DOI: 10.5336/urology.2021-81636

The Active Surveillance for Low-risk Prostate Cancer: Case Series of Single Center

Düşük Riskli Prostat Kanserleri İçin Aktif İzlem: Tek Merkezin Olgu Serisi

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ABSTRACT Objective: Up to 80% of prostate cancer cases are indolent that pose a minimal risk for morbidity and mortality throughout the life of the patient. Cancer-specific survival of the patients just followed up and those who received curative treatment were found to be similar, especially in the low-risk category. Active surveillance was described to preserve the quality of life of the patients and to protect them from the side effects of curative treatments. It has become increasingly used in low and very low risk. Although there are many studies on this subject with a large number of patients in the literature, we aimed to present our first results in this study. Material and Methods: The data of the patients, that were included in the active surveillance program between January 2012 and April 2020, were retrospectively analyzed. The patients were diagnosed with low-risk prostate cancer according to D'Amico criteria (International Society of Urological Pathology grade group 1, prostate-specific antigen <10 ng/mL, stage cT1c-T2a) via a minimum 12 core transrectal ultrasound guided prostate biopsy due to suspicious digital rectal examination and/or prostate-specific antigen elevation. Results: Thirty-six patients, who preferred active surveillance were included in the study. The mean age and prostate-specific antigen values of the patients were 66.38±8.02 years and 5.63±2.3 ng/mL, respectively. The median follow-up was 18.4 (minimum 1.63-maximum 82.4) months. In the initial biopsy, the cancer was detected in one core in 25 (69.4%), two cores in 10 (27.8%), and three cores in one (2.8%) of the patients. A total of 7 (19.4%) cases had received curative treatment. 3 cases had progression in pathological parameters and 4 cases chose to have active treatment. Conclusion: Our initial results with active surveillance are similar to the literature. Per the literature, the number of patients that chose active surveillance has increased.

Keywords: Prostate biopsy; cancer; surveillance

Anahtar Kelimeler: Prostat biyopsisi; kanser; izlem

Prostate cancer (PCa) is the most frequently diagnosed cancer in men in the USA. Also, PCa alone constitutes more than one-fifth of the new cancer cases and is the second most common cause of cancer-related deaths. It is the second most frequently diagnosed cancer in men worldwide.^{1,2} The incidence

ÖZET Amaç: Prostat kanseri vakalarının %80 kadarı indolenttir. Has-

tanın yaşamı boyunca morbidite ve mortalite için minimum risk oluş-

tururlar. Sadece takip edilenler ile küratif tedavi alan hastaların kansere

özgü sağ kalımları, özellikle düşük risk kategorisinde benzer bulun-

muştur. Aktif izlem, hastaların yaşam kalitesini korumanın yanı sıra on-

ları küratif tedavilerin yan etkilerinden korumak için tanımlandı. Aktif izlem, düşük ve çok düşük riskte giderek daha fazla kullanılmaktadır.

Literatürde, bu konuda çok sayıda hasta ile birçok çalışma olsa da ça-

lışmamızda ilk sonuclarımızı sunmayı amaçladık. Gerec ve Yöntem-

ler: Ocak 2012 ile Nisan 2020 tarihleri arasında aktif izlem programına

alınan hastaların verileri retrospektif olarak değerlendirildi. Hastalara,

şüpheli dijital rektal muayene ve/veya prostat-spesifik antijen seviye-

sinin yükselmesi nedeniyle minimum 12 kor transrektal ultrason kıla-

vuzluğunda prostat biyopsisi yapılmış olup, D'Amico kriterlerine göre

düşük riskli prostat kanseri (International Society of Urological Patho-

logy grade group 1, prostat-spesifik antijen <10 ng/mL, evre cT1c-T2a)

teşhisi konulmuştur. **Bulgular:** Çalışmaya, aktif izlemi tercih eden 36 hasta dâhil edildi. Hastaların ortalama yaş ve prostat spesifik antijen

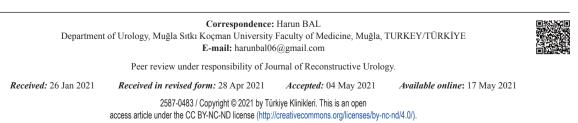
değerleri sırasıyla 66,38±8,02 yıl ve 5,63±2,3 ng/mL idi. Ortanca takip süresi 18,4 (minimum 1,63-maksimum 82,4) aydı. İlk biyopside hasta-

ların 25'inde (%69,4) 1, 10'unda (%27,8) 2 ve 1'inde (%2,8) 3 odakta kanser tespit edilmişti. Toplam 7 (%19,4) vaka, küratif tedavi almıştı.

Üç vaka, patolojik parametrelerde ilerleme gösterdi ve 4 vaka, aktif te-

davi olmayı seçti. Sonuç: Aktif izlemde ilk sonuçlarımız, literatür ile

benzerdir ve kliniğimizde, aktif izlemi tercih eden hasta sayısı artmak-



tadır

and treatment of PCa have been increased with the induction of prostate-specific antigen (PSA). The natural progression of PCa is variable, but it often progresses slowly. Up to 80% of cases, which are diagnosed with a biopsy performed after PSA screening, are indolent cancers that pose a minimal risk for morbidity and mortality throughout the life of the patient.^{3,4}

In the treatment of localized PCa, there are curative treatment options such as radical prostatectomy and radiotherapy. However, despite the advances in surgical techniques and medical technology, the side effects of local curative treatments on sexual, urinary, and bowel functions still persist.⁵ Also, these treatments have a limited effect on survival. Cancer-specific survival of the patients just followed up and those who received curative treatment were found to be similar, especially in the low-risk category.^{6,7} Considering these factors, concerns have arisen about the overdiagnosis and overtreatment of patients with PCa.³

Active surveillance (AS) was described for the first time in 2002, to preserve the quality of life of the patients, and to protect them from the side effects of curative treatments.⁸ The AS has become increasingly used in low and very low risk of PCa.^{4,9} It is also recommended for patients that have life expectancy over 10 years with low-risk disease, by the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) PCa guide-lines.^{10,11} Although there are many studies on this subject with a large number of patients in the literature, we aimed to present our first results.

MATERIAL AND METHODS

Ethical approval of the study was obtained from the ethics committee of Muğla Sıtkı Koçman University at 21.07.2020 with the decision number of 153. The data of the patients within the AS program from January 2012 to April 2020 were retrospectively analyzed.

The patients were diagnosed with PCa via a minimum 12 core transrectal ultrasound (TRUS) guided prostate biopsy due to suspicious digital rectal examination and/or PSA elevation. Only low-risk patients according to D'Amico criteria [International Society of Urological Pathology grade group (ISUP GG) 1, PSA <10 ng/mL, stage cT1c-T2a] were included in the AS program.¹² The patients with multiparametric magnetic resonance imaging (MRI) had undergone cognitive targeted biopsies of the lesions in addition to standard TRUS-guided prostate biopsies. Furthermore, the necessity of repeat laboratory test, digital rectal examination and prostate biopsies were explained to the patients and their consents have been taken. The patients with incomplete or missing data and that chose curative treatment were excluded from the study. PSA values, ISUP GG, the number of the cores with cancer, the percentage of the cancer in each positive core follow-up duration, and curative treatment status of the patients were evaluated. In the follow-up, assessment of the PSA level and digital rectal examination were performed every 3 months.

SPSS 22.0 (SPSS Inc, Chicago, IL, USA) program was used to analyze the data, and p value <0.05 was accepted as statistically significant with a 95% confidence interval. Continuous variables were evaluated by t-test, and categorical variables were evaluated by chi-square test. The research was conducted in accordance with the 1964 Helsinki Declaration.

RESULTS

Thirty-six patients who preferred AS were included in the study. The mean age and PSA values of the patients were 66.38±8.02 years, 5.63±2.3 ng/mL, respectively. The median follow-up was 18.4 (minimum 1.63-maximum 82.4) months (Table 1). There was no significant difference between first and second biopsy, regarding aforementioned variables.

In the initial biopsy, the cancer was detected in 1 core in 25 (69.4%), 2 cores in 10 (27.8%), and 3 cores in 1 (2.8%) of the patients. While the median cancer percentage in positive cores was 15 (minimum 1-maximum 50), this rate was $\leq 20\%$ in 30 (83%) of the cases.

Due to the short follow-up duration, only 19 (52.8%) patients were able to undergo a second biopsy. In the second biopsy, 2 (10.5%) patients had an increase in the ISUP GG, and the mean age of these patients was 75.48 years. There was a significant difference of the distribution of ISUP GG between first

TABLE 1: Descriptive data of the first and second biopsy.			
	First biopsy (n=36)	Second biopsy (n=19)	p value
Mean age (years)	66.38±8.02	63.91±7.28	0.267
Mean PSA (ng/mL)	5.63±2.3	5.74±2.51	0.617
Median of "cancer per core" (%)	15 (minimum 1-maximum 50)	5 (minimum 5-maximum 70)	0.249
Number of the patients with:			
ISUP GG 1	36	8	0.06
ISUP GG 2	0	2	
Number of the patients with:			
1 positive core	25 (69.4%)	2 (10.5%)	0.001
2 positive cores	10 (27.8%)	3 (15%)	
3 positive cores	1 (2.8%)	3 (15%)	
>3 positive cores	0	2 (10.6%)	
Number of patients with benign pathology	0	9	-
Median follow-up duration (months)	18.4 (minimum 1.63-maximum 82.4)	22.8 (minimum 13.7-maximum 82.4)	0.193

PSA: Prostate-specific antigen; ISUP GG: International Society of Urological Pathology Grade Group.

and second biopsy (p=0.001). While the number of positive cores increased in 5 (26.31%) of patients, only 2 of them had a positive core number above 3. An increase in the percentage of positive cores was found in 6 (31.6%) patients, but only 2 of these patients had a cancer percentage over 50. Just 2 (5.6%) of the patients underwent a third biopsy, none of these patients had a progression of the ISUP GG, number of the positive core, or the percentage of the cancer in the positive core.

Five (13.8%) of the patients had an MRI before the second biopsy. Prostate Imaging Reporting and Data System (PIRADS) 4 lesions were detected in 2 of these patients, and the others had PIRADS \leq 3 lesions. But none of the patients with pre-biopsy MRI showed progression of the ISUP GG, number of the positive core, or the percentage of the cancer in the positive core.

A total of 7 (19.4%) cases received curative treatment. Three of them showed progression in the pathological parameters (1 of the patients had increase in the ISUP GG, the other one had increase in both number of positive core and percentage of cancer, and the last patient had progression in all parameters of the biopsy pathology). The other 4 cases chose curative treatment without progression of pathological parameters. Of these patients, 2 (28.57%) underwent surgery and 5 (71.42%) received radiotherapy. The median time to curative treatment was 17.9 (minimum 3.03-maximum 26.43) months.

DISCUSSION

The diagnosis of PCa has increased rapidly after "screening with PSA" which has been shown to cause a reduction in cancer-specific death rates.¹³ However, this situation also led to an increase in the diagnosis and overtreatment of low-risk tumors that early diagnosis and treatment will not change the prognosis.¹⁴ There is debate on whether the curative treatments may provide a survival advantage in low-risk patients, but they certainly cause complications that might impair quality of life.¹⁵⁻¹⁷ AS is increasingly used in our clinic against possible overtreatment risk without losing the chance of curative treatment.

Leapman et al., reported the outcomes of over a thousand patients undergoing AS in 2017.¹⁸ In that study, the mean age of the patients was over 60, which was similar to our study, and nearly half of the patients were younger than 60 years of age. The results of both age groups were similar in that study regarding the risk of definitive treatment.¹⁸ Although the mean age of the patients in our study was similar with the literature, we could not conduct an analysis for comparation between age groups due to low number of patients.¹⁹

For the AS of patients with low-risk PCa, many different inclusion criteria (combinations of fitness for curative treatment, clinical-stage, PSA, pathological parameters, and at least 10-year life expectancy), and protocols have been used, and results of these have been reported.^{20,21} AS of intermediate-risk patients is also recommended by some centers. However, these patients have a higher risk of progression and metastasis.^{22,23} In a study where 20% of patients were at intermediate risk, despite close follow-up, the 15-year metastasis-free survival was 3.7 times lower in the intermediate-risk group. Also, when compared with the patients with ISUP GG 1, 15-year PCa mortality was determined to be 4 times more in ISUP GG 2 and 10.5 times more in ISUP GG 3.²² In our study, all patients were in the low-risk group according to the definition of D'Amico.¹² Their ISUP GG were 1, positive core numbers ≤ 3 , percentages ≤ 50 , and PSA values ≤10. Our follow-up duration was not sufficient to evaluate metastasis-free survival and mortality.

We recommended the second (verification) biopsy to the patients 12 months after the first biopsy. Although there is no consensus in the literature regarding the timing of this procedure, it is recommended to be performed 6-12 months after the first biopsy. It has also been demonstrated that the time frame between biopsies does not cause any change in the rates of detection of pathological progression.²⁴ Pathological progression, which was found in 10-40% of the cases in the literature, was detected in only 3 (8.3%) of our patients.^{25,26} Two reasons may explain the lower progression rates. Firstly, all of the cases had low-risk PCa, and secondly, as a result of the relatively low follow-up duration, only half of the patients underwent a second biopsy. In the literature, however, pathological progression rates have been shown to increase with age. In multivariate analysis, this rate was found to increase at least 2 times per decade, not only in repetitive biopsies but also in patients undergoing radical prostatectomy.²⁷ In our study, the cases with pathological progression consisted of patients of advanced age in accordance with the literature.

More than 80% of clinically important PCa patients can be diagnosed with MRI. Prospective studies have shown that targeted biopsies under MRI guidance are better in detecting clinically important cancers than systemic biopsies.²⁸ More than half of the patients who are clinically appropriate for AS have suspicious lesions on MRI, and these patients have higher rates of detection of clinically significant disease in recurrent biopsies.²⁹ Also, it has been shown that the patients who are included in AS with targeted biopsy have a lower rate of pathological progression than the patients with a systemic biopsy.³⁰ Despite its advantages, approximately 15% of clinically important cancers may be skipped with the MRI used in AS.³¹ In the guidelines, performing an MRI before the first biopsy is recommended with a combination of targeted and systemic biopsies. It is also stated that the conformation biopsy is not necessary for the patients with pre-biopsy MRI.¹¹ As a result of the technical insufficiency of our MRI scanner, only 13% of our patients had MRI scans before the biopsy, and none of these patients had pathological progression. With the new MRI device, all the patients are scanned before the biopsies, as recommended in the EAU and NCCN PCa guidelines.^{10,11}

The discontinuing rate of AS varies between 20-80%, and, as expected, increases as the duration of the follow-up duration increases (around 9% each year). While the majority of patients switch to curative treatment due to pathological and/or clinical progression, reasons such as anxiety and patient preference are the other factors.^{32,33} In our study, 20% of patients chose to switch to curative treatment per the literature. However, in half of the patients who switched to curative treatment, the patient preference was the responsible factor. Patients might need to be given more information about the safety of the AS.

The first study about AS in our country was conducted by Soydan et al. in 2013.³⁴ They analyzed the results of 41 patients on AS. The mean age of the patients was 64.9 years which is similar to our result. Their median PSA level and follow-up duration were 6.32 ng/mL and 27.7 moths, respectively. Both of these values were higher than ours. The higher PSA values would be explained with more strict PSA screening over the last decade.³⁴ One of the largest series of Turkish population with low risk PCa undergoing AS, with a long median follow-up duration of 42 moths, was reported by Bayar et al.³⁵ The patients of that study were younger than the patients in our cohort, but the median PSA value was similar. Differently, Bayar et al. performed an immediate rebiopsy (within 3 months). As a result, nearly one third of the patients underwent definitive treatment due to progression of pathological parameters in the immediate re-biopsy.³⁵ The number of the patients and the follow-up duration of our study were lower; however, these results could reflect the adoption of AS in a specific region of our country.

The most important limitation of this study was its retrospective nature. Moreover, the number of the patients with follow-up biopsies and MRI of the prostate were very low. Also, the patient with MRI underwent cognitive fusion biopsy instead of in-bore or software guided targeted fusion biopsies. Due to these limitations, the results of the statistical analysis could be flawed. Although the number of patients is low and follow-up duration is short, we think that we can present our long-term results with an increase in the number of patients and biopsies in a short time. Additionally, these results could reflect the tendency of the patients who are eligible for AS in our region.

CONCLUSION

Our initial results with AS are similar to the literature. Moreover, the number of patients that chose AS has increased over the years in our clinic.

HIGHLIGHT KEY POINTS

AS of the patients with low-risk PCa is safe and feasible.

The results of the AS are similar in the inexperienced centers with high-volume centers.

The patients with low-risk PCa should be informed about the AS option.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: İlker Akarken, Hüseyin Tarhan; Design: İlker Akarken, Harun Bal; Control/Supervision: Hayrettin Şahin, Hasan Deliktaş; Data Collection and/or Processing: Harun Bal, İlker Akarken, Hasan Deliktaş; Analysis and/or Interpretation: İlker Akarken, Hüseyin Tarhan; Literature Review: Hayrettin Şahin, Harun Bal; Writing the Article: İlker Akarken, Harun Bal; Critical Review: Hayrettin Şahin, Hasan Deliktaş, Hüseyin Tarhan.

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