Prognostic influence of 5 alpha reductase inhibitors in patients with localized prostate cancer under active surveillance

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ABSTRACT

Objective: The incidence of prostate adenocarcinoma (PCa) is increased with the use of prostate-specific antigen (PSA). In the current study, we aimed to investigate the impact of 5- alpha- reductase inhibitors (5-ARI) on pathological progression in patients followed by active surveillance (AS).

Material and methods: Records of 69 patients with localized prostate cancer under AS (PSA ≤ 15 ng/mL, PSAD ≤ 0.20 , $\leq cT2c$, Gleason sum $\leq 3+3$, the number of cancer positive cores ≤ 3) were evaluated retrospectively. Patients were followed-up with quarterly PSA testing and semiannual digital rectal examination during the first 2 years, and semiannual PSA testing thereafter. Repeat biopsies were done annually and whenever indicated by clinical findings. Pathological progression was defined as increasing Gleason grade, number of cancer-positive cores, and/or increasing percentage of cancer in any core.

Results: Patients using (29/69: 42%) and not using (40/69: 58%) 5-ARI were followed for a median of 39 (IQR: 23-45) and 23.5 (IQR: 17-37.5) months, respectively. Pathological progression was observed in 32% (22/69) of the patients at a median of 25 (IQR: 18-39) months. Pathological progression was observed in 34.5% (10/29) and 30% (12/40) of the patients using and not using 5-ARI, respectively (Log-rank $p=0.4151$). Definitive treatment was done in 31% (9/29) and 47.5% (19/40) of the patients using and not using 5-ARI, respectively. Patients who did not use 5-ARI received definitive treatment earlier than 5-ARI users (Log-rank $p=0.0342$). On multivariate analysis, more than 2 cancer-positive cores (HR: 11.62) and age (HR: 0.94) were independently associated with pathological progression ($p<0.05$), rather than 5-ARI use ($p=0.148$).

Conclusion: More than 2 cancer- positive cores at the initial biopsy was the strongest covariate associated with pathological progression; these patients should not be offered AS. There was no impact of 5-ARI use on pathological progression in AS.

Keywords: 5-alpha-reductase inhibitors; active surveillance; prostate cancer

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Introduction

Prostatic adenocarcinoma (PCa) is the second most frequent cancer in male population, and ranks sixth among cancer-related deaths.^[1] This phenomenon is a result of early diagnosis of PCa, and its slow progression. In some of the patients who received diagnosis of PCa, the disease either progresses very slowly or does not demonstrate clinical progression during the lifetime of the patient.^[2-4]

Among the treatment approaches for localized PCa patients with low Gleason scores, apart from radical radiotherapy (RT), and radical prostatectomy (RP) with similar oncological outcomes as for treatment success rates but serious side effects, active surveillance (AS) has also taken its place in the guidelines of European Association of Urology (EAU), and American Urological Association.^[5,6]

As is known, 5- α - reductase Inhibitors (5-ARIs) lead to *apoptosis* both in benign, and

malignant prostate cells.^[7] Though, prophylactic use of 5ARI in PCa is still debatable. The decision of 5ARI use should be made after a well information by patient.^[8]

We reviewed patients PCa medical treatment records, serum total prostate- specific antigen (PSA) levels, digital rectal examination (DRE) findings, and histopathological reports of transrectal ultrasound (TRUS) -guided biopsy specimen. In the present study we aimed to evaluate the effects of 5-ARIs used for lower urinary tract symptoms for patient on AS.

Material and methods

The medical records of ninety patients who had been on AS at Kocaeli University, School of Medicine in between February 2002 and April 2011 were reviewed retrospectively. The patients with Gleason sum greater than 6 (n=3), those using GnRH analogues, and/or antiandrogen or 5-ARIs, (n=9), cases with density PSA density (n=2), missing rebiopsies (n=3) or medical records (n=4) were excluded from the study. Evaluation was performed with 69 patients.

Clinical follow-up was performed in compliance with the protocol beginning from the first biopsies of the patients. Disease was staged based on 2010 TNM classification system. Control examinations of all patients whose PCa was diagnosed based on TRUS biopsy results, and managed with AS protocol were performed at 3, and 6-month-intervals within the first two years with PSA test, and DREs respectively. Follow-up after second year was scheduled as PSA test, and DREs biannually. TRUS biopsy was done promptly in the presence of increased PSA levels or an abnormal DRE findings, otherwise it is performed annually. Increase in total Gleason sum the number or percentage of cancer-positive cores during histopathological examinations of rebiopsy materials was considered as "Pathological Progression". Definitive treatment was recommended for the patients with pathological progression. The 'definitive treatment time' was defined as the date of RP or the date of RT. Inclusion and follow-up protocol was based on previously defined PRIAS criterias (Table 1).

For TRUS Toshiba SSA-550A Ultrasound device, and 6 Mhz 150° Endorectal (PVT-651VT) headpiece, and for biopsy 18G 20 cm biopsy needle were used.

Statistical analysis

For statistical analysis of the collected data, "STATA MP Parallel Edition Statistical Program" (Statistics/Data Analysis StataCorp Texas USA; version 11.2) was used. Normality of distribution was evaluated using "Shapiro-Wilk Normality Test". As descriptive statistics "arithmetic mean $\pm$ standard deviation (SD)", and "median" (interquartile range [IQR]) were used.

For continuous variables with normal or non-normal distribution, T-test, and Wilcoxon Rank-sum Test were used, respectively. For categorical variables *chi*-square test (χ^2) was used. The time to pathological progression or administration of definitive treatment was evaluated using, "Kaplan-Meier Test", and intergroup comparisons were performed using Log-Rank Test.

On Kaplan-Meier curve, ticks on X-axis of a datetime plot demonstrates "patients lost to follow-up", those below the X-axis represents the patients manifesting pathological progression or those receiving definitive treatment.

In the evaluation of independent factors which may be used in the prediction of pathological progression Cox Proportional Hazard Method was used, and evaluated utilizing "Univariate, and Multivariable Analytical methods."

In multivariable analysis, the purpose of evaluating independent factors was not to determine the pathological evaluation precisely, but to detect the influential factors. Therefore, for inclusion in and exclusion from the model in the modelling process, threshold value for *p* was accepted as <0.1 . In other tests performed $p < 0.05$ was accepted as the statistically significant threshold value.

Results

Mean age of the whole group was 67 ± 7.8 years, with a median follow-up time of 26 months (IQR: 18-42). Patients were using (42%) or not using (58%: 40/69) 5-ARI (Table 2). The distribution of used 5ARIs, finasteride and dutasteride were, 32% (n=7) and 68% (n=22), respectively.

Median follow-up time of 5-ARI users, and nonusers were 39 months (IQR:23-45 mos), and 23.5 months (IQR:17-37.5), respectively. At a median 25. month (IQR:18-39) of the follow-up time pathological progression occurred in 32% (22/69) of the patients.

Table 1. Study inclusion criteria

PSA ≤ 15 ng/mL
PSAD ≤ 0.20 ng/mL/cc
Clinical stage $\leq T2c$
Total Gleason score ≤ 6
Number of cancer-positive cores ≤ 3
Not receiving prostate cancer treatment
PSA: prostate-specific antigen; PSAD: prostate-specific antigen density

Table 2. Clinical and pathological characteristics of the patients who did or did not receive 5-ARI

	5-ARI (+) (n=29)	5-ARI (-) (n=40)	p
Age (years); mean±SD	66.5±6.1	67.7±8.9	0.3362
Initial PSA (ng/mL); median (IQR)	5.37 (4.3-6.5)	5.15 (4.0-7.1)	0.5233
PSAD (ng/mL/cc); mean ±SD	0.11±0.04	0.12±0.05	0.346
Prostate volume (mL); median (IQR)	51.9 (35-62.3)	42.8 (33.3-55.5)	0.2263
Follow-up (months); median (IQR)	39 (23-45)	23.5 (17-37.5)	0.0131
Pathological progression in rebiopsy; n (%)	10 (34.5)	12 (30)	0.693
The first rebiopsy	7 (24.1)	12 (30)	0.179
Subsequent rebiopsies	3 (10.4)	0	-
Patients with rebiopsy total Gleason scores 8-10; n (%)	3 (10.4)	1 (2.5)	0.169
Patients receiving definitive treatment upon their own preference; n (%)	0	7 (100)	0.035

5-ARI: 5-alpha-reductase inhibitors; PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; SS: standard deviation; IQR: interquartile range

Figure 1. Survival without pathological progression according to the use of 5-ARI

Histopathological examination of biopsy materials of 22 patients demonstrated pathological progression at a median 19.5 months (IQR: 14.5-35.5 mos). Increases in Gleason grade scores (n=18), number of cancer-positive biopsy cores (n=3),

and percentage of cancer-positivity (n=1) were seen in respective number of patients. Seven out of 69 (10.1%) patients were given definitive treatment upon their own preference. RP, and RT were preformed for 30.4 (21/69), and 10.6% (8/69) of the patients, respectively.

At median 39 months (IQR:23-46) follow-up a 59.4% (40/69) of the patients were still on AS. PCa-related death was not observed. Mortality rate due to non-PCa causes was 5.8% (4/69). Pathological progression was seen in 34.5% (10/29) of 5-ARI users, and 34.5% (10/29) of nonusers who were both under AS (p=0.693).

Mean follow-up time of the patients with pathological progression were 30.4±11, and 6.8±11.5 months for 5-ARI users, and nonusers, respectively. The time interval between onset of 5-ARI usage and pathological progression was evaluated, and it was found that use of 5-ARI did not slow down pathological progression (Figure 1, Log-rank p=0.4151).

When 7 patients who received definitive treatment upon their own will were excluded from the evaluation, 5-ARI had not any effect on pathological progression (Log-rank p=0.4114). Moreover none of 7 patients who received definitive treatment upon their own will were not using 5-ARI. When 7 patients who received definitive treatment upon their own request were excluded from the evaluation, 5-ARI had no effect on pathological progression (Log-rank p=0.4114). Any intergroup difference was not observed as for patient characteristics, age, initial PSA, and prostate volume (Table 2).

Median time to definitive treatment for 5-ARI users and nonusers were, 24 (IQR:20-39), and 17 (IQR:9-32) months, respectively (p=0.0386). Increases in total Gleason scores were confirmed in 85.7% (18/21) of the patients who underwent RP for definitive treatment, while total Gleason scores did not increase in 2 patients who received RP and persisted at 3+3 points. Histopathology of one patient who received RP because of total Gleason score of 5+4 was reported as pT2c N1. At postoperative 14. months, treatment with 10.8 mg goserelin + 50 mg bicalutamide was initiated because of bone metastasis.

In univariate analysis age, concomitant disease, clinical stage, 5-ARI use, PSAD, prostate volume, initial PSA and number of cancer-positive cores were not statistically significant. In multivariable analysis, a model was constructed using age, number of cancer-positive cores detected in the first biopsy material, and use of 5-ARI (p=0.047). In multivariable analysis age was associated with pathological progression (HR: 0.94 [95% CI: 0.89-0.99], p=0.017, though 5-ARI use not (p=0.148). The number of cancer-positive cores in biopsy specimen has the highest HR on pathological progression (Table 3, HR: 11.62 [95% CI: 1.28-104.97], p=0.029)).

Table 3. Results of multivariate analysis of risk factors for pathological progression

	Hazard ratio (95% CI)	p
Age, year	0.94 (0.89-0.99)	0.017
Number of samples with cancer >2	11.62 (1.28-104.97)	0.029
Nonuse of 5-ARI	1.93 (0.80-4.69)	0.148
Overall model		0.047

5-ARI: 5-alpha-reductase inhibitor; CI: confidence interval

Figure 2. Survival without definitive treatment according to the use of 5-ARI

Discussion

AS has taken its place in low-risk PCa guidelines. About 30% decrease in the progression of PCa has been reported among 5-ARI users.^[4,9] In the present study, PSA, PSA ratio, PSAD, and PSADT parameters were used not as treatment targets but as a trigger of re-biopsies. In Toronto, and Rotterdam series PSA doubling time was used as a trigger for treatment and pathological progression for definitive treated patients were reported in 48% (65/135), and 30.5% (25/82), respectively. Though detailed histopathological results of the definitive treated patients were not clearly reported.^[10,11]

In an AS study results of 262 patients were reported. Because of pathological progression about 50% (20/43) patients had RP during a median follow-up of 29 months. In final pathology reported Gleason sum was ≥ 7 , while positive surgical margin rate was 8%, extraprostatic extension rate was 15%, and positive lymph node rate was 4%.^[12] In the Johns Hopkins series which had a very strict on patient selection criteria, lymph node positivity rate was

2.1% (2/96).^[13] In the current study lymph node metastasis was detected following RP only in one patient with a Gleason sum of 9. Bone metastasis developed at the follow-up. Obviously AS has some risks, though these risks may be lowered by strict patient selection criterias.

The main objective of AS is to follow-up patient with a clinically insignificant PCa in a certain protocol. Despite implementation of strict selection criteria, the decision to with definitive treatment build by follow-up evaluations. Because of emergence of adverse outcomes of AS (ie. lymph node positivity) more precise diagnostic, and follow-up criteria (ie. genetic structure of cancer cells, genetic markers, and tumor ploidy) are needed. Biological behaviour of PCa has not been fully elucidated yet. Therefore leaving a disease untreated for a long time, which has a chance of curative treatment comes with risks.

In our study, pathological progression at the first and subsequent re-biopsies were 86.4% (19/22) and 13.6% (3/22), respectively. In a study, “rebiopsy within the first 3 months” was included in the inclusion criteria to confirm tumor histopathology.^[12] In another study by Berglund et al.^[14] on the issue, rebiopsies were performed in 104 patients scheduled for AS at median 6 months after initial biopsy. Increase in grade and/or stage of the tumor was 27% (28/104), and these patients were excluded from the AS protocol. For the selection of patients for AS, rebiopsies performed at an early stage may increase the probability of detecting clinically significant PCa.

In a study performed to evaluate the effects of dutasteride on PCa, 75 patients with low-risk prostatic adenocarcinoma were randomized into three groups and received placebo, 0.5 mg or 3.5 mg dutasteride for 4 months before RP. On the day of the surgery, when compared with placebo group more than 90% decrease in serum, and intraprostatic DHT values were detected in the dutasteride group. In the placebo group tumor volume and Gleason sum were higher than dutasteride groups.^[15] This study evaluated the effects of dutasteride in PCa patients. However patients used the dutasteride for a short term. Drop in DHT values may be one of the factors effective in decreasing tumor volume. However, long-term antitumoral effects of dutasteride is not certain yet.

In the PCPT study 9.060 patients were randomized into finasteride (n=4.368), and placebo (n=4.692) groups. At the end of 7 years follow-up, a 24.8% decrease on PCa detection rate was reported for finasteride group. The most important outcome of the PCPT study was that high-grade PCa (Gleason sum ≥ 7) was 25.5% more frequently detected in the finasteride group than Placebo group.^[4]

In the REDUCE study 6.729 patients were randomized into dutasteride, and placebo groups. PCa detection rate for dutasteride and

placebo groups were 19.9, and 25.1%, respectively.^[9] According to the results of this study, long-term dutasteride use decreased rates of low-risk PCa (Gleason sum 5-7). Though, high-grade PCa (Gleason sum 8-10) rate did not change with dutasteride treatment for the first 2 years, but increased after 4 years.

In our study pathological progression for 5-ARI users and nonusers were 34.5% (10/29), and 30% (12/40), respectively at a median follow-up of 24 months (Table 2). High-grade PCa with a Gleason sum of 8-10 was observed in 3 patients with 5-ARI, and in only 1 patient among the nonuser which was not statistically significant. Pathological progression at a median follow-up of 24 month tends to support the results of REDUCE, and PCPT studies. These studies supports that the use of 5-ARI increases incidence of high-grade PCa.

In a randomized study where the effects of short-term dutasteride use on pathological outcomes were evaluated, 148 patients with low-risk PCa detected in 12 TRUS biopsy cores were given 0.5 mg dutasteride or placebo for 3 months. In this study pathological progression in the placebo group was higher than the dutasteride group (OR:2.86, 95% CI 1.40-5.87; $p<0.0036$).^[16] In both studies 5-ARI was used for a short time, and decrease in the rate of pathological progression may become manifest due to short-term effects of 5-ARI use. Our results could not demonstrate a difference in pathological progression rate of PCa for a relatively long-term 5-ARI use ($p=0.693$).

Clinical progression may be slow down for a short time with a 5-ARI usage on AS. However long-term use of 5-ARI do not contribute to lower pathological progression rate. The REDEEM study detected that dutasteride use statistically significantly delayed pathological or therapeutical progression relative to placebo at the end of 3 years of follow-up (36 months vs. 18 months) (HR:0.62; 95% CI: 0.43-0.89).

Contrary to REDUCE, and PCPT studies, no difference reported between placebo and dutasteride groups for high-grade PCa rate at the 3. year.^[17] In the present study, time to pathological progression in the dutasteride group was statistically significantly longer than nonusers (17 vs. 24 months) similar to previously mentioned study. Any intergroup difference was not detected as for rates of high- grade cancer.

In a study by Ross et al.^[18] 5-ARI users (n=47) and nonusers (n=540) on AS were compared as for pathological progression. At the end of a median follow-up period of 1.8 years, a statistically significant difference was not detected between 5-ARI users, and nonusers as for pathological progression. As reported in this study, none of the parameters used in multivariable analysis (age, number of cancer-positive cores detected at initial biopsy material, initial PSA, f/t PSA ratio, alpha-blocker use,

PSAD, and prostate volume) had not contributed to decrease in PCa detection rates with 5-ARI use.

In the present study, presence of more than 2 cancer -positive biopsy cores was found to be effective factor for pathological progression (HR:11.62). Therefore, we suggest that patients who had more than 2 cancer-positive cores should not be followed up with the AS protocol. As a characteristic of multivariable regression analyses, studies performed with higher number of cases allow making more reliable, and accurate predictions. When compared with non 5-ARI users, 5-ARI users were relatively low and has a shorter follow-up period in both the present and Ross et al.^[18] studies. Because the non-homogeneous distribution of patients, results of both studies should be evaluated cautiously.

In a study by Finelli et al.^[19] reported the results of 288 patients under AS. After a median follow-up time of 38.5 months, they observed pathological progression in 32% (93/288). Pathological progression was statistically significantly less frequently reported in 5-ARI users (18.6%) when compared with nonusers (36.7%). Dropping AS rate among 5-ARI users were lower than nonusers. In the present study, follow-up period of the 5-ARI group was longer than non-user (23.5 vs. 39 months) which may be enough for pathological progression of the tumor. Though, 5-ARI use did not create a statistically significant difference for pathological progression. In the Finelli et al.^[19] study contrary to our study results, they reported that use of 5-ARI for a prolonged time period had significantly decreased the percentage of patients with pathological progression.

The most important limitation of our study was it was based on retrospective data. Besides, statistically significantly longer median follow-up period of the study group among 5-ARI users relative to nonusers tilted the balance between both groups. As another limitation of our study we didn't perform randomization, and use a placebo.

In conclusion, although in patients with low risk PCa, AS is a safe method for management. The progression of cancer can not be disregarded in definitive treatment. In the present study pathological progression rate was highest at the first repeat biopsy. The most important risk factor for pathological progression in AS was more than 2 cancer involved cores at the initial biopsy.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kocaeli University School of Medicine (18.04.2011 Date, Nr KAEK 3/11, Project No: 2011/40).

Informed Consent: Written informed consent was not obtained due to retrospective design of the study.

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