Pathologic Outcomes of Candidates for Active Surveillance Undergoing Radical Prostatectomy: Results from a Contemporary Turkish Patient Cohort

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Keywords
Prostate cancer · Active surveillance · Radical prostatectomy

Abstract

Introduction: To evaluate the pathological outcomes of Turkish men meeting the criteria for Active Surveillance (AS), who elected to undergo immediate radical prostatectomy (RP).

Material and Methods: Retrospective analysis including 1,212 patients with clinically localized prostate cancer (PCa) who met the eligibility criteria for AS. The primary outcomes were pathological upstaging and pathological upgrading.

Results: Nine hundred ninety-one patients were eligible for analysis after the central review of the submitted data. The mean prostate-specific antigen (PSA) level was 6.89 (0.51–15) ng/mL and the mean biopsy core number was 12 (8–47). The mean tumor positive core on final biopsy pathology was 1.95 (1–6) (16.6% [2.1–33.3%]). Overall, 30.6% of the men experienced a Gleason sum (GS) upgrade and 13.2% had pathological upstaging. For GS upgrade, the percentage of tumor-positive cores and free-to-total-PSA ratio were significant both in univariate analysis and multivariate logistic regression analysis. Variables predicting pathological upstaging were percentage of tumor-positive cores and PSA density, which were significant in univariate analysis. However, only PSA density was significant in multivariate logistic regression. Although biochemical recurrence-free survival was longer in patients without GS upgrade, it was not statistically significant between patients with and without any GS upgrade (mean 133.7 vs. 148.2 months, \( p = 0.243 \)). A similar observation was made for patients with or without pathological upstaging (mean 117.1 vs. 148.3 months, \( p = 0.190 \)).

Conclusions: Upgrading and upstaging at RP are quite common among Turkish men with clinically low-risk PCa, who are candidates for AS, and a great majority of them experienced long-term PSA control.

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Introduction

Prostate cancer (PCa) is the most common cancer among the aging male population in Europe. The incidence of PCa is the highest in Northern and Western Europe (>200 per 100,000), while rates in Eastern and Southern Europe are increasing continuously [1] and a survival difference between men diagnosed in Eastern Europe and those in the rest of Europe has been reported recently [2].

As a result of prostate-specific antigen (PSA) screening and “multicore” schemes of prostate biopsy, the incidence of small, localized, well-differentiated PCa is increasing [3]. Active surveillance (AS) has emerged as a viable treatment option for men with features of low-volume and low-risk PCa, where selected men are managed expectantly with the intention to offer a curative treatment in case of progression signs during follow-up [4]. The major concern of this strategy, limiting its use in the daily urological practice, is that it might inherently pose a risk to the patient by missing higher risk disease during biopsy and a recent consensus conference concluded that AS is underused [5, 6].

Different studies have enrolled patients with varying inclusion criteria for AS in the current literature. While all are variations of the model developed by Epstein et al. [7], variations in inclusion criteria of these studies demonstrate the uncertainty about the cut-offs of clinical PCa characteristics predicting low-risk disease. Different groups have used several eligibility criteria for patient enrollment in AS programs: clinically organ confined PCa (cT1-T2); Gleason sum (GS) <7 for most studies; PSA <10–15 ng/mL and PCa volume criteria on biopsies, for example, number of positive biopsies, maximum cancer involvement of biopsy cores [8]. Studies comparing entry criteria for AS protocols have emphasized the risk of undergrading or understaging. The incidence of these adverse pathologic findings was reported to range between 7.1 and 50.6 for upgrading and 2.4 and 17 for upstaging in upfront radical prostatectomy (RP) series, with a possibility of missing the period for curative treatment [9–11].

Another potential concern in the daily practice might be whether these criteria can be applicable to every man from different geographical areas of the world. Racial and ethnic disparities related to PCa diagnosis and treatments are well described and recently, Center et al. [12] reported international variation in PCa incidence and mortality rates [13]. Similarly, studies from different countries and geographical areas of the world also reported different pathological and patient-related outcomes of candidates for AS, who underwent RP [4, 14–16]. Recently, the first randomized prospective data from PROTECT trial showed no cancer-specific survival differences between AS, RP and radical radiotherapy at a median follow-up of 10 years, although a reduced time to metastases has been reported with radical treatments [17]. It is crucial to improve the inclusion criteria for AS and also to modify and/or validate these criteria for different patient populations.

In this study, we evaluated the pathological outcomes of Turkish men meeting criteria for AS, who elected immediate RP, to assess the risk of clinical undergrading and understaging in this patient population.

Material and Methods

Design, Patients, and Setting

Regarding the study design, all data were submitted online by the investigator of participating institution to the database, which is created specifically for this study within the “Urooncology Association, Turkey”.

We performed a retrospective analysis including 1,212 patients with clinically localized PCa who met the eligibility criteria for potential AS: clinical stage T2a or lower, PSA 15 ng/mL or lower, GS 6 or lower (without Gleason grade 4 as primary or secondary), total biopsy cores 8 or more, 33.3% (maximum 6 cores) or lower tumor positive cores on biopsy pathology and with at least 2 years follow-up after RP.

Selection criteria for the purposes of this study were determined at a consensus meeting of the “Prostate Cancer Study Group of the Urooncology Association, Turkey” after reviewing the criteria for AS published in the literature [6, 18–22].

Data Collection and Analysis

Types of data requested:

(i) Diagnosis: patient age, pre-biopsy PSA level, pre-biopsy free-PSA level, prostate volume on TRUS, and biopsy Gleason grades;

(ii) Surgery: type of the surgery (open, laparoscopic or robot-assisted), pathologic Gleason grades, presence of tertiary Gleason grade, pathologic stage (TNM 2010), and lymph node status if lymphadenectomy was performed;

(iii) Follow-up: adjuvant treatments, PSA outcomes and biochemical progression-free survival (biochemical recurrence defined as PSA >0.2 ng/mL after the RP).

None of the patients received any form of neoadjuvant treatment before RP. Senior uropathologists in each center assessed all biopsy and RP specimens. No central pathologic review was performed.

Our primary endpoint was the presence of adverse pathology, that is, GS upgrade (≥3 + 4) and/or pathological upstaging (≥pT3), at the final pathology of RP. We used logistic regression analysis to identify predictive factors for adverse pathology.

Our secondary endpoint was biochemical recurrence, defined as a PSA ≥0.2 ng/mL. Patients, who did not experience a recurrence, were censored at the date of their last clinical visit. To assess differences in biochemical recurrence-free survival, Kaplan-Meier curves were generated and compared using the log rank test.
Ethics Statement

The study protocol was approved by the Institutional Review Board of Marmara University School of Medicine (IRB No. 09.2013.0387 – date January 3, 2014).

Results

The analysis of data by the principal investigators revealed that out of 1,212 patients enrolled, 991 (81.8%) were eligible for data analysis. A total of 221 patients had missing critical data precluding their proper evaluation and excluded from final analysis. Preoperative patient and tumor characteristics are given in Table 1.

The RP technique was open, laparoscopic and robotic surgery in 833, 24, and 134 respectively. A total of 513 men (51.8%) underwent pelvic lymph node dissection and only 1 patient (0.2%) had leukemia diagnosis at the final lymph node pathology.

Overall, 30.6% of the men experienced a GS upgrade and 13.2% had pathological upstaging (12.8 pT3a and 0.4% pT3b disease – Fig. 1, 2). A tertiary Gleason grade has been reported only in 50 (5%) patients.

For GS upgrade, the percentage of tumor-positive cores (%TPC; mean 0.162 vs. 0.179, p = 0.002) and free-to-total-PSA ratio (f/tPSA) (mean 0.176 vs. 0.153, p = 0.013) were significant in univariate analysis. In multivariate logistic regression analysis, both %TPC (Odds ratio [OR] 1.433, 95% CI 1.145–1.795, p = 0.02) and f/tPSA (OR 0.044, 95% CI 0.002–0.911, p = 0.043) were statistically significant.

For pathological upstaging, %TPC (mean 0.164 vs. 0.186, p = 0.004) and PSA density (PSAD; mean 0.166 vs. 0.194, p = 0.015) were significant in univariate analysis. However, only PSAD was significant in multivariate logistic regression analysis (OR 7.853, 95% CI 1.463–42.14, p = 0.016).

A total of 24 men (2.7%) died during the follow-up from causes other than PCa. A total of 10 patients (1%) underwent adjuvant radiotherapy (RT) with hormonal treatment. These men had a higher mean pre-biopsy PSA level (7.85 vs. 6.89) with higher mean tumor positive core percentage (20.2 vs. 16.6%) compared to the whole group.

A total of 22 patients (2.4%) received only adjuvant RT and again these men had a higher mean pre-biopsy PSA level (7.3 vs. 6.89) but lower mean tumor positive core percentage (15.6 vs. 16.6%).

In the remaining 959 patients, who did not receive any adjuvant treatment, 26 (2.7%) experienced PSA failure at a mean time of 35 months (12–88) after the surgery. Although biochemical recurrence-free survival was longer in patients without GS upgrade, it was not statistically significant between patients with and without GS upgrade (mean 133.7 vs. 148.2 months, p = 0.243; Fig. 3).

Again, although BCFRS was longer in patients without pathological upstaging, it was not statistically significant between patients with and without pathological upstaging (mean 117.1 vs. 148.3 months, p = 0.190; Fig. 4).

Discussion

AS has been actively promoted to take part in contemporary practice in order to avoid risks of overtreatment for patients with low risk PCa. Definitive treatment is indicated when there is disease progression detected on follow-up biopsy and/or a progression in PSA kinetics. A potential disadvantage of AS is the downstaging and/or downgrading at the initial biopsy. This study addresses this question in the Turkish men meeting criteria for AS, who elected immediate RP.

Table 1. Preoperative characteristics for patients and tumors

<table>
<thead>
<tr>
<th>Total number</th>
<th>n = 991</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (range)</td>
<td>61.28 (41.9–77.1)</td>
</tr>
<tr>
<td>Mean PSA, ng/mL</td>
<td>6.87 (0.51–15)</td>
</tr>
<tr>
<td>Clinical stage, %</td>
<td></td>
</tr>
<tr>
<td>cT1</td>
<td>76.2</td>
</tr>
<tr>
<td>cT2</td>
<td>23.8</td>
</tr>
<tr>
<td>Biopsy cores taken</td>
<td>12.16 (8–47)</td>
</tr>
<tr>
<td>Mean number of positive cores</td>
<td>1.96 (1–6)</td>
</tr>
<tr>
<td>Percentage of tumor-positive cores, %</td>
<td>16.7 (2.1–33)</td>
</tr>
</tbody>
</table>
In this study, approximately a thousand RP cases eligible for AS were evaluated. About 1/3rd of these patients were in fact not suitable for AS according to the final RP pathology results. Overall, 30.6% of patients had GS upgrade and 13.2% had upstaging of the local disease. Biopsy grade has enjoyed greater importance in recent years with a relative increase in men undergoing therapy other than RP, such as RT or AS, where the only tissue sampled is on the needle biopsy [23]. Studies have demonstrated the frequent disparity between Gleason scores reported on prostate biopsy and at RP [9, 15] and recently Epstein et al. [23] reported that about a third of cases with a biopsy Gleason score of 5–6 were upgraded at RP. Similarly, overall, 30.6% of the men experienced a GS upgrade in our series, where 28.9% upgraded to GS 7 and 1.7% upgraded to a GS >7. Studies also have shown that the pathologic stage was predicted incorrectly in 13.9–26.7% of men who were identified as candidates for AS by the inclusion criteria of 5 different AS protocols [9]. In our study, 13.2% of patients were reported to have upstaging of the local disease.

It has been reported that up to 40% of men potentially suitable for AS had unfavorable disease at RP and these
high rates of adverse pathologic findings could be due to inadequate diagnostic biopsy sampling, which may underestimate both the aggressiveness and the extent of PCA [11, 24]. Thompson et al. [25] recently compared different biopsy techniques (standard [<12 core, median 10] vs. saturation [>12 core, median 16], and transrectal vs transperineal biopsy), which showed that the AS protocol with saturation biopsies at the initial diagnosis and during follow-up reduced treatment-free survival during AS, while the AS protocol with transperineal biopsies reduced the likelihood of unfavorable disease in patients who underwent RP during follow-up. Similarly, Da Rosa et al. [26] compared prospectively MRI-US fused targeted biopsy versus systematic ultrasound-guided biopsy for detecting clinically significant (CS) prostate cancer in patients on active surveillance and reported that MRI-ultrasound fusion biopsy detected CS cancer with far fewer cores and multiparametric MRI had a perfect negative predictive value in this population. Villa et al. [24] reported that the number of biopsy cores emerged as an independent predictor of both pathologically confirmed insignificant PCA and unfavorable disease at RP in patients eligible for AS and an extended biopsy scheme (13–18 cores) seems to be an adequate sampling to safely address patients to conservative treatment. Although we did not request the detailed information regarding the technique and image-guidance modality during prostate biopsy in our database, the mean biopsy core number was 12 (8–47) and the mean tumor positive core number on final biopsy pathology was 1.95 (1–6) with a tumor percentage of 16.6% (2.1–33.3%) in our patient cohort. These numbers are well-matched with the contemporary AS criteria in the current literature and we believe that our results based on these criteria can project the real-time status of Turkish men eligible for AS but who elected immediate RP.

Our results showed that for GS upgrade, the percentage of tumor-positive core and free-to-total-PSA ratio was significant both in univariate analysis and multivariate logistic regression analysis. For pathological upstaging, the percentage of tumor-positive core and PSA density were significant in univariate analysis; however, only PSA density was significant in multivariate logistic regression analysis. In search for more precise criteria, beyond the biopsy findings and PSA to assess the eligibility for AS among men with PCA, these parameters might help to identify potential patients with adverse RP pathology in the preoperative planning.

Racial and ethnic disparities related to PCA diagnosis and treatments are well described and recently, Center et al. [12] reported international variation in PCA incidence and mortality rates [13]. Similarly, studies from different countries and geographical areas of the world also reported different pathological and patient-related outcomes of candidates for AS who underwent RP [4, 14–16]. To the best of our knowledge, this multicenter study reports for the first time the pathological outcome status of Turkish men suitable for AS, but elected immediate RP, with a GS upgrade rate of 30.6% and a pathological upstaging rate of 13.2%.

Our results show that we need more precise criteria other than the biopsy parameters and PSA to assess eligibility for AS among men with PCA, since almost 1/3rd of the patients initially eligible for AS had in fact higher GS, which is not appropriate for AS. Similarly, 13.2% of patients had pathological T3 disease and at least a majority of these patients could have been detected initial if multiparametric MRI was included in the AS protocols for a more accurate local staging and determining CS PCA [27]. There is need for studies incorporating the biological behavior of the disease, which could improve the decision-making process for AS versus RP or RT.

**Limitations of the Study**

Our study is not without limitations. The lack of central pathologic review might have introduced bias in pathological interpretation. Multiple senior pathologists in each center assessed all biopsy and RP specimens, and the effect of intra- and interobserver variation was not calculated. A recent consensus report outlined the critical role of the pathologist in helping to determine the appropriate candidates of PCA patients, who would benefit from AS [28].

Being retrospective, collected data were dependent on individual centers’ protocols and data on lymph node status were limited as lymph node dissection for low-risk disease was performed according to surgeon’s preference and not always recorded. Similarly, we lacked detailed information regarding the technique and image-guidance modality during prostate biopsy, which can clearly affect the quality of the biopsy and therefore, the decision for the AS. However, the contemporary AS criteria in the current literature also include only the number or percentage of positive cores irrespective of the biopsy technique and image-guidance modality.

The definition of pathological upstaging might be misleading, since the clinical stage before the RP was recorded using the findings of the digital rectal examination. It would be more accurate to use the findings of preoperative pelvic or multiparametric prostate MRI for local staging. However, we did not have this type of radiological examination in the majority of the cases in our study population simply because they were not included in the clin-
tical staging procedure routinely at the time these patients were treated.

The decision on the adjuvant therapy after adverse pathology of the RP was also dependent on individual centers' protocols. Early salvage radiotherapy was considered an acceptable alternative in a majority of participating centers provided that surgical margins were clear in patients with the presence of an extracapsular extension, especially if it is microscopic and this might explain the low numbers of patients opting for adjuvant radiotherapy, especially in pT3 disease, among the current study population.

Conclusions

We need more precise criteria other than the biopsy parameters and PSA to assess eligibility for AS among men with PCa, since upgrading and upstaging at RP are quite common among Turkish men with low-risk PCa like other population groups. However, most Turkish men with low-risk PCa treated with RP experience long-term PSA control.

References


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Disclosure Statement

The authors declare that they have no conflicts of interest. For this type of study, formal consent is not required. Informed consent was obtained by the participating institution from all individual participants included in the study at the time of surgery for future studies.

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The authors have no funding to declare.

Author Contribution

I.T. was responsible for project development, data collection, data analysis, and manuscript writing. G.A., B.A., and A.Y. were involved in data collection and manuscript editing. A.R.K. and T.E. contributed to manuscript editing. H.O. was involved in project development and manuscript editing. Ş.O. and A.O. were responsible for data collection. F.Z. and O.D. undertook project development. N.B. participated in data analysis. L.T. was involved in project development and manuscript writing/editing.
AS Results from a Contemporary Turkish Patient Cohort

References:


