ORIGINAL ARTICLE

Active surveillance in low-risk prostate cancer. Patient acceptance and results

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Abstract

Objectives: To evaluate the acceptance of active monitoring by patients treated in our healthcare community and to report the clinical results of an active surveillance program in patients with low-risk prostate cancer.

Materials and methods: Prospective study of patients enrolled in an active surveillance program at our center between 2004 and 2012. The inclusion criteria were PSA < 10 ng/ml, Gleason score ≤ 6, clinical stage T1c/T2a, ≤ 2 positive cores, and no more than 50% of the core being affected. Curative treatment was proposed when faced with pathological progression over the course of the monitoring.

Results: In 2011, only 17% of the total number of potential candidate patients rejected their inclusion in a surveillance program and were treated actively. We analyzed a series of 144 patients included in our active surveillance protocol. The mean follow-up time was 3.22 years (SD 2.08). A total of 110 patients (76.3%) remained under active monitoring, with an estimated median treatment-free survival after diagnosis of 6.9 years (95% CI: 6.2–7.6). The percentage of patients who remained free of treatment at 2 and 5 years was 96.3% (95% CI: 92.8–99.8%) and 70.9% (95% CI: 59.3–85.5%), respectively. Thirty-four patients (23.6%) required curative treatment. The mean time to treatment was 4.6 years (SD 2.3).

Conclusions: Active surveillance of highly selected patients with low-risk prostate cancer is a valid alternative therapy that is accepted by patients in our community.

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Vigilancia activa en cáncer de próstata de bajo riesgo. Aceptación por el paciente y resultados

Resumen
Objetivos: Evaluar la aceptación del seguimiento activo por los pacientes en nuestro entorno asistencial y describir los resultados clínicos de un programa de vigilancia activa en pacientes con cáncer de próstata de bajo riesgo.

Material y métodos: Estudio prospectivo de pacientes incluidos en programa de vigilancia activa en nuestro centro entre 2004 y 2012. Los criterios de inclusión fueron: PSA < 10 ng/ml, Gleason ≤ 6, estadio clínico T1c/T2a, ≤ 2 cilindros positivos, con una afectación máxima del cilindro del 50%. Se propuso tratamiento curativo ante la progresión anatómopatológica a lo largo del seguimiento.

Resultados: En el año 2011, del total de pacientes potenciales candidatos, tan solo un 17% de los mismos rechazó la inclusión en un programa de vigilancia y fue tratado de forma activa. Analizamos una serie de 144 pacientes incluidos en nuestro protocolo de vigilancia activa. La media de seguimiento fue de 3,22 años (DE: 2,08). Ciento diez pacientes (76,3%) permanecen en seguimiento activo, con una mediana estimada de supervivencia libre de tratamiento tras el diagnóstico de 6,9 años (IC 95%: 6,2-7,6%). El porcentaje de pacientes que permanecen libres de tratamiento a 2 y 5 años fue de 96,3% (IC 95%: 92,8-99,8%) y 70,9% (IC 95%: 59,3-85,5%) respectivamente. Treinta y cuatro pacientes (23,6%) precisaron tratamiento curativo. La media de tiempo hasta el tratamiento fue de 4,6 años (DE: 2,3).

Conclusiones: La vigilancia activa en pacientes altamente seleccionados con cáncer de próstata de bajo riesgo es una alternativa terapéutica válida de tratamiento y aceptada por los pacientes de nuestro entorno.

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Introduction
In the last years, active surveillance is a well-consolidated option in urological practice for management of low-risk prostate cancer, and it has been included as a treatment modality in clinical guidelines of the European and American urological associations and NCCN. However, there is still no consensus on the criteria for inclusion in these programs, optimal monitoring protocol and indication criteria for active treatment. Moreover, in our health-care community it is considered as treatment option not well accepted by patients and, for this reason, difficult to apply in clinical practice (Fig. 1).

Objective
The objective of our study is to evaluate the acceptance of active surveillance by patients treated in our health-care community and to report the clinical results of an active surveillance program in patients with low-risk prostate cancer, and to assess the dwell time on this program, trying to increase the scientific evidence published to date.

Materials and methods
Prospective study of patients enrolled in an active surveillance program at our center between 2004 and 2012 were conducted.

Inclusion criteria
Active surveillance was proposed to those patients diagnosed of low-risk prostate adenocarcinoma as therapeutic option. The inclusion criteria were: PSA < 10 ng/ml, Gleason score < 6, clinical stage T1c/T2a, ≤ 2 positive prostate biopsy cylinders with no more than 50% of the core being affected. Curative treatment was proposed when faced with pathological progression over the course of the surveillance, both in...
Gleason progression and in the number of cylinders affected. All patients signed specific informed consent.

**Surveillance**

At the entrance to the active surveillance program, extended re-biopsy (18–22 core) was proposed to those patients who had less than 12 core to obtain a pathologic confirmation of diagnosis of very low-risk prostate adenocarcinoma. All patients showing pathologic progression were initially considered understaged patients, and were excluded from active surveillance program. Therefore, active treatment was proposed to all of them.

Surveillance program was carried out by PSA and digital rectal examination every 6 months, and re-biopsies every 1–3 years which were individualized depending on the age and PSA kinetics. Clinical data are collected prospectively in the institutional database.

**Active treatment**

Active treatment was proposed to all those patients in whom pathologic progression were demonstrated during the surveillance period, as well as in those patients with PSA doubling time less than 3 years. In patients treated curatively, PSA > 0.2 ng/ml in 2 consecutive measurements were considered biochemical recurrence. A rise by 2 ng/mL or more above the nadir PSA was considered as recurrence criteria, in both patients who had undergone radical prostatectomy and patients who had undergone radiotherapy.

**Statistical analysis**

Quantitative variables are expressed as mean and standard deviation (SD), or median and interquartile range (IQR). Qualitative variables are described by the absolute (N) and relative (%) frequencies. Time spent in active surveillance program was analyzed with survival analysis techniques, using Kaplan Meier survival functions and the log-rank statistic. Time in active surveillance was defined as the time elapsed between the diagnosis and treatment or, in untreated patients, between the diagnosis and final clinical examination. Patients lost to follow-up (1.4%) were censored at their last clinic visit. Confidence intervals were 95%. This test was done in all bilateral cases and with 0.05 of statistical significance level. Statistical analysis was done with statistical software SPSS (version 17).

**Results**

In last years, the percentage of patients included in active surveillance program has increased progressively. During this time, a remarkable decrease in the number of patients diagnosed of low-risk prostate cancer on treatment has been observed in our center. In 2011, only 17% of the total number of potential candidate patients rejected their inclusion in a surveillance program and were treated actively. Thus, acceptance rate of this program can be very high in our health-care community.

In this study, a series of 160 patients with low-risk prostate carcinoma were analyzed. Mean age was 66.2 years (SD: 5.88). At diagnosis, 95% of the patients showed clinical stage T1c, with mean PSA levels of 7.5 ng/ml (SD: 3.6). At first confirmatory extended re-biopsy, about 10% of the initial series (16 patients) were reclassified and left the program. These patients were initially considered under stage and not candidates for active surveillance.

Finally, 144 patients were included in our active surveillance protocol. The mean follow-up time was 3.22 years (SD 2.08). Description of series at diagnosis is presented in Table 1. From the total series of cases, 35 patients (24.3%) did not strictly meet some inclusion criteria; however they were included in the program by patient’s wish: 6 patients with Gleason 3 + 4 (all patients older than 70 years), 3 patients with more than 50% of biopsy cylinder affected, 10 patients with more than 2 biopsy cylinders affected and 19 patients with PSA 10 ng/ml.

During surveillance period patients were biopsied according to institutional protocol. Mean elapsed time to first rebiopsy was 0.99 years (SD: 0.93). Subsequently, this interval of time becomes longer, 1.8 years (SD: 0.92) to the next rebiopsy.

A total of 110 patients (76.3%) remained under active surveillance, with an estimated median treatment-free survival after diagnosis of 6.9 years (95% CI: 6.2–7.6). The percentage of patients who remained free of treatment at 2 and 5 years was 96.3% (95% CI: 92.8–99.8%) and 70.9% (95% CI: 59.3–85.5%), respectively (Fig. 2).

The reasons for leaving active surveillance program were: pathologic progression in 25 patients (17.3%), patient’s choice in 5 individuals (3.4%) and PSA progression in 4 patients (2.7%).

Thirty-four patients (23.6%) required curative treatment during surveillance period: 11 patients were treated with radiotherapy and 23 underwent radical prostatectomy. The mean time to curative treatment was 4.6 years (SD 2.3). Clinical features at treatment are shown in Table 2. Of those patients who underwent radical prostatectomy, 30% of the cases showed unfavorable pathologic findings (pT3, Gleason ≥ 8 or positive margins). During surveillance period, biochemical recurrence was found at one patient of all patients who underwent curative treatment. None of them died nor showed metastatic progression.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total = 144 patients; n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stage T1c</td>
<td>138 (95.8)</td>
</tr>
<tr>
<td>Gleason 6</td>
<td>138 (95.8)</td>
</tr>
<tr>
<td>PSA(a)</td>
<td>7.00 (3.7)</td>
</tr>
<tr>
<td>Prostatic volume (cc)(b)</td>
<td>43.6 (21.7)</td>
</tr>
<tr>
<td>Number of positive cylinders(b)</td>
<td>1.4 (0.7)</td>
</tr>
<tr>
<td>Cylinder’s maximal affectation (%)(b)</td>
<td>13.7 (13.8)</td>
</tr>
</tbody>
</table>

\(a\) Data expressed as mean (DE).

\(b\) Data expressed as mean (DE).
Discussion

Active surveillance is a consolidated therapeutic alternative in the urological community. In our health-care community, it is not yet a consolidated therapeutic practice, and our patients’ acceptance of this program has been questioned. Our study has demonstrated that more than 80% of the potential candidate patients accept their inclusion therein and during surveillance period, only 3.4% of the patients decide leaving by choice. This highlights that active surveillance is a feasible alternative in our health-care community.

Oncological results of different active surveillance programs have been published in medical literature. These protocols are not homogeneous in regard to inclusion clinical criteria, follow-up patterns and indications of active treatment.

In a recent systematic review, active surveillance series to date have been collected and differences between inclusion criteria employed and oncological results in the short and intermediate term have been analyzed. It is not yet proven that the use of strict selection criteria improve the long-term results, because although they allow accurate identification of patients with insignificant disease, strict selection criteria can reduce the number of potential candidate patients for the program. Moreover, intermediate-term oncological results are similar between series, regardless of the inclusion criteria used.

In our study, all patients included in the program who had less than 12 biopsy cylinders underwent early extended rebiopsy. A 10% of the patients with tumors clinically significant were reclassified after that rebiopsy. Percentage of underdiagnosis varies with series, but it can reach to 35%. It remains to be determined whether for patients who finally undergo curative treatment, the time that they are under active surveillance can worsen the clinical evolution of the disease. Variable rates of non-curable PC that have been collected in series published to date are similar to those patients undergoing immediate radical prostatectomy after diagnosis.

Our study is not without limitations. Confirmation of data is required. Additional randomized studies or studies with larger series of patients and longer follow-up are needed to determine the real effect of active surveillance in the cancer-specific survival data. Anxiety caused by diagnosis or deferred treatment is an important factor that has not been assessed.

Conclusions

Active surveillance of highly selected patients with low-risk prostate cancer is a valid alternative therapy. Our results are similar to others previously published and confirm the safety of this therapeutic option as well as the real possibility to develop in our community.

Conflict of interests

The authors declare that they have no conflict of interest.

References


