Original Article - Urological Oncology

Investig Clin Urol 2017;58:164-170.
https://doi.org/10.4111/icu.2017.58.3.164
pISSN 2466-0493 • eISSN 2466-054X

INVESTIGATIVE AND CLINICAL UROLOGY
ICUROLOGY

Updated clinical results of active surveillance of very-low-risk prostate cancer in Korean men: 8 years of follow-up

Ji Yong Ha, Teak Jun Shin, Wonho Jung, Byung Hoon Kim, Choal Hee Park, Chun Il Kim

Department of Urology, Keimyung University School of Medicine, Daegu, Korea

Purpose: Update and reanalysis of our experience of active surveillance (AS) for prostate cancer (PCa) in Korea.

Materials and Methods: A prospective, single-arm, cohort study was initiated in January 2008. Patients were selected according to the following criteria: Gleason sum ≤6 with single positive core with ≤30% core involvement, clinical stage≤T1c, prostate-specific antigen (PSA)≤10 ng/mL, and negative magnetic resonance imaging (MRI) results. Follow-up was by PSA measurement every 6 months, prostate biopsies at 1 year and then every 2–3 years, and MRI every year.

Results: A total of 80 patients were treated with AS. Median follow-up was 52 months (range, 6–96 months). Of them, 39 patients (48.8%) discontinued AS for various reasons (17, disease progression; 9, patient preference; 10, watchful waiting due to old age; 3, follow-up loss; 2, death). The probability of progression was 14.0% and 42.9% at 1 and 3 years, respectively. Overall survival was 97.5%. PCa-specific survival was 100%. Progression occurred in 5 of 7 patients (71.4%) with a prostate volume less than 30 mL, 7 of 40 patients (17.5%) with a prostate volume of 30 to 50 mL, and 5 of 33 patients (15.2%) with a prostate volume of 50 mL or larger. There were 8 detectable positive lesions on follow-up MRI. Of them, 6 patients (75%) had actual progressed disease.

Conclusions: Small prostate volume was associated with a tendency for cancer progression. MRI was helpful and promising for managing AS. Nevertheless, regular biopsies should be performed. AS is a safe and feasible treatment option for very-low-risk PCa in Korea. However, AS should continue to be used in carefully selected patients.

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

INTRODUCTION

Prostate cancer (PCa) screening leads to a 21% to 30% reduction in disease-specific mortality [1,2]. However, screening and early detection also lead to the diagnosis of clinically insignificant disease, which can result in overdiagnosis and overtreatment [3,4]. In 2012, the US Preventive Services Task Force (USPSTF) discouraged prostate-specific antigen (PSA)-based PCa screening [5].

Currently, the literature on active surveillance (AS) outcomes is largely from Western countries. There is an established disparity in incidence and PCa aggressiveness between Western and Asian nations [6], which brings into question the safety and efficacy of AS in Asia. Klotz et

Received: 15 November, 2016 • **Accepted:** 20 February, 2017
Corresponding Author: Chun Il Kim
Department of Urology, Keimyung University School of Medicine, 56 Dalseong-ro, Jung-gu, Daegu 41931, Korea
TEL: +82-53-250-7646, FAX: +82-53-250-8340, E-mail: cikim@dsmc.or.kr

al. [7] reported the 10-year cancer-specific survival for AS to be 97.2%, which is comparable to that for robot-assisted laparoscopic radical prostatectomy (RALP). Long-term results of AS have already been published in the United States and Europe [8].

AS is now mandatory, not optional, for low-grade PCa. However, in African American men, the progression risk is significantly increased with AS. The pathology outcome in African American men who qualify for AS but elect immediate surgery suggests that African American men have a tendency for more aggressive disease [9]. For a similar reason, AS is rarely utilized in Korea, because pathological upgrading and upstaging of patients eligible for AS were reported to be much higher after RALP than the corresponding rates in Western countries [10-12]. The rates of misclassification varied from 44.5% to 54.8%.

Thus, currently available AS criteria might not be suitable in Korean patients. We need to use stricter criteria for AS than used in Western countries. Therefore, there are limited data to inform the safety of AS in Korean men. Data are also lacking to assess the risk and determine the safety of AS. We have used AS for low-risk PCa from 2008 and our 5 years of experience was reported in 2014 [13]. This report represents an update and reanalysis of our experience of AS [13]. These data can be used to revise the strategy for follow-up and definitive treatment by AS.

MATERIALS AND METHODS

A cohort study was initiated in January 2008. Patients were enrolled in this study when they met our inclusion criteria for histologically well-defined, newly developed PCa.

1. Patient population

Clinical data were collected retrospectively from 80 patients who were treated with AS as a treatment for PCa (approval number: DSMC 2016-10-032).

2. Criteria for AS

The selection criteria for AS included biopsy Gleason sum ≤6 with a single positive core with ≤30% core involvement, clinical stage≤T1c, PSA≤10 ng/mL, and negative magnetic resonance imaging (MRI) results. The 12-core biopsy scheme was done by using transrectal ultrasonography. Patients should have more than 12 cores taken on biopsy. If the number of initial biopsies was less than 12, a second confirmatory biopsy was done, which tended to detect higher-grade cancer that had been missed on the original biopsy. The criteria were not changed after our initial report.

3. Follow-up

PSA was measured every 6 months; prostate biopsies were performed at 1 and then every 2 to 3 years. The confirmatory biopsy after the first year was intended to identify higher-grade cancer that had been missed on the original biopsy [7]. MRI was further included in a follow-up study after our initial report. MRI was performed prior to repeat biopsy. When the MRI detected a positive lesion, targeted biopsy was done. The PSA test interval was increased because PSA was not useful in the prediction of disease progression in our initial experience. During the follow-up, if the patient's age exceeded 80 years, AS was converted to watchful waiting.

4. Prediction of disease progression

Patients were reclassified after prostate biopsy was performed. Earlier prostate biopsy was performed if PSA doubling time (DT) was less than 3 years or suspicious clinical progression was seen. PSA DT was not useful in the prediction of disease progression in our initial experience. Nevertheless, the number of patients was insufficient to evaluate the association between PSA DT and disease progression, so PSA DT was measured after the initial report. PSA DT was calculated by use of the following formula:

$$\text{PSA DT} = \log 2 \times dT / (\log B - \log A)$$

where A & B are the initial (A) and final (B) PSA measurements and dT is the time difference between the calendar dates of the 2 PSA measurements [14].

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 (2 or more than 1 lobe).

6. Statistical methods

Chi-square was used to analyze prediction of disease progression. The Kaplan-Meier method was used to analyze the progression-free survival rates for prostate volume after division into tertile values. Statistical analysis was performed by using IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA). A p-value of <0.05 was taken to be significant.

RESULTS

A total of 80 patients were enrolled and treated with AS. The patients' mean age was 68 years (range, 55–80 years), their mean PSA was 6.93 ng/mL (range, 2.31–10.0 ng/mL), their mean prostate volume was 62.0 mL (range, 20–171 mL), their mean Gleason sum was 4.96 (range, 3–6), and their mean PSA density was 0.14 ng/mL (range, 0.04–0.53 ng/mL). Median follow-up duration was 49.0 months (interquartile range, 30.8–65.0 months) (Table 1).

In the first year of follow-up, 50 patients (62.5%) underwent repeat biopsy (43 patients, single core Gleason 6 without progression or negative for cancer; 7 patients, progression). Three patients were lost to follow-up. A total of 15 patients wanted to change the treatment modality before the repeat biopsy. Twelve patients awaited the scheduled first-year follow-up biopsy (some of them were delayed). Of the patients who experienced progression, 5 patients underwent radical prostatectomy, whereas 2 patients requested a transfer to another hospital of their choice.

In the third year of follow-up, repeat biopsies were performed in 21 patients (12 patients, stable; 9 patients, progressed). In the fifth year of follow-up, repeat biopsies were performed in 4 patients (3 patients, stable; 1 patient, progression, treated with radical prostatectomy).

During the entire period, 39 patients (48.8%) discontinued AS for various reasons (17, disease progression [13 RALP, 3

Table 1. Characteristics of patients undergoing active surveillance

Characteristic	Value
No. of patients	80
Age (y)	68 (55–80)
PSA (ng/mL)	6.93 (2.31–10.0)
Prostate volume (mL)	62.0 (20–171)
PSAD	0.14 (0.04–0.53)
Gleason score	4.96 (3–6)
Follow-up duration (mo), median (IQR)	49.0 (30.8–65.0)

Values are presented as mean (range) unless otherwise indicated.
PSA, prostate-specific antigen; PSAD, PSA density; IQR, interquartile range.

Table 2. Reasons for discontinuing active surveillance

Reason	No. of patients
Disease progression	17
RALP	13
Transfer to another hospital	3
WW	1
Patient preference	9
RALP	6
Hormone therapy	3
WW conversion	10
Follow-up loss	3
Dead from other cause	2 (2; on WW)
Total	39

RALP, robot-assisted laparoscopic radical prostatectomy; WW, watchful waiting.

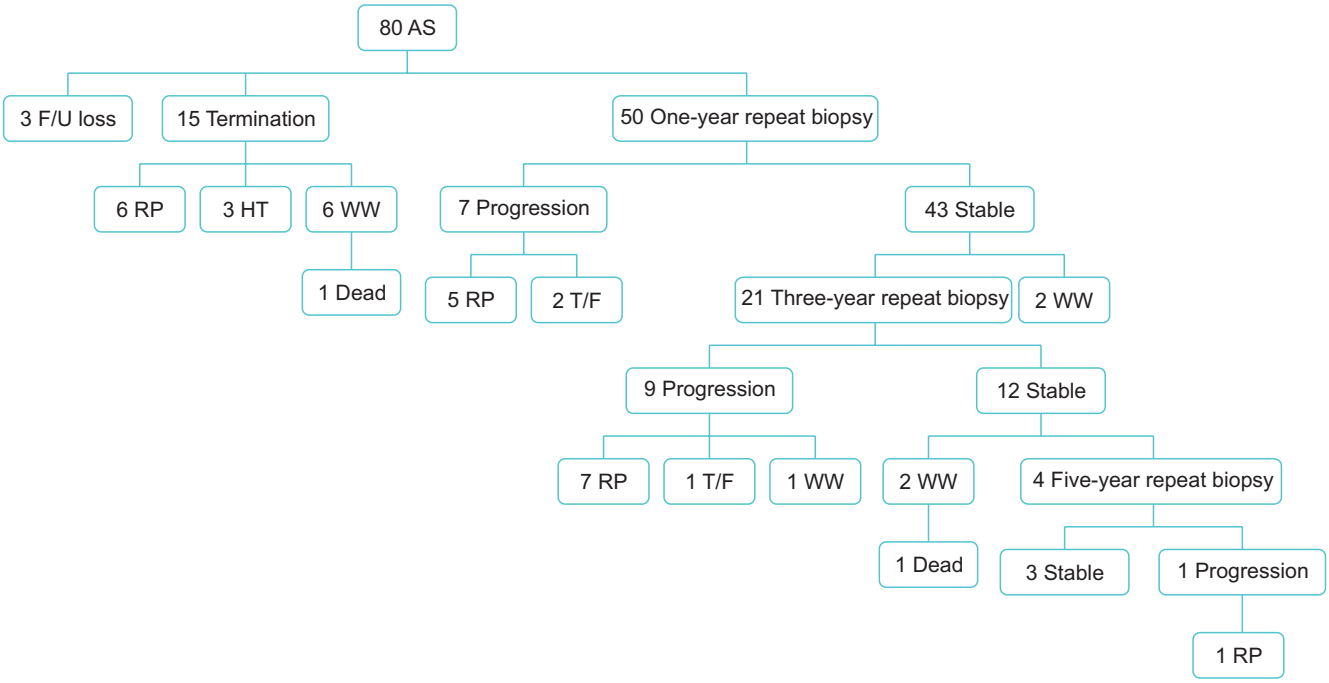

Fig. 1. Flow chart of active surveillance. AS, active surveillance; F/U, follow-up; RP, radical prostatectomy; HT, hormone therapy; T/F, transfer; WW, watchful waiting.

https://doi.org/10.4111/icu.2017.58.3.164

transfer to another hospital, 1 watchful waiting]; 9, patient preference [6 RALP, 3 hormone therapy]; 10, watchful waiting due to old age; 3, follow-up loss; 2, death from other cause). Therefore, 41 patients (51.3%) remained on AS (Fig. 1, Table 2). In the patients who experienced progression, 2 had a Gleason score of 6 with 2 or 3 core involvements, 13 had a Gleason score of 7 with 1 to 7 core involvements, and 2 had a Gleason score of 8 with 2 or 3 core involvements.

The probability of progression was 14.0% (7 of 50 patients) and 42.9% (9 of 21 patients) at 1 and 3 years, respectively. Overall survival was 97.5% (78 of 80 patients). PCa-specific survival was 100%.

RALP was performed in 19 patients. Two patients had extracapsular extended disease (pathologic T3a, Gleason score 3+4 and 4+3). However, there was no recurrence after definitive treatment.

A total of 19 patients underwent prostate biopsy earlier owing to a PSA DT of less than 3 years. However, only 4 of them (21.1%) had cancer progression. A total of 17 patients with disease progression had a mean PSA DT of 9.95 years (Table 3). Progression occurred in 5 of 7 patients (71.4%) with a prostate volume less than 30 mL, 7 of 40 patients (17.5%) with a prostate volume of 30 to 50 mL, and 5 of 33 patients (15.2%) with a prostate volume of 50 mL or larger (Fig. 2). The progression rate was significantly lower in the patients with a larger prostate (p=0.002).

During the follow-up, 22 patients had MRI. There were 8 detectable positive lesions at follow-up MRI. Of them, 6 patients (75.0%) had actual progressed disease (Table 4). Diagnostic properties of MRI to predict progression were sensitivity of 100%, specificity of 87.5%, positive predictive value of 75.0%, and negative predictive value of 100% (Table 5).

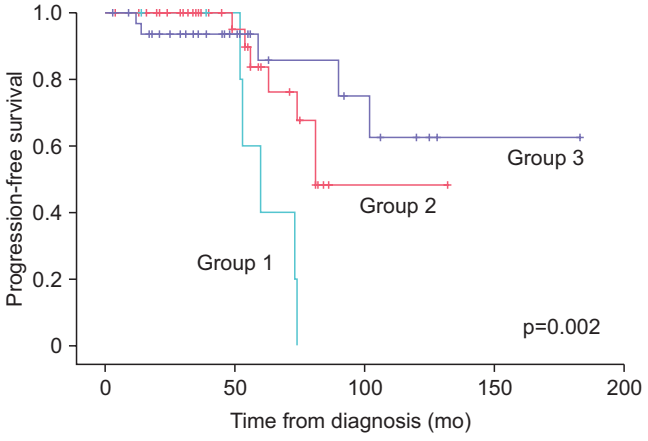

Fig. 2. Progression-free survival for prostate volume. Group 1, prostate volume<30 mL; group 2, prostate volume 30 to 50 mL; group 3, prostate volume≥50 mL.

DISCUSSION

The USPSTF recommendation against PSA screenings was based on concern about overdiagnosis and overtreatment [5]. This message was reinforced by the results of the PIVOT study [15]. Klotz et al. [7] reported the 10-year cancer-specific survival for AS to be 97.2%, which is comparable to that for RALP. AS is mandatory, not optional, for low-grade PCa. AS is an effective method for reducing overtreatment because PCa with a Gleason score of 6 is rarely lethal.

We used the following inclusion criteria for AS in Korea for very-low-risk PCa: biopsy Gleason sum ≤6 with a single positive core, clinical stage≤T1c, PSA≤10 ng/mL, and negative MRI results [16]. Our inclusion criteria were the strictest criteria for AS. AS is rarely used in Korea, because pathological upgrading and upstaging of patients eligible for

Table 4. True progression and false progression in MRI follow-up

MRI at follow-up	True progression, n	False progression, n	Subtotal, n
Positive finding	6	2	8
Negative finding	0	14	14
Subtotal	6	16	22

MRI, magnetic resonance imaging.

Table 3. Stratification by prostate-specific antigen doubling time and prostate-specific antigen density

PSA time & PSAD	No. of patients	Progression, n			p-value
		1 Year	3 Years	5 Years	
PSA doubling time (y)					0.218
>3	19	0	3	1	
≤3	31	7	6	0	
PSAD					0.261
>0.15	21	4	4	1	
≤0.15	29	3	5	0	
Total	50	7	9	1	

PSA, prostate-specific antigen; PSAD, PSA density.

Table 5. Predictive value of magnetic resonance imaging at follow-up

	Sensitivity	Specificity	PPV	NPV	Accuracy
MRI at follow-up (%)	100	87.5	75.0	100	90.9

MRI, magnetic resonance imaging; PPV, positive predictive value; NPV, negative predictive value.

AS were reported after RALP in comparison with Western countries [10-12,17]. The rate of upgrading ranged from 41.6% to 50.6%. Extracapsular extension was reported in 4.1% to 8.5%. The rate of upstaging varied from 4.5% to 9.3% and the rates of misclassification varied from 44.5% to 54.8%. Therefore, we did distinguish between low-risk disease and very-low-risk disease. We also used strict definitions of disease progression and intervention criteria.

In our study, the probability of progression was 14.0% (7 of 50 patients) and 42.9% (9 of 21 patients) at 1 and 3 years, respectively, despite the strict inclusion criteria. Nevertheless, overall survival was 97.5% (78 of 80 patients). PCa-specific survival was 100%. Therefore, AS can be used in Korea.

It is difficult to determine the individual risk of disease progression in someone with PCa with Gleason 6. In several recent reports, PSA kinetics has been used to predict disease progression [7]. Klotz et al. [7] also focused on PSA kinetics to determine a definite intervention. However, in our initial experience, PSA was not associated with cancer progression. In the 8-year analysis, PSA DT also could not predict disease progression. After diagnosis, PSA tended to decrease or stabilize in most of the patients with PCa. We think that lifestyle changes made this possible.

In our study, PSA density was not associated with progression. After stratification, prostate volume was related to progression. Progression occurred more often in cases of PCa with a small prostate. The progression rate was significantly lower in patients with a larger prostate (p=0.002). Several studies have reported that higher PSA density at baseline predicts a greater risk of progression [8,18,19]. Tosoian et al. [20] reported in a comparative analysis of men electing AS and immediate surgery that PSA density per 0.1-unit increase was identified as a significant predictor of adverse pathology. Jin et al. [21] also reported PSA density as a strong predictor of Gleason score upgrading after radical prostatectomy in patients eligible for AS. In our study, small prostate volume tended to be associated with cancer progression. However, one limitation of our study was the use of unusual statistics because of the small numbers.

We used MRI at follow-up to determine upgrading and upstaging of PCa. Recently, the usefulness of MRI has been consistently reported [22,23]. MRI with various imaging techniques has improved tumor detection. If the tumor has progressed, MRI can be used to detect the lesion. At the beginning of our study, all patients had negative findings for MRI. A total of 22 patients underwent MRI at the yearly follow-up. There were 8 detectable positive lesions on MRI. Of them, 6 patients (75.0%) had actual progressed disease. Henderson et al. [24] focused on MRI in AS and concluded that MRI is a useful marker when selecting patients for AS and may help in predicting whether patients should receive close monitoring or whether immediate treatment should be given. We think that MRI is very useful for selecting patients for AS and for detecting cancer upgrading [25]. Especially, lesions in the apex or anterior of the prostate are difficult to find. In these cases, MRI is useful for identifying occult anterior lesion cancers [26]. However, the purpose of the follow-up MRI in our study was not to detect upgrading or upstaging but to make a decision about early biopsy or to make target biopsy easier. Nevertheless, we believe that every patient undergoing AS should have a repeat biopsy to detect disease progression periodically. PSA kinetics and MRI can miss disease progression. Quon et al. [27] reported the risk of false-positive and false-negative diagnosis of PCa with multiparametric prostate MRI in AS. Lee et al. [28] reported that nonvisible tumors on multiparametric MRI do not predict low-risk PCa. In order to carry out AS safely, a new biomarker or a new tool for detecting disease progression is needed.

AS can minimize overtreatment of indolent PCa and avoid or postpone the side effects of definite therapy. Thus, AS can give quality of life to men with low-risk PCa. Klotz et al. [7] reported the 10-year cancer-specific survival for AS to be 97.2%. In our study, overall survival was 97.5% (78 of 80 patients). Prostate-cancer-specific survival was 100%. Thus, AS is also a feasible treatment option for low-risk PCa patients in Korea.

However, our study had several limitations. First, many patients are reluctant to undergo repeat biopsy and thus postpone follow-up or transfer to another hospital. Second, considering the long life-span of PCa, the total follow-up period of this study was too short to ensure the safety of AS. Third, because of the small numbers, we used unusual statistics. Therefore, further study will be needed.

https://doi.org/10.4111/icu.2017.58.3.164

CONCLUSIONS

Early outcomes of AS showed it to be safe and feasible in carefully selected men with very-low-risk PCa in Korea. There was no incurable progression and PCa-specific survival was 100%. As in our first report, PSA DT was not helpful in predicting PCa progression. However, we did know that a small prostate volume is associated with a tendency for cancer progression. MRI showed benefit for the detection of progression. MRI may reduce the rate of serial biopsy and improve the early identification of occult high-grade disease. Nevertheless, regular biopsies should be performed. Further study is needed to reduce the number of biopsies. Also, longer follow-up is needed to assess the effectiveness of AS.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012;366:981-90.
2. Roobol MJ, Kerkhof M, Schröder FH, Cuzick J, Sasieni P, Hakama M, et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2009;56:584-91.
3. Klotz L. Active surveillance versus radical treatment for favorable-risk localized prostate cancer. Curr Treat Options Oncol 2006;7:355-62.
4. Lawrentschuk N, Klotz L. Active surveillance for low-risk prostate cancer: an update. Nat Rev Urol 2011;8:312-20.
5. Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012;157:120-34.
6. Chung JS, Choi HY, Song HR, Byun SS, Seo Si, Song C, et al. Preoperative nomograms for predicting extracapsular extension in Korean men with localized prostate cancer: a multi-institutional clinicopathologic study. J Korean Med Sci 2010;25:1443-8.
7. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 2010;28:126-31.
8. Loeb S, Bruinsma SM, Nicholson J, Briganti A, Pickles T, Kakehi Y, et al. Active surveillance for prostate cancer: a systematic review of clinicopathologic variables and biomarkers for risk stratification. Eur Urol 2015;67:619-26.
9. Sundi D, Ross AE, Humphreys EB, Han M, Partin AW, Carter HB, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? J Clin Oncol 2013;31:2991-7.
10. Hwang I, Lim D, Jeong YB, Park SC, Noh JH, Kwon DD, et al. Upgrading and upstaging of low-risk prostate cancer among Korean patients: a multicenter study. Asian J Androl 2015;17:811-4.
11. Ahn HJ, Ko YH, Jang HA, Kang SG, Kang SH, Park HS, et al. Single positive core prostate cancer in a 12-core transrectal biopsy scheme: clinicopathological implications compared with multifocal counterpart. Korean J Urol 2010;51:671-6.
12. Lee SE, Kim DS, Lee WK, Park HZ, Lee CJ, Doo SH, et al. Application of the Epstein criteria for prediction of clinically insignificant prostate cancer in Korean men. BJU Int 2010;105:1526-30.
13. Ha JY, Kim BH, Park CH, Kim CI. Early experience with active surveillance in low-risk prostate cancer treated. Korean J Urol 2014;55:167-71.
14. Schillaci O, Calabria F, Tavolozza M, Caracciolo CR, Finazzi Agrò E, Miano R, et al. Influence of PSA, PSA velocity and PSA doubling time on contrast-enhanced 18F-choline PET/CT detection rate in patients with rising PSA after radical prostatectomy. Eur J Nucl Med Mol Imaging 2012;39:589-96.
15. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-13.
16. Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol 2012;62:976-83.
17. Kang M, Song B, Lee I, Lee SE, Byun SS, Hong SK. Predictors of pathological upgrading in low-risk prostate cancer patients without hypointense lesions on an apparent diffusion coefficient map of multiparametric magnetic resonance imaging. World J Urol 2016;34:1541-6.
18. Babaian KN. Active surveillance for prostate cancer: when to recommend delayed intervention. Asian J Androl 2015;17:885-7.
19. Ha YS, Yu J, Salmasi AH, Patel N, Parihar J, Singer EA, et al. Prostate-specific antigen density toward a better cutoff to identify better candidates for active surveillance. Urology 2014;84:365-71.
20. Tosoian JJ, Sundi D, Trock BJ, Landis P, Epstein JI, Schaeffer EM, et al. Pathologic outcomes in favorable-risk prostate cancer: comparative analysis of men electing active surveillance and immediate surgery. Eur Urol 2016;69:576-81.

21. Jin BS, Kang SH, Kim DY, Oh HG, Kim CI, Moon GH, et al. Pathological upgrading in prostate cancer patients eligible for active surveillance: does prostate-specific antigen density matter? Korean J Urol 2015;56:624-9.
22. Bjurlin MA, Mendhiratta N, Wysock JS, Taneja SS. Multiparametric MRI and targeted prostate biopsy: improvements in cancer detection, localization, and risk assessment. Cent European J Urol 2016;69:9-18.
23. Jeong CW, Park YH, Hwang SI, Lee S, Jeong SJ, Hong SK, et al. The role of 3-tesla diffusion-weighted magnetic resonance imaging in selecting prostate cancer patients for active surveillance. Prostate Int 2014;2:169-75.
24. Henderson DR, de Souza NM, Thomas K, Riches SF, Morgan VA, Sohaib SA, et al. Nine-year follow-up for a study of diffusion-weighted magnetic resonance imaging in a prospective prostate cancer active surveillance cohort. Eur Urol 2016;69:1028-33.
25. Marliere F, Puech P, Benkirane A, Villers A, Lemaitre L, Leroy X, et al. The role of MRI-targeted and confirmatory biopsies for cancer upstaging at selection in patients considered for active surveillance for clinically low-risk prostate cancer. World J Urol 2014;32:951-8.
26. Kim M, Choi SK, Park M, Shim M, Song C, Jeong IG, et al. Characteristics of anteriorly located prostate cancer and the usefulness of multiparametric magnetic resonance imaging for diagnosis. J Urol 2016;196:367-73.
27. Quon JS, Moosavi B, Khanna M, Flood TA, Lim CS, Schieda N. False positive and false negative diagnoses of prostate cancer at multi-parametric prostate MRI in active surveillance. Insights Imaging 2015;6:449-63.
28. Lee SH, Koo KC, Lee DH, Chung BH. Nonvisible tumors on multiparametric magnetic resonance imaging does not predict low-risk prostate cancer. Prostate Int 2015;3:127-31.

https://doi.org/10.4111/icu.2017.58.3.164