At what stage are we in active surveillance for localized prostate cancer? Our clinical experience

Lokalize prostat kanseri için aktif izlemde hangi aşamadayız? Klinik deneyimimiz

İsmail Evren, Yavuz Onur Danacıoğlu, Mithat Ekşi, Deniz Noyan Özlü, Ahmet Hacıislamoğlu, Yusuf Arıkan, Ali Ayten, Hakan Polat

University of Health Sciences Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Urology, İstanbul, Turkey

Geliş tarihi (Submitted): 2022-06-20
Kabul tarihi (Accepted): 2022-10-20

Yazışma / Correspondence
Deniz Noyan Özlü
Zuhuratbaba Mah, Dr. Tevfik Sağlam Cd No:11, 34147 Bakırköy/İstanbul
Email: noyanozlu@hotmail.com
Tel: +90 535 233 64 40
Fax: +90 212 414 72 80

ORCID

İ.E.	0000-0003-4008-8038
Y.O.D.	0000-0002-3170-062X
M.E.	0000-0003-1490-3756
D.N.Ö.	0000-0003-2435-5482
A.H.	0000-0002-6117-2098
Y.A.	0000-0003-0823-7400
A.A.	0000-0001-8441-1293
H.P.	0000-0003-1525-1243

Özet

Amaç: Prostat kanseri (PCa) erkeklerde en sık görülen bir malignitedir ve taramayla erken tanı konulabilir. Aktif izlem (Aİ), düşük riskli prostat kanserli (DRPK) hastalarda tedavi yönetimi seçeneklerinden biridir. Bu çalışmada prostat kanserinde Aİ ile ilgili klinik deneyimimizi değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Ocak 2014 ile Aralık 2019 tarihleri arasında PCa tanısı konan 1650 hastanın verileri retrospektif olarak incelendi. Dahil edilme kriterleri; 75 yaş altı olma ve 10 yıllık yaşam beklentisi mevcudiyeti, klinik T1-T2a evre, PSA düzeyi <10 ng/dl, biyopsi kor ≤2 pozitif olmak ve biyopsi örneğinin patolojik incelemesinin sonucu olarak Gleason skoru ≤6 olunması olarak tanımlandı. Dahil edilme kriterlerinden herhangi birini karşılamayan hastalar çalışma dışı bırakıldı.

Bulgular: Dahil etme ve hariç tutma kriterlerinden sonra 176 hasta Aİ'i kabul etti ve çalışmaya dahil edildi. Ortalama takip süresi 25,2 ± 13 aydı. Toplam 57 hasta (32,3%) kesin tedavi için Aİ programından ayrıldı. Kesin tedavi 38 (65,5%) hastada radikal prostatektomi, 18 (31%) hastada radyoterapi ve bir (1,7%) hastada hormonoterapi idi.

Sonuç: Aİ, DRPK hastalarında kesin tedavinin komplikasyonlarını önlemeye yardımcı olan bir yöntemdir. Bu hastalarının yönetiminde kesin tedaviye alternatif bir seçenek olarak kullanılabilir. Ancak Aİ hastalarının 30%'unda definitif tedavi ihtiyacı doğuran patolojik upgrade'ler olabileceği unutulmamalıdır.

Anahtar Kelimeler: prostat kanseri, aktif izlem, düşük riskli prostat kanseri

Abstract

Objective: Prostate cancer (PCa) is the most common malignancy in men and early diagnosis can be made by screening. Active surveillance (AS) is one of the options for disease management in patients with low-risk prostate cancer (LRPC). In this study, we aimed to evaluate our clinical experience in AS for prostate cancer.

Material and Methods: Data from 1650 patients who were diagnosed with PCa in the period between January 2014 and December 2019, were retrospectively reviewed. Inclusion criteria were defined as being under 75 years of age and having a 10-year life expectancy, being at clinical stages of T1-T2a, having a PSA level of <10 ng/dl, having positive biopsy cores of ≤2, and having a Gleason score of ≤6 as the result of the pathological examination of the biopsy specimen. Patients not meeting any of the inclusion criteria were excluded from the study.

Results: After the inclusion and exclusion criteria, 176 patients agreed to undergo AS and were included in the study. The mean follow-up duration was 25.2 ± 13 months. A total of 57 patients (32.3%) left the AS program to undergo definitive treatment. Definitive treatment was radical prostatectomy in 38 (65.5%) patients, radiotherapy in 18 (31%) patients, and hormonotherapy in one (1.7%) patient.

Conclusion: AS is a method that helps avoid the complications of definitive treatment in LRPC patients. It can be used as an alternative option to definitive treatment in the management of these patients. However, it should not be forgotten that pathological upgrades may occur in 30% of AS patients, indicating the need for definitive treatment.

Keywords: prostate cancer, active surveillance, low-risk prostate cancer

The study was approved by Bakırköy Dr.Sadi Konuk Training and Research Hospital Clinic Investigations Ethic Committee (Approval No: 2020-19-11, Date: 21/09/2020). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Prostate cancer (PCa) ranks first among non-cutaneous cancers in men and is the second leading cause of cancer death in American men (1). The introduction of prostate-specific antigen (PSA) testing and the improvements in diagnostic procedures such as imaging studies and ultrasound-guided biopsy techniques have led to an increase in the diagnosis of PCa. It is seen that the majority of patients present with localized and low-risk prostate cancer (LRPC) (2). Along with increasing rates of early diagnosis, a decline has occurred in PCa mortality (3-5). It receives the attention that individuals with low-risk disease (Gleason scores of ≤ 6, PSA levels of <10 ng/mL, and a clinical stage T2a tumor; LRPC) have a better prognosis among all PCa patients. The options in the management of localized PCa include active surveillance (AS), radical prostatectomy (RP), and radiotherapy (RT). Conservative treatment strategies including AS are critical to decreasing complication rates associated with RT and RP. Such complications may include erectile dysfunction, urinary incontinence, cosmetic problems, surgically-induced hernia, ileus, and infections. The use of conservative treatment in the management of LRPC is gradually increasing in our country and the world (6).

In this study, we aimed to evaluate our clinic's experience in AS for prostate cancer.

MATERIAL AND METHODS

Data from 1650 patients who were diagnosed with PCa at Bakırköy Dr. Sadi Konuk Health Training and Research Hospital in the period between January 2014 and December 2019, were retrospectively reviewed. Inclusion criteria were defined as being under 75 years of age and having a 10-year life expectancy, being at clinical stages of T1-T2a, having a PSA level of <10 ng/dl, having positive biopsy cores of ≤2, and having a Gleason score of ≤6 as the result of the pathological examination of the biopsy specimen. Patients not meeting any of the inclusion criteria were excluded from the study.

AS and other options for definitive treatment were explained to the patients. Patients; who accepted the AS protocol, were included in the study. The demographic and clinical characteristics of the patients at the time of diagnosis, the follow-up times, multiparametric magnetic resonance imaging (mpMRI) lesion scores, pathological examination results of biopsy specimens, numbers and percentages of cores, and reasons for dropping out from the AS protocol were recorded retrospectively. All these processes were carried out in compliance with the principles of the Declaration of Helsinki. Permission was obtained from the local ethics committee to retrospectively screen the clinical data for the objectives of our study.

Follow-up Protocol

The recommended AS protocol required PSA testing and digital rectal examinations (DRE) at 3-month intervals and obtaining follow-up mpMRI images within 12 months. In addition to the standard confirmation biopsy, MRI fusion-guided biopsies were performed in the same session in patients with PIRADS 3 lesions or above. A standard confirmation biopsy was performed on patients, who did not have any lesions detected in mpMRI. Patients meeting the follow-up criteria were instructed to undergo biopsy or mpMRI annually. After the confirmation of the diagnosis via standard procedures, periodic transrectal ultrasound-guided surveillance biopsy or MRI fusion biopsy procedures were performed every 12 to 24 months based on clinical risks and observed disease processes. Diagnostic biopsy specimens obtained from referring institutions were reviewed by experienced genitourinary pathologists. Surveillance biopsies were performed by extended octant sampling to obtain a minimum of 10 cores. Indications for recommending definitive treatment to the patient included patient preferences, clinical progression, advancing Gleason grade, an advanced clinical stage, an increased tumor volume, elevated PSA levels, and an increased level of patient anxiety. The date of obtaining the first positive biopsy specimen at any institution was recorded as the date of diagnosis; which was recorded at the time of enrollment. The duration of follow-up was calculated as the time from the date of diagnosis to the date of the last contact with the patient.

Statistical Analysis

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used for

the statistical analysis. Descriptive statistical methods (mean, standard deviation, frequency, percent, minimum, and maximum) were used to evaluate the study data. The conformity of the quantitative data to a normal distribution was tested by the Shapiro-Wilk test and graphical methods.

RESULTS

Of 243 patients meeting the inclusion and none of the exclusion criteria, 176 agreed to undergo AS and were included in the study. Of the patients undergoing AS the mean age was 63±7 years and the mean follow-up duration was 25.2 ± 13 months. The demographic data of the patients and the characteristics for inclusion in the AS program are shown in Table 1. Of the patients included in the study, 100 patients underwent a confirmation biopsy. Seventy-six patients (43.2%) did not undergo a confirmation biopsy and were followed up with mpMRI. mpMRI was used in the follow-up of 175 (99.4%) patients included in the AS protocol. One patient could not undergo follow-up mpMRI due to contrast allergy. A total of 57 patients (32.3%) left the AS program to undergo definitive treatment. The reasons for switching the patients to definitive treatment are presented in Table 2. Pathological examination results of the confirmation biopsy specimens or RP specimens led to upgrading in 34.1% of the patients. Definitive treatment was RP in 38 (65.5%) patients, RT in 18 (31%) patients, and hormonotherapy in one (1.7%) patient. Findings obtained during the AS program and the results of curative treatment are listed in Table 2.

DISCUSSION

The majority of the patients are found to have LRPC at the time of diagnosis, in which overtreatment is associated with the high cost and increased need for post-intervention care. For these reasons, it is important to distinguish the fatal disease from others to prevent overtreatment (2). AS is a suitable option for patients; who are candidates for undergoing curative treatment but do not require immediate intervention at the time of diagnosis. Most LRPCs are slow-growing and eligible for surveillance through the examination of biopsy samples as they remain within the definitive curability limits (7). AS protocols include PSA testing, DRE, the use of imaging methods, and TRUS-guided biopsies. Such protocols may vary according to the institutions, where they are applied. The majority of the protocols only include patients with Gleason 3+3 disease; however, some institutions accept moderate-risk patients with Gleason 3+4 disease eligible for AS (8, 9). In different studies using the data from the "Cancer of the Prostate Strategic Urologic Research Endeavor" study; AS was preferred in the United States of America (USA) at a rate of 6.2% at the beginning of the 2000s, 10% at the year 2006, and 40% for low-risk tumors in the period between the years 2010 and 2013. That rate was reported to be 76.2% in patients over 75 years of age (10,11).

One of the most important steps in selecting AS as an option for the management of localized PCa is patient eligibility. Patient eligibility depends on the grade of the tumor, clinical characteristics of the patient, and finally patient preferences. Tumor-related features; including primarily the Gleason scoring and PSA testing, provide information about the clinical stage, progression, and extent of the disease (6). PCa is a slow-growing disease; in which the patient's age, comorbidities, expected life span, and patient preferences about living with cancer and treatment side effects are the other important parameters involved in the decision-making process (6, 12, 13). However, it has attracted the attention of the researchers that the primary diagnosis based on the needle biopsy results may not always be correct and that patients may be in the high-risk group despite the diagnosis of low-risk disease. Epstein et al. evaluated the total prostatectomy specimens of 7643 patients, who underwent RP and who were previously diagnosed with Gleason 5-6 disease based on needle biopsy findings. They found that only 36% of the patients had high-grade tumors (14).

The criteria used in the studies in the literature may vary across centers. Such criteria are summarized in Table 3. Those series usually include patients with T1c and T2a stage diseases, Gleason scores of <7, PSA levels of <10 ng/mL, and less than 50% involvement in positive cores (15-23). Recommendations about AS are similar to the American and European urology guidelines. Such guidelines recommend AS for patients with a

Table 1. The demographic data of the patients and the characteristics for inclusion in the AS programme.

Variables	Mean ± SD
Age at diagnosis (years)	63.07 ± 7.04
Follow-up period (months)	25.29 ± 13.94
Charlson Comorbidity Index	2.26 ± 0.96
Prostate volume (cc)	53.27 ± 22.5
PSA at the time of diagnosis (ng/dl)	5.93 ± 1.97
Lesion size on MRI (mm)	6.97 ± 2.7
Number of total biopsy cores (n)	10.78 ± 2.42
Number of positive biopsy cores (n)	1.29 ± 0.52

PSA: *prostate-specific antigen,* ***MRI:*** *magnetic resonance imaging*

Table 2. Findings obtained during the AS programme and the outcomes of curative treatment

Variables	N (%)
Confirmation biopsy	100 (56.8)
Confirmation biopsy Gleason Score	
Benign	30 (30)
3+3	51 (51)
3+4	10 (10)
4+3	8 (8)
4+4	1 (1)
Higher	0 (0)
Curative Treatment	57 (32.4)
Reason for leaving active surveillance	
Patient request	10 (17.5)
PSA increase	7 (12.2)
Positive core increase	20 (35)
Gleason score increase	19 (33.3)
Metastasis	1 (1.7)
Curative treatment option	
Radiotherapy	18 (31.5)
Radical prostatectomy	38 (66.6)
Hormonotherapy	1 (1.7)
Radical Prostatectomy Spesmen Gleason Score	
3+3	13 (34.2)
3+4	15 (39.5)
4+3	6 (15.8)
4+4	3 (7.9)
4+5	1 (2.6)
Extraprostatic extension	4 (10.5)
Seminal vesicle invasion	1 (2.6)
Surgical margin	5 (13.2)

Table 3. Inclusion criteria that are applied in various treatment centers

Center	Gleason score	Number of positive core	Tumor percentage	PSA	T stage
Royal Marsden NHS Trust	≤ 3+4	_	≤%50	≤15 ng/mL	≤2a
Miami University	≤ 3+3	≤ 2	≤%20	≤10 ng/mL	≤2
Johns Hopkins University	≤ 3+3	≤ 2	≤%50	PSAD≤0,15 ng/mL/ mL	1
University of California	≤ 3+3	≤ %33	≤%50	≤10 ng/mL	≤2
University of Toronto	≤ 3+3	≤ 2	≤%50	≤10 ng/mL	≤2
ERSPC*	≤ 3+3	≤ 2	_	PSA≤10ng/mL PSAD≤0,2ng/mL/m	1c-2
Bakirkoy Dr. Sadi Konuk	≤ 3+3	≤ 2	≤%50	≤10 ng/mL	≤2a

ERSPC: *The European Randomized Study of Screening for Prostate Cancer* ***PSA:*** *Prostate spesific antigen*
PSAD: *Prostate spesific antigen density*

low risk of tumor progression (24, 25). The AS criteria that have been applied in our clinic include PSA levels of <10 ng/mL, ≤2 positive cores in the rectal ultrasound-guided prostate biopsy, 50% rate of tumor presence in positive cores, a ≤ PIRADS 3 lesion, and T ≤ 2a lesion in mpMRI.

The rationale for the AS option may seem reasonable to physicians dealing with PCa but the reasons for not treating a potentially fatal disease at a treatable stage may not always be adequately understood by patients and their families. It has been reported that men frequently prefer to undergo AS to avoid unfavorable treatment effects on urinary and sexual functions (26-29). Long-term outcomes of AS, as a treatment option, are still unavailable. In a limited number of studies; the psychological conditions of patients, who preferred to participate in an AS program, were examined both at the time of the diagnosis and during the follow-up period. The number of patients switching from AS to definitive treatment for psychological reasons is substantial. Therefore, it should be kept in mind that the provision of information and psychological support to AS patients are critical (26-29). It has been reported that patients were switched to definitive therapy because they no longer met the AS criteria such as having increased Gleason scores in the confirmation biopsy results, increased numbers or percentages of cores, or elevated PSA levels. It has also been reported that patients were switched to definitive therapy solely based on the patient's request (26-29). In our study, 10 patients voluntarily withdrew their consent from participating in the AS program and decided to undergo definitive treatment despite continuing to meet the inclusion criteria.

The main reason for patients' selection of AS at the time of diagnosis is to avoid the potential complications of radical treatment such as urinary incontinence and erectile dysfunction (30, 31). On the other hand, patients have reported that they did not prefer to undergo AS at the time of diagnosis mainly because of the concern that cancer might progress to an incurable stage (30, 32). In the study conducted by Duffield et al; it was found that the disease was limited in the organ in 65% of the patients, who underwent radical surgery due to the detection of progression in the follow-up biopsy after a mean of 29.5 months in the AS program. However, 71% of the patients were found to have at least one of the following untoward histopathological characteristics; including extracapsular extension (EPE), a Gleason score of 4, or a tumor volume of > 1 cm^3 (33). It was reported in a study from Johns Hopkins that; among patients with stage progression in a control biopsy, 23% of RP patients had unfavorable histopathological pathological findings resulting in less than 75% chance of being disease-free in the 10 years after surgery (34). However; this rate was not different from that of patients, who had the same clinical features and who underwent radical surgery within 3 months after the diagnosis of PCa (34). The international multicenter prospective Prostate Cancer

Research International: Active Surveillance (PRIAS) study reported RP outcomes in LRPC patients, who were followed up in an AS program. The study reported that; of the patients, who underwent radical surgery after a median period of 1.3 years, the organ-limited disease was found in 80.8% but 29% of the patients had unfavorable histopathological findings including pT3-4 disease and/or a Gleason score of ≥4 + 3 (35). In our study, the rate of having upgraded disease in AS patients was found to be 34.1% after a confirmation biopsy or RP. Of our study patients, who preferred to undergo RP as a definitive treatment, the histopathological examination results were Gleason scores of 4+4 in three patients and 4+5 in one patient. Again, in this patient group, four patients had EPE and one patient had seminal vesicle invasion (SVI). When the results of the studies in the literature are evaluated together, it is seen that information about the outcomes of radical surgery after AS is still limited in LRPC patients and it is too early to reach a certain conclusion. However, it is observed that the pathological features of the disease meet the criteria indicating the need for treatment in at least a quarter of the patients. It remains to be a matter of curiosity about how this ratio will change in longer periods of surveillance and what the prognosis of such patients will be after treatment. In this context; considering the increasing experience in mpMRI, the inclusion of mpMRI in AS criteria will help the clinician to identify a second index lesion, anteriorly located or small-sized tumors, and difficult to detect tumors.

The number of patients included in this study could be considered small as a limitation of this study. Another limitation could be that our long-term results are not available.

CONCLUSION

AS is a method that helps avoid the complications of definitive treatment in LRPC patients. AS can be used as an alternative option to definitive treatment in the management of LRPC patients. However, it should not be forgotten that pathological upgrades may occur in 30% of AS patients, indicating the need for definitive treatment. Therefore; detailed information about all possibilities and options should be provided to patients, who are recommended to be followed up in an AS program.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Bakırköy Dr.Sadi Konuk Training and Research Hospital Clinic Investigations Ethic Committee (Approval No: 2020-11-19, Date: 2020/09/21) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Evren İ, Danacıoğlu YO, Hacıislamoğlu A, Polat H, Data acquisition; Danacıoğlu YO, Ayten A, Polat H, Data analysis and interpretation; Özlü DN, Ayten A, Drafting the manuscript; Danacıoğlu YO, Ekşi M, Özlü DN, Arıkan Y, Critical revision of the manuscript for scientific and factual content; Evren İ, Ekşi M, Özlü DN, Arıkan Y, Statistical analysis; Evren İ, Hacıislamoğlu A, Ayten A, Supervision; Evren İ, Hacıislamoğlu A, Polat H.

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