity index (≥2)	11 (19.00)	3 (15.0)	0.723
Family history	4 (6.9)	2 (10.0)	0.655
PSA (ng/mL)	5.7 ± 1.8	6.4 ± 3.1	0.615
Prostate volume (cc)	41.6 ± 16.6	40.3 ± 11.7	0.864
PSA density (ng/mL/cc)	0.15 ± 0.07	0.17 ± 0.08	0.672
Gleason Grade group 2	12 (20.7)	3 (15.0)	0.580
Clinical stage (cT2)	10 (17.2)	5 (25.0)	0.452
No. of positive biopsy cores	1.4 ± 0.5	1.1 ± 0.5	0.026
% of maximum core involvement (≤50)	17.4 ± 14.0	11.7 ± 15.6	0.007
Incidental PCa after TURP	0 (0.0)	4 (20.0)	0.001
% of positive biopsy chips	–	7.6 ± 11.6	
Follow-up duration (mo)	47.4 ± 28.7	51.2 ± 24.8	0.563
AS adherence duration (mo)		23.7 ± 15.7	
Risk stratification (FI)	8 (13.8)	6 (30.0)	0.035
Pathologic stage (pT3)	2 (3.4)	3 (15.0)	0.183
pathologic Gleason Grade group 2	24 (41.4)	9 (45.0)	0.660
Tumor volume (cc)	1.0 ± 1.0	1.2 ± 1.4	0.362
No. of significant PCa	31.0 (53.4)	15 (75.0)	0.093
No. of upgrading	2 (3.4)	3 (15.0)	0.303
No. of upstaging	16 (27.6)	8 (40.0)	0.071
No. of upgrading or upstaging	17 (29.3)	10 (50.0)	0.096

Data are n (%) or mean ± standard deviation.

AS, active surveillance; FI, favorable intermediate; PCa, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy; TURP, transurethral resection of prostate.

kinetics may be useful for defining the indications for prostate biopsy in AS patients who are followed up with regular biopsies for more than 3–4 years.²⁰ A recent study demonstrated the monitoring of AS patients using MRI without a repeat biopsy.²¹ Although we agree with the usefulness of PSA kinetics in monitoring patients

opting for AS, our cohort was not appropriate for investigating this point, as some patients received 5 α -reductase inhibitors or TURP to relieve voiding symptoms.

It might be difficult to confirm disease progression by solely monitoring patients using MRI findings. Indeed, the authors agree

Table 4

Comparison of clinical characteristics of patients who underwent AS according to diagnostic methods.

	AS after PBx	AS after TURP	<i>P</i>
No. of patients	83	39	
Age (yr)	69.1 ± 7.4	73.5 ± 8.5	0.022
Charlson comorbidity index (≥2)	6 (7.2)	2 (5.1)	0.663
Family history	1 (1.2)	2 (5.1)	0.194
PSA (ng/mL)	5.9 ± 3.0	4.3 ± 3.2	0.004
Prostate volume (cc)	45.6 ± 18.5	49.5 ± 20.0	0.249
PSA density (ng/mL/cc)	0.14 ± 0.08	0.09 ± 0.07	<0.001
Gleason Grade group			0.126
1	76 (91.6)	32 (82.1)	
2	7 (8.4)	7 (18.9)	
Clinical stage			0.144
cT1c	60 (72.3)		
cT1a		30 (77.0)	
cT1b		3 (7.6)	
cT2	23 (27.7)	6 (15.4)	
No. of positive biopsy cores			<0.001
1	75 (90.4)	3 (7.7)	
2	8 (9.6)	1 (2.6)	
Maximum percentage involvement			<0.001
≤50%	81 (97.6)	1 (2.6)	
>50%	2 (2.4)	1 (2.6)	
% of positive biopsy chips		4.9 ± 6.2	
Risk stratification			0.959
Very low	0 (0.0)	0 (0.0)	
Low	65 (78.3)	28 (71.8)	
Favorable intermediate	16 (19.3)	10 (25.6)	
Unfavorable intermediate	2 (2.4)	1 (2.6)	
Follow-up duration (mo)	41.3 (25.7–57.7)	52.2 (29.1–84.3)	0.047
AS adherence duration (mo)	28.5 (16.0–46.2)	41.3 (27.9–71.6)	0.001
Termination of AS	51 (61.4)	19 (48.7)	>0.999

Data are n (%), mean ± standard deviation or median (interquartile range).

AS, active surveillance; PBx, prostate biopsy; PSA, Prostate-specific antigen; RP, radical prostatectomy; TURP, transurethral resection of prostate.

with this point from a previous study in that nonvisible tumor on MRI does not predict low-risk prostate cancer.²² Furthermore, mimicking lesion may exist on MRI due to chronic prostatitis or other reasons, such as previous prostate biopsy. However, it is generally known that the presence of visible lesions increases the probability of cancer, and especially increases the presence of clinically significant prostate cancer. Moreover, the recent usage of PI-RADS developed to assess clinically significant prostate cancer can be useful for monitoring AS patients.¹³ Considering that most AS patients had no visible lesion by MRI at diagnosis, remarkable changes with visible lesions were assumed to be strongly suspicious of disease progression.

Potential obstacles to introducing the AS strategy in Korea could be represented by the environmental and hereditary factors of Asians, including the family history or genetic background of prostate cancer.^{23,24} Regular confirmative biopsies can lead to perceptions of progression, resulting in anxiety and a wish to change to definitive treatment.²⁵ Several studies showed that 3–9% of patients who decided to terminate the AS strategy considered anxiety as the primary reason.^{17,26} In the present study, anxiety ($n = 6$, 8.6%) was the main cause of termination for the AS strategy in patients without disease progression. In addition, it is likely that the 18 patients who cited follow-up loss as the primary reason for termination also had anxiety-related issues. Anxiety and distress generally remain favorably low during the first 9 months of AS.²⁵ Considering that the median duration of AS for the patients who terminated AS due to anxiety or follow-up loss in our cohort was 29.2 months, the second instance of reclassification might be a threshold for the decision to continue with AS. Although we mainly recommended an MRI follow-up instead of a repeat biopsy, a relatively high proportion of patients terminated the AS strategy. Interestingly, the present study suggested that the source of our patients' anxiety might be related to disease progression, rather than the fear of a repeat biopsy and frequent PSA checks.

The prevalence of incidental prostate cancer has been reported to be 5–6%.²⁷ Although oncologic outcomes for incidental prostate cancer patients was satisfactory regardless of the initial treatment, there are few studies on patients undergoing AS. Compared to the termination rate on AS in 14–41% of patients by prostate biopsy, those in incidental prostate cancer patients of 11–19% are likely lower.^{28,29} In the present study, no significant differences were observed in the termination rates on AS (48.7% vs. 61.4%; $P > 0.99$) according to diagnostic methods. However, patients with incidental prostate cancer had longer AS adherence duration and follow-up duration. Considering the higher age, lower PSA, and PSA density of incidental prostate cancer patients, we concluded that these were suitable for AS enrollment.

The present study showed the experience relying on MRI findings as a trigger to follow-up and intervention for AS patients instead of regular repeat biopsy. Considering OS and CSS, our protocol of AS patients is feasible. Patients who terminated AS and deferred RP showed no significant difference in advanced pathological events compared to those with initial RP. Despite presenting novel findings, this study had several limitations. First, the study was hampered by the small number of patients and short-term follow-up duration, which could lead to statistical insufficiency, in addition to fact that our protocol has yet to be externally validated. To overcome this limitation, studies with sufficiently large data and better study designs should be conducted. The performance and duration of follow-up MRI in the Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance cohort were varied.³⁰ Since our AS protocol was developed based on reimbursement by the insurance for the cost of annual MRI, our results may differ from those of other institutions or other patient populations. Second, despite having different characteristics,

incidental prostate cancer was analyzed in combination with biopsy-proven prostate cancer; most patients with incidental prostate cancer selected AS instead of definitive treatment as the initial treatment option. Upon subsequent disease progression, non-invasive therapies, such as radiotherapy or androgen deprivation therapy, were more likely to be selected over RP. Such trends could be one of the major causes of the differences between our findings and those of previous studies. Nevertheless, our protocol was confirmed to be safe and efficacious, even in patients with incidental prostate cancer. Furthermore, our protocol is useful for reducing the anxiety levels and complications associated with repeat biopsy, and it avoids the relatively low accuracy of other reclassification methods while maximizing patient safety.

Conflicts of interest

All of the authors declare that they have no conflict of interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pnml.2020.11.003>.

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