Are active surveillance criteria sufficient for predicting advanced stage prostate cancer patients? 

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Abstract

Objectives: To examine the treatment outcomes of the prostate cancer (PCa) patients treated by radical prostatectomy (RP) who could be good candidates for active surveillance (AS) and test the confidence and reliability of the AS criteria for predicting advanced stage disease (RP Gleason score ≥7 or pathological stage T3).

Methods: Between 2005 and 2012 the records of the 401 patients who underwent RP with a diagnosis of PCa were examined. Of these patients, 173 were found to be candidates of AS. The inclusion criteria were as follows: clinical stage T2a or less, PSA<10 ng/ml, 2 or fewer cores involved with cancer, no single core with 50% or greater maximum involvement of cancer, and no Gleason grade greater than 3 in the specimen.

Results: Univariate analyses revealed that patients with advanced stage disease have higher prostate specific antigen density (PSAD), higher maximum percent (max%) in positive cores and higher RP tumor volumes. In multivariate analyses PSAD, max% in positive cores and RP tumor volumes were statistically significant determinants for advanced stage disease. ROC analyses revealed that the RP tumor volume is a good test on advanced stage disease.

Conclusions: Decreasing the cutoff values for PSAD and max% in positive cores should be considered for AS inclusion criteria. If we could calculate the tumor volume before RP, we can minimize the treatment failures (over or undertreatment) of PCa. Perhaps new biopsy protocols, tissue biomarkers, and molecular imaging technology may refine AS criteria.

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KEYWORDS
Neoplasm staging; Prostatectomy; Prostatic neoplasms; Tumor burden


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¿Son los criterios de vigilancia activa suficientes para predecir el cáncer de próstata de estadio avanzado?

Resumen

Objetivos: Examinar los resultados del tratamiento en pacientes con cáncer de próstata (CP) tratados con prostatectomía radical (PR) que podrían ser buenos candidatos para vigilancia activa (VA) y evaluar la confianza y fiabilidad de los criterios de VA para predecir la enfermedad en estadios avanzados (puntuación de Gleason en PR ≥ 7 o estadio patológico T3).

Métodos: Entre 2005 y 2012 se examinaron los registros de 401 pacientes sometidos a PR con un diagnóstico de CP. De estos pacientes 173 resultaron ser candidatos para VA. Los criterios de inclusión fueron los siguientes: estadio clínico T2a o inferior, PSA < 10 ng/ml, 2 o menos núcleos afectados por cáncer, ningún núcleo con una afectación máxima por cáncer del 50% o más y ninguna puntuación de Gleason mayor de 3 en la muestra.

Resultados: Los análisis univariantes revelaron que los pacientes con un estadio más avanzado de la enfermedad tenían una densidad del antígeno prostático específico (PSAD) más elevada, un mayor porcentaje máximo (%máx) de núcleos positivos y un mayor volumen tumoral en PR. En los análisis multivariantes la PSAD, el %máx de núcleos positivos y el volumen tumoral en PR eran factores estadísticamente significativos de enfermedad en estadios avanzados. Los análisis ROC revelaron que el volumen tumoral en PR es un buen test de la enfermedad en estadio avanzado.

Conclusiones: Se debería considerar reducir los valores umbral de PSAD y %máx en núcleos positivos como criterios de inclusión para VA. Si se pudiera calcular el volumen tumoral antes de la PR podríamos minimizar los fracasos del tratamiento (exceso o falta de tratamiento) de CP. Quizás los nuevos protocolos de biopsias, los biomarcadores de tejidos y la tecnología de imágenes moleculares puedan perfeccionar los criterios para VA.

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Introduction

With the widespread use of prostate specific antigen (PSA) and extended prostate biopsy protocols, more men are diagnosed with prostate cancer (PCa). Of the men screened over their lifetime, 17% were diagnosed with PCa and only 3% died from the disease.1 The difficulty to predict which tumors will be clinically significant makes the treatment decisions complicated. Active surveillance (AS) is an acceptable treatment option for carefully selected men with low-risk prostate cancer as defined by grade, stage, volume and serum PSA levels. For low risk PCa, AS is recently being studied as an option to prevent overtreatment and possible morbidity for indolent disease. This has raised the concern regarding overtreatment of low-risk lesions and emphasizes the need for new prognostic tumor markers and more accurate identification of candidates for AS.

Currently, there is no consensus on the optimum management for low-risk PCa that, with no treatment, might never become life-threatening. Offering curative treatment to all men with localized disease results in an unnecessary treatment for many, as 25% of men have “insignificant disease” when radical prostatectomy (RP) specimens are examined.2,4 Unfortunately, there are no diagnostic markers sensitive or specific enough to predict which tumors will progress. There are many prospective cohort studies designed to find out the role of AS as a treatment strategy. The variations in inclusion criteria of these studies demonstrate the uncertainty surrounding which cutoffs of clinical PCa characteristics best suggest low-risk disease.

In this study, we retrospectively selected PCa patients treated by RP who could be good candidates for AS. The inclusion criteria of the “very low-risk prostate cancer” for AS were adopted from the European Association of Urology (EAU) Prostate Cancer Guideline.4 The aim of this study was to examine the treatment outcomes of the prostate cancer (PCa) patients treated by radical prostatectomy (RP) who could be good candidates for active surveillance (AS) and test the confidence and reliability of the AS criteria for predicting advanced-stage disease (RP Gleason score ≥7 or pathological stage T3).

Materials and methods

Between January 2005 and June 2012, the records of the 401 patients whose clinical and pathological data were available and who underwent RP with a diagnosis of PCa were examined. In our database, 173 patients were found to be candidates of “very low-risk PCa” criteria for AS. The inclusion criteria were as follows: clinical stage T2a or less, PSA < 10 ng/ml, 2 or fewer cores involved with cancer, no single core with 50% or greater maximum involvement of cancer, and no Gleason grade greater than 3 in the specimen.4 All the patients underwent RP within 6 months of initial diagnosis and none of them received other types of primary treatment. Biochemical recurrence is defined as a PSA value of 0.2 ng/ml or greater after RP.

Minimum 10 biopsy cores were taken at diagnosis. RP specimens were fixed in 10% neutral buffered formaldehyde.
solution for 24–48 h, inked, cut at 3-mm intervals in the plane perpendicular to the rectal surface. Each section was cut to 4 pieces, processed totally, and embedded in paraffin. Sections were cut from each block, stained with hematoxylin and eosin. The sections were evaluated and tumor volumes were assessed stereologically. The margin of the tumor was marked under low-power magnification in each slide. A grid with a set of regularly spaced points was superposed to the slide, and the points hitting the tumor were counted. The area associated with one point in the grid was multiplied by the sum of the points hitting the tumor and by 3 (the third dimension), and by 1.2 (shrinkage ratio in formalin). Gleason score, extraprostatic extension, surgical margin status, and seminal vesicle involvement were also assessed in the prostatectomy specimens. The Gleason scores of both the biopsy and prostatectomy specimens were re-assessed according to the ISUP 2005 revisions.4

We analyzed independent predictors of advanced-stage disease (RP Gleason score ≥7 or pathological stage T3) for candidates of “very low-risk PCa” criteria using univariate tests (Student’s t-test and Mann–Whitney U) and multivariate logistic regression analysis. We included age at the diagnosis, preoperative serum PSA level, prostate specific antigen density (PSAD), percentage of positive cores, number of positive cores, and tumor volume at RP as covariates for univariate analyses. Variables found to be statistically independently significant in univariate analyses were included to multivariate logistic regression analysis. Characteristics of patients were compared by using the Pearson χ² test and univariate tests (Student’s t-test and Mann–Whitney U). We also studied these variables in ROC analysis to find their predictive value for advanced-stage disease. The Statistical Package for Social Sciences (SPSS) version 15.0 was used for statistical analysis. p < 0.05 was considered to indicate statistical significance.

Results

Clinical and pathological characteristics of all patients and eligible for AS criteria are given in Table 1. The mean age, PSA level and PSAD of the patients eligible for AS criteria were significantly lower than the other patients (not eligible for AS criteria). Upgrading rates were significantly higher in the patients eligible for AS criteria. T2 pathological stage was higher in the patients eligible for AS criteria and T3 was higher in the other patients. The mean tumor volume of the patients eligible for AS criteria was also significantly lower.

For the patients eligible for AS criteria, 148 (85.5%) patients were T1c, 25 (14.5%) were T2a, the mean number of biopsy cores was 11.5 (SD 2.04) and the mean prostate volume was 58.2±21.9 cm³. One hundred and seven (61.8%) patients had one positive biopsy core, 66 (38.2%) had two positive biopsy cores. Of the men eligible for AS according to the selection criteria, a Gleason sum upgrading that is ≥7 was observed in 37% (64), extraprostatic extension (EPE) in 12.7% (22) and seminal vesicle involvement (SVI) in 2.3% (4) of the surgical specimens. Median follow-up was 5.0 years. Biochemical recurrence occurred in 10 (5.7%) patients of these men eligible for AS. The median time from RP to biochemical recurrence was 12 months.

Univariate analyses revealed that patients with advanced-stage disease had higher PSAD, higher maximum percentage (max%) in positive cores, and higher RP tumor volume (p < 0.05). So, we included PSAD, max% in positive cores and RP tumor volume as covariates for logistic regression analysis. Results of logistic regression analyses for predicting advanced stage disease (RP Gleason score ≥7 or Pathological stage T3) are given in Table 2. Increase of the tumor volume at the RP by 1 cm³ increased the chance of Gleason score upgrading or upstaging at least 2.4 times (Table 2). Also increase of the PSAD(x10) and max% in positive cores by one unit increased the chance of Gleason score upgrading or upstaging at least 1.12 and 1.03 times, respectively. ROC analyses revealed that the RP tumor volume is a good test on advanced stage disease. The best cut-off that maximizes (sensitivity + specificity) is 0.465 cm³ for RP tumor volume. At this duration, the sensitivity was 0.899 and specificity was 0.587. The best cut-off that maximizes (sensitivity + specificity) for max% in positive cores and PSAD were 12.5% and 0.10 respectively. Through these cut-off values, sensitivity was 0.464 for max% in positive cores and 0.652 for PSAD, specificity was for 0.750 max% in positive cores and 0.558 for PSAD.

For the patients eligible for AS criteria, 41.6% (72) of their PSAD were <0.10 and 66.4% (115) of their max% in positive cores were <12.5. When these cut-off values (PSAD <0.10 and max% in positive cores <12.5) are applied to the patients eligible for AS, advanced-stage disease rate is found significantly lower (p < 0.05). Upstaging, upgrading and advanced-stage disease rates for these cut-off values of the patients eligible for AS are given in Table 3.

Discussion

PCa patients with low-grade and volume on biopsy may be offered the option of AS to prevent them from the morbidity and complications of the curative interventions. But for low-risk PCa, the role of AS is still controversial. AS would resolve the morbidity risk of treatments without compromising survival in patients with low-risk disease. Identifying the patients with really low-risk disease is a dilemma and significant excellent criteria are needed for describing AS candidates.

Apart from some trials with a small number and short follow-up, there are no available prospective randomized trials for AS. Defining eligibility for AS is immensely challenging so there are various eligibility criteria in the literature. It is not clear whether these small differences in selecting criteria would translate into worse outcome.

Prognostic impact of tumor volume in prostate cancer is controversial, and there are many opposite results. This controversy is due to the measuring of the tumor volumes which is not straightforward. There are many methods for tumor volume measurement. Most of these methods are semiquantitative and most pathologists prefer these. Tumor volume should be measured in fully embedded tissues, shrinkage of tissue should be calculated, and a quantitative method should be selected. There are only two quantitative methods, which are computer-assisted morphometry and stereologic quantification.
Table 1  Clinical and pathological characteristics of all patients included in the study and the patients eligible for AS criteria.

<table>
<thead>
<tr>
<th>Eligible patients for AS criteria (n = 173)</th>
<th>Other patients (n = 228)</th>
<th>Total (n = 401)</th>
<th>t/χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.43±6.22 (47–74)</td>
<td>63.00±5.86 (43–80)</td>
<td>62.32±6.06 (43–80)</td>
<td>–2.599**</td>
</tr>
<tr>
<td>Mean PSA level (ng/ml)</td>
<td>6.25±2.10 (2.5–9.9)</td>
<td>10.37±8.17 (2.4–47.0)</td>
<td>8.59±6.63 (2.4–47.0)</td>
<td>–7.293**</td>
</tr>
<tr>
<td>PSAD (ng/ml/cm³)</td>
<td>0.11±0.05 (0.03–0.30)</td>
<td>0.23±0.20 (0.04–1.61)</td>
<td>0.18±0.16 (0.03–1.61)</td>
<td>–7.904**</td>
</tr>
<tr>
<td>Upgrading</td>
<td>65 (36.9%)</td>
<td>49 (21.5%)</td>
<td>113 (28.2%)</td>
<td>11.6***</td>
</tr>
<tr>
<td>RP Gleason score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+3 = 6</td>
<td>109 (63%)</td>
<td>28 (12.3%)</td>
<td>137 (34.2%)</td>
<td>112.5***</td>
</tr>
<tr>
<td>3+4 = 7</td>
<td>62 (35.8%)</td>
<td>158 (69.3%)</td>
<td>220 (54.9%)</td>
<td>44.4***</td>
</tr>
<tr>
<td>4+3 = 7</td>
<td>1 (0.6%)</td>
<td>24 (10.5%)</td>
<td>25 (6.2%)</td>
<td>16.6***</td>
</tr>
<tr>
<td>≥8</td>
<td>1 (0.6%)</td>
<td>18 (7.9%)</td>
<td>19 (4.7%)</td>
<td>11.6***</td>
</tr>
<tr>
<td>Pathological stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a-b</td>
<td>43 (24.9%)</td>
<td>11 (4.8)</td>
<td>54 (13.5%)</td>
<td>33.8***</td>
</tr>
<tr>
<td>T2c</td>
<td>104 (60.1%)</td>
<td>112 (49.1%)</td>
<td>216 (53.9%)</td>
<td>4.7***</td>
</tr>
<tr>
<td>T3a</td>
<td>22 (12.7%)</td>
<td>73 (32.0%)</td>
<td>95 (23.7%)</td>
<td>20.2***</td>
</tr>
<tr>
<td>T3b</td>
<td>4 (2.3%)</td>
<td>32 (14.0%)</td>
<td>36 (9.0%)</td>
<td>16.5***</td>
</tr>
<tr>
<td>Tumor volume (cc)</td>
<td>1.25±1.57 (0.01–12.6)</td>
<td>5.38±7.85 (0.02–42.0)</td>
<td>3.59±6.34 (0.01–42.0)</td>
<td>–7.729**</td>
</tr>
</tbody>
</table>

a Data presented as mean ± standard deviation and min–max.
b Student’s t-test.
c Pearson χ² test.
morphometry needs special equipment and software. However, stereological tumor volume calculation may be easily assessed in every laboratory. Stereological methods quantify the measurement in an accuracy of ±5%.

It should be stressed that we try to select the patients who have small tumors in their prostates when trying to define active surveillance candidates. The selection parameters are related to the volume of the tumor in the prostate. However, we had some problems at this point: (1) tumor volume in the biopsies is related to the tumor volume of the prostate but it is entirely dependent on the biopsy and sampling technique. (2) Gleason score shows differentiation of the tumor, and the differentiation is directly related to progression of the disease. (3) Serum PSA level is both related to differentiation and tumor volume. They explain why tumor volume in the prostate is an independent factor for selecting active surveillance patients. If we can assess prostate tumor volume of the patients diagnosed to have prostate cancer by means of biopsies, by radiologic techniques we may select the active surveillance patients without requiring any other parameters.

In our study, tumor volume at RP is found to be the most important predictor of advanced-stage disease. In contrast, the important question at this point is to predict the tumor volume before RP. In a recent report, it was noted that urinary levels of PCA3 do not appear to be elevated with increasing prostate size but do correlate with tumor volume.\(^1\) In another study, the PCA3 score was significantly correlated with total tumor volume in RP specimens and it was also associated with prostatectomy Gleason score.\(^12\) So PCA3 could be a helpful parameter for the prediction of low-volume disease. Nowadays, it is not possible to predict tumor volume accurately before the surgery; but if we manage it, we believe that this will lower overtreatment and undertreatment rates of PCa.

Imaging techniques could be the solution to calculate the tumor volume before RP. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging could be helpful to define an insignificant cancer (organ-confined, <0.5 mL, no poorly differentiated elements in the prostatectomy specimen) in an individual PCa patient.\(^13\) Also diffusion-weighted MRI of peripheral zone PCa may be useful in the discrimination of low-risk and intermediate-risk.\(^14\) In a study, multiparametric MRI demonstrated excellent specificity and negative predictive value for the detection of pathological index lesions; multiparametric MRI may also be useful for the selection of AS patients.\(^15\) In another study, multiparametric 3T endorectal coil MRI accurately estimated index tumor volume.\(^16\)

Biopsy and prostatectomy Gleason score are not highly correlated because of the believed reasons that are sampling errors and/or heterogeneity of PCa. In some studies, Gleason upgrading to 7 or more is about 40%.\(^17\) Concurrent with the literature, Gleason upgrading to 7 or more was observed in 37% of men in our study. This under-grading at diagnosis puts men who are actually in an intermediate-risk category (Gleason 7) in a low-risk category (Gleason 6 or less) and delaying other treatments. Although our inclusion criteria

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**Table 2** The results of logistic regression analyses for predicting advanced stage disease (RP Gleason score ≥7 or Pathological stage T3) \((p < 0.05)\).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>Standard error</th>
<th>(p)</th>
<th>OR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>−1.194</td>
<td>0.626</td>
<td>0.057</td>
<td>0.303</td>
</tr>
<tr>
<td>RP tumor volume</td>
<td>0.939</td>
<td>0.188</td>
<td>&lt;0.001</td>
<td>2.559 (1.769–3.701)</td>
</tr>
<tr>
<td>PSAD (X10)</td>
<td>0.116</td>
<td>0.047</td>
<td>0.013</td>
<td>1.123 (1.025–1.231)</td>
</tr>
<tr>
<td>Max% in positive cores</td>
<td>0.033</td>
<td>0.015</td>
<td>0.031</td>
<td>1.033 (1.003–1.065)</td>
</tr>
</tbody>
</table>

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**Table 3** Upstaging, upgrading and advanced stage disease rates of the patients eligible for AS, PSAD < 0.10 and max % in positive core < 12.5.

<table>
<thead>
<tr>
<th>PSAD</th>
<th>Max % in positive cores</th>
<th>PSAD &lt; 0.10</th>
<th>1) and 2) max% in positive cores</th>
<th>PSAD &gt; 0.10</th>
<th>(\chi^2)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.10</td>
<td>(n = 72)</td>
<td>≥0.10</td>
<td>(n = 101)</td>
<td>&lt;12.5 (n = 48)</td>
<td>≥12.5 (n = 58)</td>
<td></td>
</tr>
<tr>
<td>Upgrading (RP Gleason score ≥7)</td>
<td>%44 (22)</td>
<td>%41.5 (42)</td>
<td>%29.5 (34)</td>
<td>%51.7 (30)</td>
<td>%18.75 (9)</td>
<td>%44 (55)</td>
</tr>
<tr>
<td>Upstaging (pathological stage T3)</td>
<td>%2.8 (2)</td>
<td>%23.7 (24)</td>
<td>%13.0 (15)</td>
<td>%18.9 (11)</td>
<td>%2 (1)</td>
<td>%20 (25)</td>
</tr>
<tr>
<td>Advanced stage disease (upgrading or upstaging)</td>
<td>%30.5 (22)</td>
<td>%46.5 (47)</td>
<td>%32.1 (37)</td>
<td>%55.1 (32)</td>
<td>%18.75 (9)</td>
<td>%48 (60)</td>
</tr>
</tbody>
</table>
are defined as "very low-risk prostate cancer", the EPE and SVI rates were not unexpectedly low (15%). AS protocols may enable men with higher risk to miss the opportunity of more effective treatment, that is why selecting inclusion criteria for AS is so difficult.

PSA density is found to be useful to identify the aggressiveness of clinically localized PCa. PSAD was also used as an inclusion criterion in several AS clinical trials. In these studies, cut-off values of PSAD were 0.15 ng/ml/cm^3 and 0.2 ng/ml/cm^3. In our study, the mean PSAD in patients undergoing RP with a Gleason score 6 and pathological stage T2 was 0.11 ng/ml/cm^3. Our statistical analyses revealed that PSAD is a useful determinant for predicting very low-risk prostate cancer. We believe that a cut-off value of PSAD lower than 0.10 ng/ml/cm^3 would be helpful in lowering the failure rates in AS.

Sampling errors lead to anxiety both of the patient and the physician, and they inhibit the acceptance and maintenance of AS. Inaccurate sampling in PCa patients is somewhat reduced by the use of extended biopsy protocols. In our present study, the mean number of biopsy cores was 11.5 and all of the patients diagnosed with sextant biopsies were excluded. The results of our study revealed that a low-grade and small-volume cancer diagnosed with biopsies was not always an indicator for good pathological assessment on RP specimens. So one can conclude that prostate biopsies are not always confiding. In rebiopsy series of low-risk PCa patients, 61% of the patients showed no cancer or 27% being upgraded or upstaged. Re-biopsies may be a solution for undergrading. Also transperineal template-guided mapping biopsy is another alternative to increase the rate of cancer detection.

Max% in positive cores is a factor for predicting pathological outcomes of RP. Max% in positive cores has also been used as an inclusion criterion in several AS clinical trials, and in these trials cut-off values are changing 20–50. In our study, the mean max% in positive cores in patients with RP Gleason score 6 and pathological stage T2 was 11%. Our statistical analyses also revealed that lower % in positive cores are very useful for predicting very low-risk prostate cancer. We believe that lower cut-off values for max% in positive cores for AS would be helpful in reducing the failure rates.

Many physicians consider AS for selected low-risk PCa patients. The difficulty is in defining “low risk”. Now, with the developing imaging technology, most of the solid tumors are easily diagnosed and their volume could be more easily calculated than before. As it is a solid tumor as well, we believe that modern imaging techniques are promising tools for more accurately assessing the size, grade, and extent of the Pca. Decreasing the cut-off values of PSAD and max% in positive cores should be considered as AS inclusion criteria as well.

Given the relatively low incidence of stage, EPE, and SVI in men qualifying for AS according to criteria, some of the patients’ tumors are not insignificant. Decreasing the cut-off values of PSAD and max% in positive cores should be considered for AS inclusion criteria. If we could calculate the tumor volume before RP, we would minimize the overtreatment and undertreatment rates of PCa. New biopsy protocols, tissue biomarkers and molecular imaging technology may refine AS criteria.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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Predicting advanced stage prostate cancer patients


