ORIGINAL ARTICLE

Changes in Gleason score grading on serial follow-up biopsies in prostate cancer patients undergoing active surveillance

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KEYWORDS
Prostate cancer; Active surveillance; Follow-up biopsies

Abstract
Introduction: Active surveillance for prostate cancer has grown systematically in the recent years with more robust mid-term outcomes. However, changes in Gleason score during serial biopsies are not detailed in many of these reports.
Objectives: To evaluate changes in Gleason score on follow-up biopsies in low-risk prostate cancer in patients undergoing AS program in our center.
Materials and methods: Series of patients diagnosed of prostate cancer between 2004 and 2013 have been analyzed. The inclusion criteria were: PSA ≤ 10 ng/ml + Gleason ≤ 6 + T1c/T2a ≤ 2 positive cores, and no more than 50% of affected core. The pathology of each of the biopsies was analyzed.
Results: We studied a series of 175 patients undergoing AS. Mean follow-up was 3.96 years (SD 2.4). Follow-up biopsies with Gleason scores ≥ 7 were: 5.72% in the first biopsy, 7.39% and 7.41% in subsequent biopsies. By contrast, 42.03% of cases did not show evident tumor involvement in the first biopsy, 40.74% and 51.85% in the second and third biopsies respectively. Median stay in the AS program was: 90.99 months (CI 95%: 53.53–128.46) in patients with first positive biopsy vs. 96.66 months (CI 95%: 63.19–130.13) in those without evidence of tumor.
Conclusions: In our series the pathological data of the first 3 biopsies remain stable in terms of the positive biopsy rate, Gleason score, or indication of active treatment proportions. Those patients who do not show evidence of malignancy in the first follow-up biopsy are less likely to need active treatment than the other patients in the series.
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Cambios en el grado de Gleason en las biopsias de seguimiento de pacientes con cáncer de próstata en programa de vigilancia activa

Resumen

Introducción: Las series publicadas sobre vigilancia activa (VA) son cada vez más numerosas. La variación del Gleason a lo largo de las biopsias de seguimiento no se detalla en muchas de estas publicaciones.

Objetivos: Evaluar los cambios en el grado de Gleason de las biopsias de seguimiento en pacientes con cáncer de próstata de bajo riesgo en programa de VA.

Material y métodos: Análisis de pacientes diagnosticados entre 2004 y 2013. Criterios de inclusión: PSA ≤ 10 ng/ml, Gleason ≤ 6, T1c/T2a, ≤ 2 cilindros positivos, afectación máxima del cilindro de un 50%. Se analizaron los datos anatompato pathologicals de cada una de las biopsias.

Resultados: Serie de 175 pacientes incluidos en vigilancia activa con media de seguimiento de 3,96 años (DE: 2,4).

Las tasas de Gleason ≥ 7 en las biopsias de seguimiento fueron: 5,72% en la primera biopsia, 7,39% y 7,41% en las biopsias sucesivas. Por el contrario, no se evidenció afectación tumoral en el 42,03% de los casos en la primera biopsia, 40,74% y 51,85% en segunda y terceras biopsias respectivamente.

La mediana de permanencia en el programa en los pacientes con la primera biopsia positiva fue 90,99 meses (IC 95%: 53,53-128,46) vs 96,66 meses (IC 95%: 63,19-130,13) en aquellos sin evidencia de malignidad.

Conclusiones: En nuestra serie las 3 primeras biopsias se mantienen con unas proporciones estábles en cuanto a positividad de la biopsia, grado de Gleason o indicación de tratamiento activo. Los pacientes que en la primera biopsia de seguimiento no tienen evidencia de malignidad tienen menor probabilidad de necesitar tratamiento activo que el resto de la serie.

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Introduction

In the last few years, active surveillance (AS) has taken an increasingly important role in the management of low-risk prostate cancer.1,2 All the patients included in an AS program periodically undergo serial biopsies, so that curative treatment can be proposed against anatompato pathological progression, both in terms of Gleason score and the increase in the number of cores involved.1

Despite the existence of series with a large number of patients included in these programs, this change in Gleason score throughout the biopsies of those patients under surveillance for an extended period of time is not developed in detail in many of these publications.4-7

Objective

To assess changes in Gleason score on surveillance biopsies of patients with low-risk prostate cancer under an AS program at our center.

Materials and methods

We conducted a retrospective analysis of patients diagnosed with low-risk prostate cancer prospectively included in the AS institutional database between 2004 and 2013.

An AS protocol was proposed as a therapeutic choice for those patients diagnosed with low-risk prostate adenocarcinoma who met the following criteria: PSA < 10 ng/ml + Gleason < 6 + clinical stage T1c/T2a + number of positive cores < 2 + maximum core involvement of 50%. In all patients, it was estimated, by age and comorbidities and as measured according to the Charlson index, that life expectancy at the time of inclusion in the program was over 10 years and that, therefore, they were candidates for curative treatment.

Patients were included in the program after detailed clinical information had been recorded. In all cases, therapeutic alternatives were proposed, verbal informed consent was obtained and the patient was given a written report with the diagnosis, possible treatments and the need for protocolized surveillance. The protocol was approved by the institutional ethics committee.

At the beginning of the study, most patients were diagnosed by octant biopsy, so they underwent an initial saturation rebiopsy (within less than 3 months after diagnosis) for result confirmation, which in the analysis was considered as the first surveillance biopsy. Since 2012, initial biopsies in the protocol at our center have been 12-core biopsies, so patients included in the program directly undergo a first surveillance biopsy throughout the first year which is much wider (>18 cores). All patients on AS were subsequently followed up with PSA measurements and digital rectal examination every 6 months, and they undergo repeated biopsies conducted under local anesthesia on an outpatient basis with at least 12 cores each after 3 years, depending on the patient’s age and PSA kinetics. All biopsies were conducted transrectally, regardless of prostate size.

The anatompato pathological analysis at our center was performed by 2 uropathologists, and each core was independently assessed in order to obtain greater precision in the
number of cores involved and in the percentage of involvement of each core.

Other imaging tests, such as multiparametric magnetic resonance, were carried out without following any protocol.

We proposed active treatment to all those patients who showed anatomo-pathological progression in the biopsies conducted throughout follow-up, as well as by the patient’s own choice at any time of follow-up, with anatomo-pathological progression being considered as: involvement of more than 2 positive cores, Gleason > 7 or core involvement > 50%.

Anatomo-pathological data of each of the biopsies performed were analyzed. Permanence time in the AS program was analyzed by using survival analysis techniques with Kaplan–Meier curves. We considered time in AS as the time elapsed from diagnosis to treatment, the date of death or to the last clinical checkup of untreated patients.

All these analyses were carried out using the statistical package SPSS version 17.

Results

We analyzed a series of 175 patients with low-risk prostate cancer included in the AS program. 42 (24%) out of the total patients did not strictly meet the inclusion criteria mentioned above, but were included in the program by the patient’s own decision. A description of the series at diagnosis is shown in Table 1.

The mean follow-up was 3.96 years (SD: 2.4). One hundred and thirty-four patients (76.6%) are still under active surveillance, with a median estimated treatment-free survival of 104.16 months (CI 95%: 92.93–115.38). Nine patients (5.14%) were lost through follow-up.

96 (54.9%) out of the total patients in the series were included with an octant diagnostic biopsy, so they immediately underwent a confirmatory extended rebiopsy, which was considered as the first surveillance biopsy. 21 (12%) out of the remaining patients were included following a 12-core diagnostic biopsy, and in 58 (33.2%) diagnosis was made following a 16-core biopsy or more (these patients had prior negative biopsies). Eighty-one patients (46.28%) underwent 2 or more biopsies throughout follow-up, 27 (15.43%) 3 or more and 5 (0.3%) 4 or more biopsies. The number of patients with 5 or more biopsies throughout follow-up was very low, so the present work refers only to data of the first 4 biopsies.

The anatomo-pathological results of the surveillance biopsies are shown in Fig. 1. The mean time to the first biopsy was 11.5 months (SD: 8.9), the subsequent intervals, as well as the percentage of patients requiring active treatment after each biopsy are shown in Fig. 2. The rates of active treatment made by the patient’s own decision, and not due to anatomo-pathological progression, were of: 22.7% (5 patients) in the first biopsy, 0% in the second biopsy and 33.3% (2 patients) in the third one.

In the 3 first surveillance biopsies, the number of patients with no tumor involvement was: 66 (42.03%), 33 (40.74%) and 14 (51.85%) respectively, with the percentage of patients with Gleason score > 7 being lower than 10% in each one (5.76%, 7.39% and 7.41% respectively). Out of the patients with tumor involvement in the surveillance biopsies, positivity was proven in more than 2 cores in 32.22%, 27.08%, 38.46% and 25% respectively.

Those patients on whom tumor involvement in any core was detected in the first biopsy (90 patients) had a higher likelihood of requiring active treatment than the rest of the series (Fig. 3), with the median permanence time in the AS program of this subgroup being 90.99 months (CI 95%: 53.53–128.46) vs. 96.66 months (CI 95%: 63.19–130.13) in the case of those without evidence of malignancy (p = 0.001).

Out of the patients who in the first surveillance biopsy showed no tumor involvement (66 patients), 19 (28.78%) had a negative second biopsy, and out of these, 6 patients still had negative results in the third biopsy. Similarly, those patients who had any negative biopsy prior to program enrolment (36.6%) had a lower risk for progression than the rest, with an OR 0.5 (CI 95%: 0.3–0.8); p = 0.013.

Besides, we assessed progression in the first surveillance biopsy in patients diagnosed by octant biopsy and patients with 12 or more cores. The percentage of progression in this first biopsy was 16.67% in patients with octant biopsy vs. 10.13% in patients with a 12-core biopsy or more (p = 0.2).

### Table 1 Characteristics of patients at diagnosis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>175 (100)</td>
</tr>
<tr>
<td>Age (years)(^a)</td>
<td>66.20 (6.58)</td>
</tr>
<tr>
<td>Clinical stage T1c</td>
<td>166 (94.9)</td>
</tr>
<tr>
<td>Gleason 6</td>
<td>170 (91.7)</td>
</tr>
<tr>
<td>PSA (ng/ml)(^a)</td>
<td>6.5 (1.97)</td>
</tr>
<tr>
<td>Prostate volume(^b)</td>
<td>45.6 (24.8)</td>
</tr>
<tr>
<td>No. of positive cylinders(^b)</td>
<td>1.4 (0.71)</td>
</tr>
<tr>
<td>Maximum percentage of cylinder involvement(^b)</td>
<td>11.5 (9.9)</td>
</tr>
<tr>
<td>Patients who do not meet some inclusion criteria</td>
<td>42 (24)</td>
</tr>
<tr>
<td>PSA (&gt; 10 ng/ml)</td>
<td>25 (59.5)</td>
</tr>
<tr>
<td>Gleason 7</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Involvement &gt; 2 cylinders</td>
<td>14 (33.3)</td>
</tr>
<tr>
<td>Maximum percentage of cylinder involvement &gt; 50%</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>

\(^a\) Data expressed as mean (SD).

![Figure 1 Pathological results in the active surveillance follow-up biopsies. Bx: biopsy.](image-url)
However, have At the Congress of the active biopsy.

Figure 2 Percentage of patients requiring active treatment in each biopsy of the follow-up. Bx: biopsy; AS: active surveillance.

Discussion

Active surveillance in the treatment of low-risk prostate cancer is currently a recommendation accepted by all international clinical guidelines. The series described in the literature are not homogeneous in terms of the inclusion criteria used, follow-up or in terms of the indications for active treatment. The protocols used at different centers show variations regarding the type of biopsies conducted, the time of its performance, as well as the use of other complementary imaging tests; however, the oncological results of them all are comparable, with medium-term follow-up. Results of the longest active surveillance series have been reported (Klotz, European Association of Urology Congress 2014), with equally acceptable long-term results, and a 9.7-times higher risk of death from other causes than the risk of death from prostate cancer.

The protocols of the active surveillance series with longer follow-up have been modified over time, both in terms of inclusion criteria and follow-up schemes, as well as in the indications for active treatment in some cases. Our protocol has also undergone modifications since 2004. At the start of the program, all the patients diagnosed by octant biopsy underwent an immediate 18- or 20-core rebiopsy for diagnostic confirmation. The biopsies currently performed at our center are 12-core biopsies as stipulated by the protocol, so patients do not immediately undergo a confirmation rebiopsy, but within the first year of follow-up.

In general, it is considered that the patients receiving active treatment after the first biopsy are in fact understaged patients at diagnosis. These underdiagnosis rates vary depending on the series, but can reach up to 35%. At our center, 57% of the patients showed tumor in this first biopsy, but only 14.1% of the patients showed progression requiring active treatment, a slightly lower percentage than those described in the literature.

In the subsequent biopsies, the results remained the same with stable proportions in terms of biopsy positivity, Gleason score or indication for active treatment, except for the fourth biopsy where the number of patients was so low that it did not allow for conclusions in this regard.

Differences in progression in the first surveillance biopsy of patients diagnosed by octant biopsy vs. 12-core biopsy or more were not statistically significant, possibly due to the number of patients in each group, and therefore we can only assume that it is a reflection of the higher underdiagnosis rates in 8-core biopsies.

Besides, in our study we can observe how the patient group with a first positive biopsy during follow-up showed a higher active treatment rate than those patients on whom this first biopsy was negative, thus reproducing what has already been described by Adami et al. However, despite the increased risk for needing active treatment, 70% of the patients with a first positive biopsy remained in the active surveillance program 7 years after being diagnosed.

In our series, there were 6 patients (3.42%) who had negative results in the first 3 surveillance biopsies; out of these, one had a fourth positive biopsy, the rest have not undergone a fourth biopsy yet. According to what has been described in the literature, around 2–5% of patients keep having negative biopsies throughout follow-up, so our study is in line with what other authors have described. These results, if confirmed by longer-term studies, would indicate that patients who undergo multiple negative biopsies suffer from such a minor illness that more lax follow-up could be proposed, increasing the interval between biopsies.

Similarly, those patients with a history of prior negative biopsies at the time of time enrolment showed better prognosis than the rest. Determining if these patient subgroups are candidates for reducing the number of biopsies they currently undergo will be the subject of future studies with longer follow-up.
The limitations of our study are due to the fact that it is a retrospective analysis, with moderate follow-up. Given the low number of patients who underwent a fourth biopsy, we cannot draw any conclusion from it. Likewise, the number of patients who underwent 5 or more biopsies was so low that it was not included in the analysis. Neither did we analyze the complication rate of biopsies nor the impact that repeated biopsies might have on our patients’ quality of life.

Conclusions

In our series, the anatomopathological data of the first 3 biopsies maintained stable proportions in terms of biopsy positivity, Gleason score or in the indication for active treatment. Those patients who in the first surveillance biopsy had no evidence of malignancy were less likely to need active treatment throughout follow-up than the rest of the series.

Conflict of interest

The authors declare that they have no conflict of interest.

References


