Our results of active surveillance for localized prostate cancer patients

Hasan Soydan, Furkan Dursun, Ömer Yılmaz, Sezgin Okçelik, Ferhat Ateş, Kenan Karademir

ABSTRACT

Objective: Active surveillance has become a management option for low-risk prostate cancer patients, while keeping the curative treatment option available. In this study, we evaluated the our results of active surveillance for localized prostate cancer patients.

Material and methods: Patients diagnosed with localized prostate cancer who chose an active surveillance protocol were followed with PSA measurements, digital rectal examinations, and TRUS-guided biopsies. The patients' data and rebiopsy results were evaluated. The results were compared with the results of the patients who had definitive treatment.

Results: Forty-one patients on active surveillance and 34 patients with at least one rebiopsy were included in the study. Twenty-seven patients who had more than one rebiopsy were followed for an average of 27.7 (12-78) months. Twelve patients (44.4%) had undergone definitive treatment including radical prostatectomy (n=9), and radiotherapy (n=3). There were 17 patients under surveillance after a second biopsy, and 9 (33%) of them had a third biopsy. Among these 9 patients, 7 patients were kept under surveillance, and 2 (7%) them had a fourth biopsy. Active surveillance of 15 out of 17 patients who have not undergone definitive treatment is still ongoing.

Conclusion: Active surveillance is a treatment option refrains low-risk prostate cancer patients from the complications of an early or unnecessary definitive treatment and related reduction in the quality of their lives. while keeping the curative treatment option available. Active surveillance can be applied safely with the appropriate patient selection, regular examinations and tests.

Key words: Active surveillance; prostate biopsy; prostate cancer.

Introduction

Prostate cancer is the most frequently seen cancer in men, and ranks third among cancer-related deaths.^[1,2] Nowadays, increasing use of prostate-specific antigen (PSA) as a prostate screening test, and increase in the number of core biopsies performed, rapid rises in the incidence of low-risk prostate cancer are evidenced.^[3,4] When we reviewed data reported for the years between 1993, and 2003, the probability of detection of clinically localized prostate cancer among newly diagnosed patients was 91 percent.^[1] Screening tests detected a 20-50 decrease in prostate cancer mortality rates.^[5-7] However, 97% of the patients with localized prostate cancer die because of other etiologies, and 48 patients have to be treated to prevent one patient's death from prostate cancer.^[8-10]

Nowadays, advances in surgical technique, and technologies have decreased complications seen after radical prostatectomy (RP) or radiotherapy. However, when the results of large-scale studies are reviewed, urinary incontinence, and sexual dysfunction are seen after treatment of prostate cancer.^[11] Therefore, determination of prostate cancer patients who really don't need treatment will prevent these patients from unnecessary treatments, and their potential deleterious effects. Active surveillance seems to be a treatment modality which will overcome unwanted effects of superfluous treatment, and it was implemented firstly in the year 2002.^[12] It is based on monitoring patients with PSA, digital rectal examination (DRE), and prostate biopsies, and applying active surveillance when criteria of disease progression are met. Active surveillance was defined, and it was defined, implemented, and its applicability has been demonstrated in

Clinic of Urology, Gülhane
Military Medical Academy
Haydarpaşa Teaching Hospital,
Istanbul, Turkey

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Correspondence:
Furkan Dursun
Clinic of Urology, Gülhane
Military Medical Academy
Haydarpaşa Teaching Hospital,
34668 Üsküdar, Istanbul, Turkey
Phone: +90 532 700 83 54
E-mail:
drfurkandursun@hotmail.com

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large-scale studies. Indeed, American Urological Association (AUA), European Association of Urology (EAU), National Comprehensive Cancer Network (NCCN) have accepted active surveillance as an alternative in localized prostate cancer.^[13-15]

In this study we evaluated our active surveillance results in patients with localized prostate cancer.

Material and methods

Active surveillance (AS) was offered to the patients who would undergo definitive treatment with clinical stage T1C, and T2A, Gleason score ≤ 6 , PSA levels <10 ng/mL, and tumors in ≤ 2 core biopsies among those diagnosed as localized prostate cancer based on analyses, and examinations performed in GATA Haydarpaşa Training and Research Hospital, Clinics of Urology and who would undergo definitive treatment.^[16] Patients who approved active surveillance were included in the study after obtaining their informed consent forms.

Those with a follow-up period of less than twelve months were not included in the evaluation. The patients were followed up with PSA measurements, and DREs performed at 3-4 months. During the follow-up period the patients underwent at least 12 core TRUS-guided prostatic rebiopsies. Definitive treatment modalities were administered to those who demonstrated increases both in the number of positive core biopsies (≥ 2 positive cores), and Gleason scores, and patients who changed their preferences in favour of definitive treatment.

Statistical analysis

Patients' data relevant to therapeutic indications, and their rebiopsy results were evaluated. The results of the patients who had or had not undergone definitive treatments were compared. For comparisons Statistical Package for the Social Sciences (SPSS Inc, Chicago, USA) 16.0 program was used.

Results

In our clinic, 41 (20.9%) of 196 patients diagnosed as localized prostate cancer between the years 2006, and 2012 preferred active surveillance alternative. Thirty-four (17.3%) of these patients who had undergone at least one rebiopsy were included in the study. Mean age of the patients was 64.9 (55-73 yrs) years, and mean PSA value at diagnosis was 6.33 (2-10) ng/mL, while clinical stages of T1c (n=30), and T2a (n=4) were detected. Number of core biopsies obtained also differed (3, 12, and 18 biopsies in 6, 28, and 3 patients, respectively). Number of positive core biopsies also varied (1, 2, and 6 positive core biopsies in 31, 2, and 1 patient, respectively). Gleason score of all patients was 3+3 (Table 1).

Second biopsies were performed for 27 patients at an average of 14 (4-22) months later. Average number of 13 core biopsies

(12-21) were performed. On histopathological examination of the second biopsies of 11 patients, any evidence of tumor was not detected. Mean PSA value of these patients at the time of their admission, was 6.6 (4.3-9.2) ng/mL, and 7.1 (5.6-8.9) ng/mL on their first rebiopsies. Five of 6 patients who had tumor in one core was reported as Gleason score 3+3 prostate adenocarcinoma, and atypical small-cell acinar proliferation (ASAP) was detected in the remaining patient.

Mean PSA levels of these patients at diagnosis and on the first rebiopsies was 6.45 (3.1-9.4) ng/mL, and 7.5 (4-12.47) ng/mL, respectively. For a total of 17 (62.9%) patients without any evidence of tumor or with a tumoral invasion in one core, active surveillance was maintained. In the remaining 10 (37.1%) patients, 2-6 tumor positive cores were detected, and their Gleason scores were 3+3 in 7, 3+4 in 2, and 4+3 in 1 patient, respectively. Mean PSA levels of these patients at admission were 6.72 (4.2-10) ng/mL, and on rebiopsy 6.79 (1.18-11.3) ng/mL. Definitive treatment was administered to 10 patients with an increase in the number of positive cores and/or Gleason scores. These 10 patients were treated with radical prostatectomy (n=7) or radiotherapy (n=3) (Table 2).

Third biopsies were performed, at an average of 16 (5-38) months later in 9 (33.3%) out of 17 patients who were still under active surveillance. Tumor was not detected in five patients. In 4 patients, tumor-positivity was detected in only one core. Radical prostatectomy was performed on these 4 cases either because of patient's preference (n=1) or higher Gleason scores (3+4) (n=3). Fourth biopsies were performed at an average of 12 (11-13) months later on 2 out of 7 patients who were still monitored, and histopathological analyses of the specimens were reported as benign lesions (Table 2).

Third biopsies were done on 4 out of 10 patients whose second biopsy results were histopathologically reported as benign

Table 1. Baseline demographic, and clinicopathologic characteristics of the patients under active surveillance

Age (year)	64.9 (55-73)	
PSA (ng/mL)	6.32 (2-10)	
Clinical stage	T1c	30
	T2a	4
Number of biopsy specimens harvested	6 core	3
	12 core	28
	18 core	3
Number of prostate core biopsies	1	31
	2	3
Gleason score	3+3	34

Table 2. Treatment modalities applied based on histopathological results of rebiopsies

	Second biopsies (27 patients)					Third biopsies (9 patients)					Fourth biopsies (2 patients)				
	3+3 ≥2 cores	3+4	4+3	3+3 One core	Benign	3+3 ≥2 cores	3+4	4+3	3+3 One core	Benign	3+3 ≥2 cores	3+4	4+3	3+3 One core	Benign
RRP*	5	1	1	-	-	-	1	-	1	-	-	-	-	-	-
RT†	2	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Under surveillance	-	-	-	7	10	-	-	-	2	5	-	-	-	-	2
Lost to follow-up	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

*RRP, radical retroperitoneal prostatectomy; †RT, radiotherapy

lesions. Third biopsy results were reported as benign in 2 cases, while Gleason score 3+3 prostate adenocarcinoma was detected in other 2 cases. One of 2 patients with reportedly benign lesions underwent 4. biopsy which confirmed benign nature of the specimen.

Histopathologically, Gleason score of 3+3 in 5, and 3+4 in 3 patients was reported for surgical specimens of 5 out of 9 patients who had undergone radical prostatectomy during active surveillance, while any evidence of tumor was not detected in the radical prostatectomy specimen of the remaining patient. Mean tumor volume was 2.3 (0.2-4) cc. All patients were in pathologic stage T2. and in only one patient surgical margin positivity was detected. Gleason scores of 3 patients increased from 3+3 to 3+4, while those of 2 patients decreased. Gleason scores of 3 patients did not change, and reported as 3+3. Any evidence of tumor was not detected in radical prostatectomy specimen of one patient.

Generally, 27 patients under active surveillance who had undergone multiple biopsies were followed up for an average of 27.7 (12-78) months. As definitive therapy radical prostatectomy (n=9) or radiotherapy (n=3) was used for 12 (44.4%) patients. Nine (33.3%) out of 17 patients who were still monitored, underwent their third biopsies. Fourth biopsies were realized in 2 (7%) cases out of 7 patients who were still monitored. Monitorization of 15 out of 17 patients who had not undergone definitive treatment is still continuing.

Discussion

Though active surveillance is included in various treatment guidelines, it has not been used frequently. In the USA, since PSA screening test is used prevalently, patients eligible for active surveillance reaches to 69 percent. However, a study encompassing 800 males demonstrated that patients had preferred surgery (40%) radiotherapy (31%), brachytherapy (21%), and active surveillance (only 8%) in indicated frequencies. In that study, 60% of the patients who had preferred surgery expressed their intention of being freed from cancer.^[17,18] In our

study, 41 (20.9%) out of 196 patients diagnosed as localized prostate cancer in our clinic between the years 2006, and 2012 preferred active surveillance from offered treatment alternatives. As an outcome of increased number of PSA screenings, and developments in the biopsy technique, in recent years significant increases have occurred in the number of newly diagnosed low-risk prostate cancers. At the same time, 5-year survival rates related to prostate cancer have improved greatly from 75% to 99 percent.^[19] Sharing these data with patients in detail effects the preferences of the patients in favour of active surveillance during their decision-making process.

Though criteria of active surveillance have demonstrated variations, generally patients with clinical stage T1-T2a, PSA ≤10 ng/mL, Gleason score ≤3+3, and PSA density <0.15-0.2, and ≤2 positive cores were considered as eligible candidates for active surveillance. These patients were accepted as cases in the lower risk group with small-volume tumors.^[20] Although number of biopsy cores obtained varied in studies performed, 12-core biopsies are used at the time of the first diagnosis, and during routine follow-ups.^[16] Also 6 core biopsies were performed in 2 patients included in our study in 2006, at the time of diagnosis, and detected tumor in one core. Subsequent controls of these patients were performed with 12 core biopsies. In all other patients, in compliance with current literature, 12 core biopsies were performed. In some series, active surveillance was also implemented in patients with Gleason score 3+4, while usually active surveillance has been applied in cases with Gleason scores 3+3.^[21] Indeed, groups which also contained patients with moderate risk have higher probability of progressing into locally advanced stage, and PSA recurrence after radical prostatectomy.^[22] In our study, inclusion criteria into active surveillance were similar to those of PRIAS (Prostate Cancer Research International: Active Surveillance Study) study excepting PSA density.^[23] We didn't consider PSA density as one of our patient selection criteria.

Timing of follow-up, and biopsy differs among studies. In the PRIAS study, rebiopsies are recommended at 1., 4., and 7. years, while Johns Hopkins group prefers annual rebiopsies.^[23,24] In our

study, we applied the first rebiopsies approximately 14 months later, and the third biopsies an average of 16 months after the second rebiopsies. Criteria for the initiation of the therapy also differ among study groups. Excluding Toronto group, generally PSA kinetics are used alone as a criterion for initiating therapy. As criteria for initiating therapy, histopathological data retrieved from examination of biopsy material, and number of tumor-positive cores are taken into consideration.^[20] Increase in Gleason scores has been accepted as one of the indicators of disease progression. However, whether increase in Gleason score detected in histopathological analysis of rebiopsy material indicates actual score or it is related to the underestimation of the first biopsy score can not be precisely discriminated, and these two possibilities are taken into consideration.^[25] In our study, we also determined presence of ≥ 2 tumor-positive cores in the biopsy material and/or increase in the Gleason score as criteria for switching to definitive treatment. Lack of correlation or minimal correlation was found between PSA doubling time (DT), and PSA velocity on one, and deterioration of biopsy Gleason score, and increase in the number of positive cores on the other hand.^[26,27] In another study, it was suggested that only increase in PSA can not be an indicator of histopathological deterioration detected in biopsy materials, and promote earlier biopsy.^[21] In our study, we couldn't find any difference between PSA levels estimated at first diagnosis, and on second biopsy in patients requiring or not requiring definitive treatments. In consideration of the first rebiopsy results obtained in PRIAS study, in 21.5% of the patients, increase in Gleason score or tumor volume requiring cessation of active surveillance was detected. Disease progression was more advanced in patients with higher PSA density, and tumor positivity in 2 cores.^[28] In our study, on first biopsies of 2 out of 12 patients who required active treatment, tumor positivity in 2 cores was detected, while the remaining 10 patients had tumor positivity in only one core. Besides after the first rebiopsy, 37% the patients withdraw from the active surveillance. This higher rate of withdrawal might suggest understaging of the tumor on first biopsy specimens despite our scarce number of our patient population.

In a study where the patients with median follow-up periods ranging between 1.8, and 6.8 years were evaluated, 11-33% of the patients under active surveillance had been switched to definitive treatment.^[21] In our study group, 44.4% of our patients with a mean follow-up period of 27.7 months were switched to definitive treatment. In another review encompassing 3600 patients who had undergone active surveillance, only 6 patients had died from prostate cancer.^[21] However, it should be taken into consideration that these two studies included patients who hadn't fully complied with the criteria of active surveillance.^[22,23] Disease-specific survival ranged between 97, and 100% in an average follow-up period of 43 months.^[29] In our study, metastasis or prostate cancer death

was not detected in any patient during an average follow-up period of 27.7 months.

In our study, during active surveillance, pathology score was determined as Gleason score 3+4 prostate adenocarcinoma in 3 of 9 patients. All patients with a mean tumor volume of 2.3 (0.2-4) cc had a pathologic stage of T2, and only one patient had a surgical margin positivity. Histopathological evaluation of biopsy, and prostatectomy specimens of radical prostatectomized patients eligible for active surveillance revealed an increase in 45% of the patients, and progression to T2 stage in 20% of the cases.^[30] The possibility of pT3 in radical prostatectomized patients varies between 0, and 58 percent.^[29] When data of the PRIAS study were analyzed, in 38% of the delayed radical prostatectomized patients, surgical margin positivity was detected.^[28] Differences in selection criteria of the patients included in the active surveillance might create this large gap. However, in our study, only in one (11%) out of 9 radical prostatectomized patients surgical margin positivity was detected, and the tumors of the remaining 8 patients were prostate gland confined cancers.

Another point that drew our attention in our study, were patients whose first rebiopsy materials were reported histopathologically as benign. In none of these patients, treatment was required because of number of tumor-positive cores, and progression of Gleason score. Only one patient had undergone radical prostatectomy with his own preference after the third biopsy.

Scarce number of study patients is a limitation of our study. However, our study carries importance in that it is the first study conducted on this issue in Turkey.

In conclusion, active surveillance protects low-risk prostate cancer patients from complications of premature, and unnecessary radical treatment, while keeping the curative treatment option at hand. Active surveillance can be applied safely with appropriate patient selection, periodic examinations, and control.

Conflict of Interest: No conflict of interest was declared by the authors.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225-49.
2. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010;46:765-81.
3. O'Donnell H, Parker C. What is low-risk prostate cancer and what is its natural history? *World J Urol* 2008;26:415-22.
4. Cooperberg MR, Moul JW, Carroll PR. The changing face of prostate cancer. *J Clin Oncol* 2005;23:8146-51.

5. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320-8.
6. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol* 2010;11:725-32.
7. Etzioni R, Tsodikov A, Mariotto A, Szabo A, Falcon S, Wegelin J, et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. *Cancer Causes Control* 2008;19:175-81.
8. Dall'Era MA, Cooperberg MR, Chan JM, Davies BJ, Albertsen PC, Klotz LH, et al. Active surveillance for early-stage prostate cancer: review of the current literature. *Cancer* 2008;112:1650-9.
9. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320-8.
10. Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y, DiPaola RS, et al. Outcomes of localized prostate cancer following conservative management. *JAMA* 2009;302:1202-9.
11. Huang GJ, Sadetsky N, Penson DF. Health related quality of life for men treated for localized prostate cancer with long-term followup. *J Urol* 2010;183:2206-12.
12. Choo R, Klotz L, Danjoux C, Morton GC, DeBoer G, Szumacher E, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. *J Urol* 2002;167:1664-9.
13. Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hagino ED, Cookson MS, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol* 2007;177:2106-31.
14. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *Eur Urol* 2011;59:61-71.
15. Mohler J, Bahnson RR, Boston B, Busby JE, D'Amico A, Eastham JA, et al. NCCN clinical practice guide-lines in oncology: prostate cancer. *J Natl Compr Canc Netw* 2010; 8:162-200.
16. Prostate Cancer Research International: Active Surveillance. Active surveillance of early prostate cancer. PRIAS Web site. <http://www.prias-project.org>. Accessed November 14, 2011.
17. Iremashvili V, Pelaez L, Manoharan M, Jorda M, Rosenberg DL, Soloway MS. Pathologic prostate cancer characteristics in patients eligible for active surveillance: a head-to-head comparison of contemporary protocols. *Eur Urol* 2012;62:462-8.
18. Anandadas CN, Clarke NW, Davidson SE, O'Reilly PH, Logue JP, Gilmore L, et al. Early prostate cancer-which treatment do men prefer and why? *BJU Int* 2011;107:1762-8.
19. Catalona WJ. Screening and the Early Diagnosis of Prostate Cancer. Presentation 137-1, <http://2006.confex.com/uicc/uicc/techprogram/P10005.HTM>, UICC World Cancer Congress, Washington, USA, July 8-12, 2006.
20. Lawrentschuk N, Klotz L. Active surveillance for low-risk prostate cancer: an update. *Nat Rev Urol* 2011;8:312-20.
21. 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. *European Urology* 2012;62:976-83.
22. 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.
23. Van den Bergh RC, Roemeling S, Roobol MJ, Aus G, Hugosson J, Rannikko AS, et al. Outcomes of men with screen-detected prostate cancer eligible for active surveillance who were managed expectantly. *Eur Urol* 2009;55:1-8.
24. Tosoian JJ, Trock BJ, Landis P, Feng Z, Epstein JI, Partin AW, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol* 2011;29:2185-90.
25. Epstein JI, Walsh PC, Carter HB. Dedifferentiation of prostate cancer grade with time in men followed expectantly for stage T1c disease. *J Urol* 2001;166:1688-91.
26. Ross AE, Loeb S, Landis P, Partin AW, Epstein JI, Kettermann A, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. *J Clin Oncol* 2010;28:2810-6.
27. Whitson JM, Porten SP, Hilton JF, Cowan JE, Perez N, Cooperberg MR, et al. The relationship between prostate specific antigen change and biopsy progression in patients on active surveillance for prostate cancer. *J Urol* 2011;185:1656-60.
28. Bul M, Van den Bergh RC, Rannikko A, Valdagni R, Pickles T, Bangma CH, et al. Predictors of unfavourable repeat biopsy results in men participating in a prospective active surveillance program. *Eur Urol* 2012;61:370-7.
29. Klotz L. Active surveillance for favorable-risk prostate cancer: background, patient selection, triggers for intervention, and outcomes. *Curr Urol Rep* 2012;13:153-9.
30. El Hajj A, Ploussard G, de la Taille A, Allory Y, Vordos D, Hoznek A, et al. Analysis of outcomes after radical prostatectomy in patients eligible for active surveillance (PRIAS). *BJU* 2012;111:53-9.