Araştırma Makalesi / Research Article

Are current criteria eligible for active surveillance in patients with localized prostate cancer?

Lokalize prostat kanserli hastalarda aktif kriterler mevcut kriterler uygun mu?

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Abstract

Background: We aimed to determine the parameters on the Gleason scoring system to upgrade in patients with the low-risk prostate cancer (PCa) that were suitable for active surveillance (AS).
Methods: We retrospectively analyzed medical records of 153 patients who underwent radical prostatectomy because of PCa between 2007 and 2017. Potential predictors of upgrading were evaluated between the biopsy and surgical Gleason score. All patients had clinical low-risk PCa according to D'Amico risk classification. Demographic and clinical parameters including age, body mass index (BMI), Prostate Specific Antigen density (PSAD), and smoking status were evaluated. We examined the effects of recorded parameters on the Gleason scoring system to upgrade. All pathology materials were evaluated by an experienced pathology clinic. Significant p was accepted as p<0.05.
Results: Median follow-up period was 113,4 months (range, 1-144 months). Mean age was 62.9± 6.07 years. Causes to upgrade in Gleason grading system were BMI≥30, PSA density≥0.15, to be an active smoker, and age≥ 65 years in Kaplan-Meier and log-rank tests analyses, respectively (all p<0.05). Univariate analyses showed that Age, BMI, PSA density≥0.15 and active smoker statuses were statistically significant prognostic factors (respectively; p:0.007, p<0.001, p<0.001, p<0.001).
Conclusion: Current Criteria for AS could not be useful for all PCa low-risk PCa patients. AS does not seem to be appropriate for PCa patients with Elevated BMI.

Keywords: Active surveillance, Body mass index, Gleason score, Prostate cancer

Öz.

Amaç: Gleason skorlama sistemindeki parametreleri, aktif sürveyansa (AS) uygun düşük riskli prostat kanserli hastalarda (PCa) belirlemeyi hedefledik.
Materyal ve Metod: 2007-2017 yılları arasında PCa nedeniyle radikal prostatektomi yapılan 153 hastanın tıbbi kayıtlarını geriye dönük olarak inceledik. Biyopsi ile cerrahi Gleason skoru arasında potansiyel yükselme öngören parametreler değerlendirildi. Tüm hastalarda D'Amico risk sınıflamasına göre düşük riskli klinik PCa vardı. Yaş, vücut kitle indeksi (VKİ), Prostat Spesifik Antijen yoğunluğu (PSAD) ve sigara içme durumu gibi demografik ve klinik parametreler değerlendirildi. Kaydedilen parametrelerin, yükseltme için Gleason skorlama sistemi üzerindeki etkilerini inceledik. Tüm patoloji materyalleri deneyimli bir patoloji kliniği tarafından değerlendirildi. Anlamlı p, p <0.05 olarak kabul edildi.
Bulgular: Ortanca takip süresi 113,4 ay (1-144 ay) idi. Ortalama yaş 62.9 ± 6.07 idi. Gleason derecelendirme sisteminde yükselme nedenleri aktif sigara içicisi olmak için BMI≥30, PSA yoğunluğu .1.15, Kaplan-Meier ve log-rank testleri analizlerinde sırasıyla 65 yıl (hepsi p <0.05) idi. Tek değişkenli analizler Yaş, VKİI, PSA yoğunluğu >0.15 ve aktif sigara tiryakisi durumlarının istatistiksel olarak anlamlı prognostik faktörler olduğunu gösterdi (sırasıyla; p:0.007, p <0.001, p <0.001, p <0.001).
Sonuç: Mevcut Kriterler, PCa düşük riskli PCa hastalarının tümü için yararlı olamamıştır. AS, VKİ yükselmiş olan PCa hastaları için uygun görünmemektedir.

Anahtar kelimeler: Aktif izlem, Gleason skoru, Prostat kanseri, Vücut kitle indeksi

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Introduction

Prostate cancer (PCa) accounts for nearly 30% of all diagnosed male cancers and the second leading cause of cancer death among men (1). PCa has become more common after prostate specific antigen (PSA) screening; low-risk localized PCa has also increased. Consequently, treatment of this disease has changed significantly (2). Patient with localized PCa has been treated by not only with surgery, but also by external beam radiation. Active surveillance (AS) is eligible and can be another option for this patient population (3).

However, PCa treatment is determined by risk classification at the first level, all interventional treatment options can decrease quality of life of patients (4). In the case of low risk PCa, over diagnosing may be one of thre major concerns for clinicans (5).

The AS can give up-and-coming results for low risk PCa patients. Thus, AS can provide to continue good quality of life without any functional disabilitites (erectile dysfunction, urinary incontinence). Additionally, the AS patients would not experience complications of radical surgery and / or other complications associated with radical surgery an/or radiation. (6). However, this might lead to misdiagnose an aggressive PCa. This might lead to delay treatment. D'Amico risk classification (7) and Epstein criteria (8) are the most used criteria for selecting PCa patients for AS.

It is a well-known truth that there cannot be concordance between the prostate biopsy Gleason score (GS) and the radical prostatectomy's report. The GS progress can be at 30% of the patients, however 63% had the same GS after prostatectomy (9). There is lack of study on this issue by making criticism of current criteria for AS in PCa patients.

In this study, we aimed to determine the parameters on Gleason scoring system to upgrade in patients with low risk localized PCa that were suitable for AS. Additionally, we determined which criteria are not eligible for AS for patients with PCa.

Material and Methods

We researched the clinicopathological data of 560 patients with PCa that underwent radical prostatectomy between 2007 and 2017. One hundred fifty three patients with low risk PCa were suitable for AS underwent radical prostatectomy were included. All clinical, imaging, pathological and laboratory tests were collected through the patients' medical records from urology department and the electronic database of the hospital.

The ethical committee of Izmir Katip Celebi University approved the study as numbered "170" and signed consents forms were obtained from all patients. The exclusion criteria were irregular follow-up, to get radiation to pelvis, to have other cancer, previous transurethral resection of prostate.

Preoperative patient age, prostate specific antigen (PSA) level, PSA density (PSAD), body mass index (BMI), smoking status, biopsy and surgical Gleason score and follow up time data were noted on Microsoft Excel sheets. Effective parameters on Gleason score upgrading were evaluated. Clinical risk evaluation made according to D'Amico risk classification. We only examined low risk patients as PSA<10 ng/mL, biopsy Gleason score ≤6, ≤2 positive biopsies, minimal biopsy core involvement (≤50% cancer per biopsy) (10,11). We made analyses to determine whether there was upgrading in pathology specimen of low risk PCa patients. In case of biochemical recurrence, patients referred to prostate biopsy again.

The analyses were performed using SPSS version 22 (SPSS Inc, Chicago, IL) software. Continuous variables were presented as mean±standard deviation and range. Categorical data were presented in percentages. Statisrtical significant p was $p<0.05$.

Results

Median follow-up period was 113.4 months (1-144 months). There was 560 patients in our database, however 153 patients with low risk PCa were suitable for AS that were included to the study. The mean age was 62.9± 6.07 years. The mean body mass index (BMI) was 25.75 ± 4.41 kg /m^2, PSA level was 6.49 ± 1.9; preoperative PSAD was 0.13 ± 0.06 ng/ml^2.

The clinic and demographic features of patients with/without Gleason upgrading is presented in Table 1. According to Kaplan-Meier analyses and log-rank test BMI ≥30, PSA density≥0.15, active smokers, and age≥ 65 years showed GS upgrading (respectively $p<0.001$, $p<0.001$, $p<0.001$ and $p=0.019$) (Figure 1.).

Table 2 shows the results of univariate analyses for independent predictors of GS upgrading. Age, BMI, PSA density≥ 0,15 and active smoker status were statistically significant prognostic factors for upgrading (respectively; p:0.007, $p<0.001$, $p<0.001$, $p<0.001$).

Discussion

It is supposed that patients with low-risk PCa would not become clinically symptomatic within their lifetime without progressing (12). Nowadays, AS is one of the treatment options for low-risk PCa (13). Several standards were used to assess the utility of AS (14-16). There is no consensus around the appropriate conduct of AS and differences may exist between strictly controlled cohorts and real life clinical practice (17). In this study, we investigated the effect of patient related features such as age, body mass index, PSAD and smoking status on GS upgrading.

Table 1. Characteristics of patients with and without an upgrade for Gleason score.

Characteristics	Total	Upgrade	No upgrade	P value
Age (n(%))				
Age<65	87(56.9)	14(9.1)	73(47.8)	0.013[a]
Age>65	66(43.1)	22(14.3)	44(28.8)	
Age (years)				
Median/Min-Max	63/45-78	66/51-78	63/45-76	0.064[b]
BMI (n(%))				
BMI<30	120(78.4)	5(3.3)	115(75.1)	<0.001[a]
BMI≥30	33(21.6)	31(20.3)	2(1.3)	
BMI (kg/m^2)				
Median/Min-Max	24/19-36	33/26-36	23/19-32	<0.001[b]
Smoking (n(%))				
Non-smoker Active smoker	103(67.5)	7(4.5)	96(63)	<0.001[b]
	50(32.5)	30(19.5)	20(13)	
PSA (ng/mL)				
Median/Min-Max	6.12/2.99-9.91	6.8/4-9.9	6/2.99-9.91	0.251[b]
PSA density				
Median/Min-Max	0.12/0.04-0.39	0.18/0.09-0.39	0.11/0.04-0.25	<0.001[b]
Prostate volume				
Median/Min-Max	52/19-103	35.5/20-93	56/19-103	<0.001[b]

[a] X^2 test.
[b]Mann-Whitney U test.
Abbreviations: BMI: Body mass index, PSA: Prostate specific antigen

The PCa incidence strongly increases with age. Furthermore, that rate increases at between 70–74 years (18). The PCa grows slowly. In addition, autopsy series showed that men would have PCa in the case of living more than 100 years (19). Additionally, high-risk PCa is more common in elderly patients and lower overall and cancer-specific survival (20,21). In our study, patients aged 65 years or older had significantly GS upgrading. Therefore, young patients seem to be more suitable for AS.

The body mass index is a convenient and reliable indicator of obesity (22,23). It is categorized BMI as obese when ≥ 30.0. The World Health Organization pointed the association between cancer and obesity (24). Peng et al. reported increased cancer-specific mortality in obeses with various cancer types, such as cancers of the liver, pancreas, prostate, breast, etc. (25). A recent study showed a modest increase in PCa risk at a rate ratio (RR) of 1.05, 95% confidence interval (CI) 1.01-1.08, with increase of every 5 BMI unit (26). Some metabolic changes observed in obese patients, like increased insulin level, insulin-like growth factor-1 (IGF-1), and leptin might lead to progress PCa (26). In patients with low-risk PCa under AS, obesity has been associated with a 50% increased risk of pathological progression (27). In the current study, we showed that increased BMI is an important factor for GS upgrading. In the majority of patients with BMI≥30 had GS upgrading. Thus, this patient population is not suitable for AS.

Klotz reported low prostate volume and more specifically high PSAD were predictors of risk progression, pointing possibility of undetected aggressive PCa (6). The PSAD can be strongly releated with cancer progression in low-risk patients on AS. Moreover, if the PSAD is used with radiological imaging (PI-RADS) score, these could detect accurately more details (28). Jin et al. emphasized impact of PSAD as the strong predictor of GS progress patients with GS 6 disease (29). However, the debate is still continuing for the cut-off value. Similarly, PSAD is also one of the important parameters for PCa active surveillance. Increased PSAD should be considered for disease progression.

Table 2. Independent predictors of upgrading (univariate regression)

Characteristics	p Value
Age (years)	0.007*
BMI (kg/m²)	<0.001*
Smoking (Non-smoker vs active smoker)	<0.001*
PSA density **(<0.15 vs ≥0.15)**	<0.001*

Abbreviations: BMI: Body mass index, PSA: Prostate specific antigen

Smoking status is estimated to cause some some malignancies; however smoking has not been noted the risk factor for PCa. Besides, Grasgruber et al. swowed a statistically important increase in PCa risk for heavy smokers. In view of this, smoking can be strongly associated with PCa mortality and greater risk of dying from smoker PCa patients than non-smokers (30). It is supposed that that smoking might help to develope more aggressive, hormone-sensitive tumours affecting carcinogens. Thus, there might be an association between smoking and PCa, patients who are active smoker had GS upgrading in the present study.

The multiparametric magnetic resonance imaging (mpMRI) are mostly used for the diagnosis and staging of PCa nowadays (28). However, there are no strict rules for the use of mpMRI for the selection of clinically suitable patients. Furthermore, the mpMRI and MRI-guided fusion biopsies could provide high sensitivity and specificity specifically for determining unidentified significant prostate cancer. Looking into the future, mpMRI appears to play an critical role in the AS protocol and preventing unnecessary prostate biopsies.

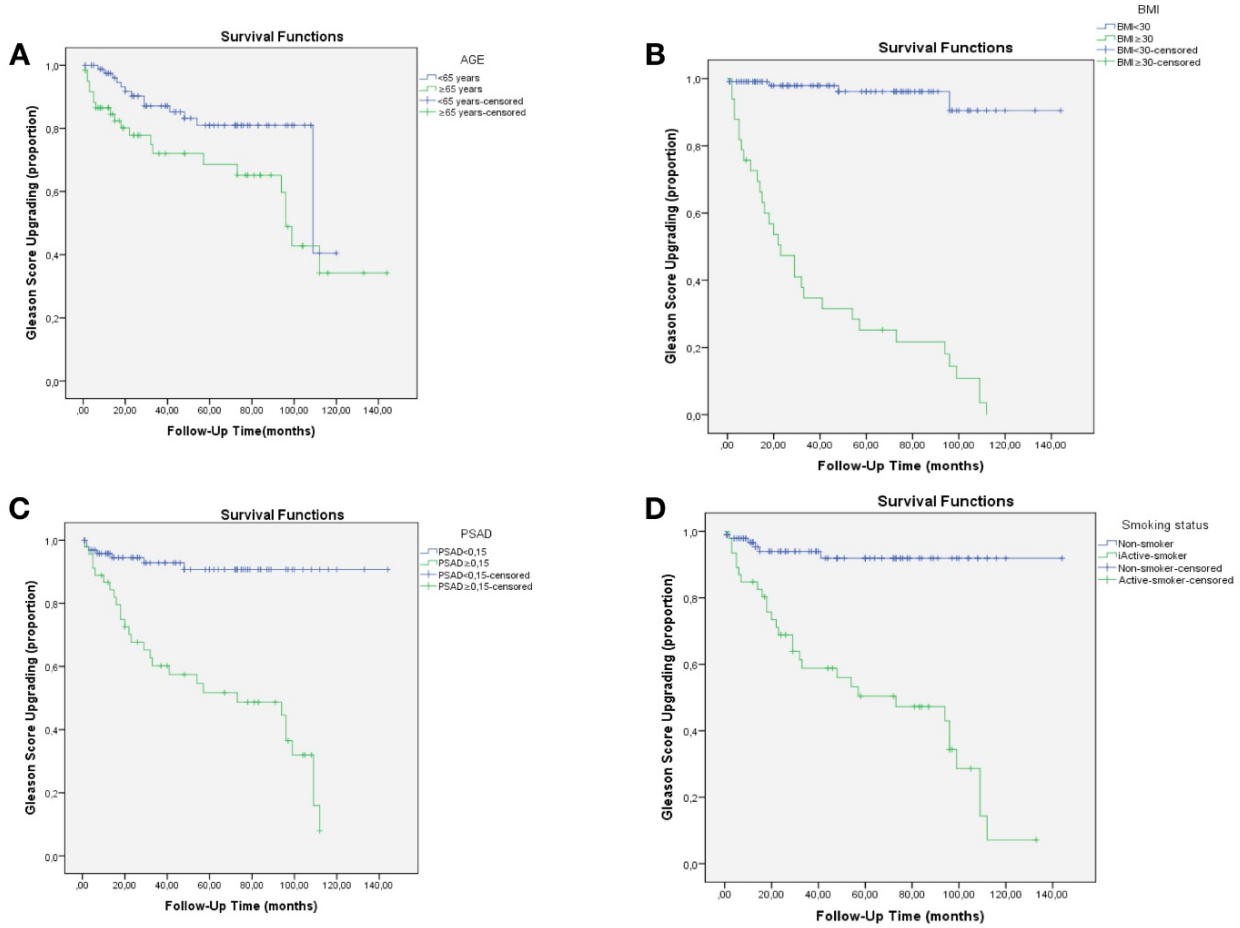

Figure 1. Kaplan-Meier analyses and log-rank tests of Gleason Scoring update; A. Age ≥65 years, B. BMI ≥30, C. Prostate Specific Antigen Density (PSAD) ≥0.15, D. Being active smoker.

Overview of all these, higher BMI might not suitable for AS. Our findings are parallel to them. Not only BMI but also age, PSAD, and, smoking status might lead progression worse in obese patients.

We have some limitations. The first one is the retrospective pattern of the study. Second one is low

numbers of PCa patients with low risk. Therefore multi-centred, prospective studies are still needed with higher patient population. Molecular studies were not performed in the present study. However, molecular markers can open another era in AS. Finally, we just focused on "which criteria are not eligible for AS for patients with PCa". Biochemical recurrence, also follow up can be topic of future study.

The goal of the present study showed us that if low risk PCa patient's BMI is higher than 30, the patient is not suitable for AS. Higher BMI is a risk of high risk PCa as well as a criterion to be considered for AS. Thus, we strongly think that clinicians should consider additional risk factors such as BMI, PSAD, and smoking status for AS in low risk PCa.

Conclusion

The current criteria for AS could not be suitable for all low risk PCa. Elevated BMI could be an independent prognostic factor to upgrade in Gleason scoring system. The AS does not seem to be appropriate for obese patients according to current criteria and the primary approach in these patients should be definitive treatment. Future randomized studies with large samples can help to enlarge results of the present study. In addition to the previously defined active surveillance criteria, if patient related factors and radiological evaluation are considered, more proper patient selection can be made.

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