Obligatory information that a patient diagnosed of prostate cancer and candidate for an active surveillance protocol must know

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Received 3 February 2014; accepted 6 February 2014
Available online 12 October 2014

KEYWORDS
Prostate cancer; Active surveillance; Prognostic; Patients; Information

Abstract

Objectives: To know the necessary information to reproduce the results found in the literature on active surveillance (AS) in prostate cancer (PCa) in our own center so that the information would be objective and correctly given to the patients. We have aimed to study the percentage of candidates for AS chosen in our setting, and the data on infrastaging, subgrading and prediction of insignificant PCa, debugging the predictive value of clinical variables to improve our selection criteria and finally to analyze the results of our patients enrolled in AS.

Materials and methods: A retro- and prospective review of our databases was performed. A one-year period was analyzed to know AS candidates. Analysis of our radical prostatectomy specimens for infrastaging, subgrading and prediction of insignificant PCa (Epstein’s criteria) was made as well as a uni/multivariate analysis of clinical variables in patients with insignificant PCa in the specimen. A prospective validation was performed with overall survival and survival free of active treatment (SFAT) as endpoints in patients enrolled in AS.

Results: Between October-2010 and October-2011, 44.7% of our PCa were candidates for AS, but only 11.2% chose it. The percentages found for infrastaging, subgrading and prediction of insignificant PCa were 14%, 31.4% and 55.7%, respectively. However, only just 6 patients (6.97%) had ≥pT3a + Gleason ≥7 + volume >0.5 cc PCa. The multivariate analysis showed that PSA density and number of affected cores were independent predictors of insignificant PCa. With a mean follow-up of 36 ± 39 months, 63 out of 232 patients enrolled in AS went on to active treatment.


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Introduction

Overtreatment of prostate cancer (PCa) due to early diagnosis or opportunistic screening\(^1\,^2\) is well-known, also in Spain.\(^3\) One of the strategies attempting to counteract such a phenomenon is active surveillance (AS), defined as a wait-and-see approach toward potentially curable low/intermediate-risk PCa, which can be proposed to any patient with a life expectancy > 10 years and which involves rigorous clinico-pathological control (rebiopsies) until objective progression criteria support the active treatment of that PCa with a curative intent (unlike monitoring until palliative care for the metastatic disease). AS, theoretically feasible at any hospital, is now accepted in the European Clinical Guidelines with a level of evidence of 2a.\(^4\)

Nevertheless, we believe that for this extrapolation to any center to be legitimate, minimum standards should be required regarding quality and knowledge about its casuistry, the quality of pathologists, biopsy standardization (Bx) and regarding its possibilities when faced with a strict surveillance protocol so that results can be reproduced in the literature, which on the other hand are still under investigation and need time judgment.\(^5\)
AS is an alternative which is gaining more and more
importance among urologists and patients (who are increas-
ingly better informed). Our aim in this study was to
recapitulate all the information that can be extracted from
our own casuistry in an attempt to be able to provide our
own information to patients if they choose AS at our center.
To that end, we believe that, like any other group offering
AS, we should analyze certain data in order to frame and
develop an AS program, which given its specificity should
not be totally extrapolated from one hospital to another.
Therefore, we aimed at: (1) quantifying those patients in
our environment who are candidates for AS and getting to
know who chooses it, (2) knowing our infrastaging, infra-
graduation and insignificant PCa prediction data, (3) improving
our candidate selection criteria for AS and (4) knowing the
initial active-therapy-free-survival (ATFS) outcomes and the
estimated 5-year global ATFS of our patients included in AS
programs in order to be able to provide those data to our
future candidates for AS.

Methods

We retrospectively reviewed the databases of the Valencian
Institute of Oncology of PCa patients; the database of Bx
biopsies, patients who had undergone radical prostatectomy
(RP) in the period 1986–2013, patients included in AS pro-
grams, patients treated with brachytherapy (BT) and with
external radiotherapy (RT). It is important to emphasize that
our center does not have any assigned population area and
that not all the patients treated there were biopsied at our
center, since it is a monographic center of oncology which
receives patients from other areas. We have the approval of
the Ethics Committee for the implementation of these
databases and for retrospectively carrying out this study.

1. Quantification of patients candidates for AS: we ran-
domly chose a period of one year (October 2010/October
2011) and we descriptively analyzed how many patients
were considered candidates for AS, establishing the
following criteria: patients included in the low-risk
group NCCN + Bx with at least 10 cylinders taken + ≤ 33%
affected cylinders. According to these criteria, we
reviewed the patients included in prostate Bxs,
AS and RP, BT, RT and cryotherapy databases. All
databases were cross-checked to avoid duplications and
over-estimations.

2. Knowledge of our data on infrastaging, infra-
graduation and indolent PCa prediction: retrospective review of
our RP database from 1986 to June 2013 with the same
criteria for AS inclusion previously described adding a
maximum ceiling of 3 affected cylinders for this purpose.

3. Knowledge in our environment of the clinicopathological
characteristics which may predict an indolent tumor in
a RP specimen: retrospective review of the RP database,
excluding those with adjuvant hormonotherapy, which
were pT0 or tumors with a tumor volume <0.5 cc, and
which were used along with a Gleason-specimen score
≤6 and pT2a as a definition for insignificant PCa. Tumor
volume was recorded in a standardized way since 2007,
so to this end we selected 535 patients from April 1,

4. Knowledge of the initial results in our patients included
in AS: retro- and prospective review of the database
of those patients included in AS. Our current inclusion
criteria are inspired by the PRIAS’ selection criteria and
which we consider, although not exactly the same, the
reference standard since they are the most commonly
used ones in the literature. These are the following:
PSA ≤10 ng/ml, Bx Gleason score (Bx-Gl) ≤3 + 3 (we
accepted a Bx-Gl score of 3 + 4 in patients over 70 years
of age), cT1a-b-c, PSA density (PSAD) <0.20, a maximum
of 2 affected cylinders and a Bx of at least 10 cylinders.
Patients must have a life expectancy of >10 years, be
under 80 years of age at the time of PCa diagnosis and
have an intellectual level enabling them to understand
the AS protocol and to sign the corresponding informed
consent form. Besides, in order to get to know our own
reality, and as in many other publications on AS, we also
included patients with variables which were different to
those mentioned above and who entered AS for various
reasons (the patient’s desire, comorbidities, the need
for initial treatment of another tumor, etc.), a group we
referred to as induced AS.

In the current protocol, we have considered since 2010
the performance of a first confirmation Bx at 6 months after
diagnosis guided by previous 1.5-T multiparametric nuclear
magnetic resonance imaging in agreement with the patient
through a transrectal approach (18 cylinders) or through a
transperineal approach with a BT rack (24–32 cylinders)
depending on their tolerance to diagnostic Bx, prostate
volume and on the findings of multiparametric nuclear mag-
netic resonance imaging. Follow-up Bxs were performed at
8 months and then every 3 years until the age of 80 or
until the occurrence of a medical event which may imply
a decrease in life expectancy. All Bxs were analyzed by
a uropathologist (AC). The progression criteria were an
increase in Bx-Gl (according to inclusion) and ≥ 2 positive
cylinders.

Results

1. Quantification of patients candidate for AS: of the 199
patients with localized PCa who were referred to or diag-

nosed at our center during the chosen period, 89 (44.7%)
met criteria for being included in AS. For different rea-
sons which are explained further below, only 10 of them
(11.2%) chose AS. Twenty-nine of the 145 RPs (20%),
21 of the 53 cases of BT (39.6%) and 5 of the 30 cases
of RT (16.6%) performed respectively met criteria for AS.
The remaining 24 patients up to 89 correspond to patients
who were candidates for observation but were lost during
follow-up.

The mean of cylinders taken from candidate patients
was 11.8 ± 2.1 (range 10–18), the mean PSA was
5.95 ± 2.23 ng/ml (range 0.73–9.93 ng/dl). The mean age
was 61.2 ± 7.3 years (41–76), and the median 61 years.
Regarding age and the choice of AS, there were sig-
ificant differences between active treatment and AS
(p = 0.001), with a higher percentage of patients older
than 64 in the AS group than in the active treatment
group. There were no significant differences in IPSS
score among the patients candidates for AS who chose it (average 11.8 ± 7.4) versus those who chose active treatment (7.8 ± 5.7), neither in the quality-of-life item (2.8 ± 1.7 vs. 2 ± 1.5), nor in the IIEF-5 score (16 ± 5.8 vs. 16.2 ± 8.7) respectively.

2. Knowledge of our data on infrastaging, infradlegation and indolent PCA prediction: out of 1449 RPs, 86 patients (5.9%) pre-surgically belonged to the NCCN low-risk group, had a minimum of 10 cylinders taken at Bx, with <33% of affected cylinders and a maximum of 3 affected cylinders (17 patients), 32 had 2 affected cylinders and 37 only one. Taking into consideration only the 589 RPs performed on low-risk patients, 14.6% of this group would have been candidates for AS. The number would have probably been higher if we had known the number of cylinders taken and affected within the entire series, but this was unknown in 560 patients since this was a historical series which took into account the RPs performed since 1986.

Table 1 shows that 14% of tumors were non-organ-confined tumors, 3 patients (3.5%) were pT3b, that 31.4% were infragraded and that more than half had a clinically significant volume. The mean tumor volume was 1.27 ± 1.67 cc. Only 6 patients (6.97%) were ≥pT3a + Gleason ≥ 7 + volume > 0.5 cc. The mean follow-up of this series of 86 patients was 19.20 ± 19.93 months (range 1–68 months). Seven patients out of 86 (8.1%) had biochemical progression (PSA > 0.4 ng/ml) over this period, which implies an estimated biochemical progression-free survival rate of 92.5% at 24 months (CI 95%: 83.8–100%) and of 73.6% at 60 months (52.4–94.8%).

3. Knowledge in our environment of the clinicopathological characteristics which may predict an insignificant tumor in RP specimen: among the 335 RPs we were able to analyze for this purpose, 69 (12.9%) were specimens with a Gleason score of 3 + 3; <pT2a and with <0.5 cc of tumor volume (study group), 25 of which (4.6%) were pT0. Among the pre-RP variables, there were no differences in age, body mass index, a history of PCa in their families, ASA score nor in the number of cylinders taken when compared to the rest of RPs (control group). Table 2 shows the different pre-RP variables which did show statistically significant differences between the study/control groups.

We observed that the study patients showed higher prostate volumes and therefore lower PSAD values as compared with the control group. Similarly, a percentage of affected cylinders >33% entails in 97.8% of cases a clinically significant tumor in our series.

4. Knowledge of the initial results in our patients included in AS: from 1996 to July 2013, we included 232 patients in AS, 111 of whom (47.8%) belonged to the induced AS group. Fig. 1 shows the growing evolution of the indication for AS over the last few years, preferably at the expense of AS but fulfilling the inclusion criteria (true AS).

Out of 232 patients, 148 underwent at least one follow-up Bx, at a median time of 11 months; 76 were negative, 27 were positive with no progression criteria and 45 were positive with progression criteria. Just considering confirmation Bxs (defined as those performed before the year of AS inclusion), those performed in the true AS group reclassified the patient in 22.9% of cases, versus 31% of those included in the induced AS group (p = 0.082). During follow-up, 50 patients (21.6%) were cataloged in pathological progression, with statistically significant differences between the true AS group (17 patients, 14%) and the induced AS group (33 patients, 29.7%) (p = 0.004).

With a mean follow-up of 36 ± 39 months (median 23, range 1–232 months), 63 patients (27.1%) were crossed over to active treatment, only 13 of them as a result of the patient’s anxiety with no pathological progression. The median ATFS time was 72.7% (CI 95%: 30.9–114.4). Fig. 2 shows that ATFS at 24 months was 76.4% (69.7–83.1%) whereas it was 58.1% (48.8–67.4%) at 48 months.

During follow-up, of the 23 patients, 10 (4.3%) died, 8 of them during AS and 2 during hormonotherapy as an active
treatment. 90% of deaths occurred in the induced AS group. Therefore, the estimated 5-year overall survival, assessing follow-up time from the beginning of AS until exitus or the end of follow-up, either under AS or active treatment, was 92.8% in our series (CI 95%: 86.7–98.9%), with no statistically significant differences between the true AS and the induced AS groups (p = 0.282). Of the 63 patients who were crossed over to active treatment, only 3 in the induced AS group developed metastatic progression and one died due to tumor progression.

Discussion

Good medical practice with regard to a patient diagnosed with organ-confined PCa forces the urologist to have a critical understanding of all his therapeutic strategies. Technological or casuistry limitations should be dodged for the sake of the sick and thus justify patient referral to other centers with those services or with a higher casuistry if we really believe that the patient will benefit from that. AS is, nevertheless, a potentially feasible strategy at any center, regardless of its casuistry. However, we think that it is imperative to know several data regarding its implementation at each center in order to be able to deliver the local results of this strategy to any PCa patient candidate for AS.

Our low enrollment rate in AS (11.2%) was calculated over the period from October 2010 to October 2011, but it is biased since in all the cases of patients who were referred from other centers for the performance of RP, BT, RT or cryotherapy at ours, we respected the dispatcher’s indications.

This contrasts with the rate close to 50% of diagnosed patients who chose AS in the Swedish branch of the ERSPC, similar to the potential candidates for AS in our country too. However, the increased acceptance of this strategy comes from both the conviction of the professionals involved in PCa and better information on the part of patients, and both Fig. 1 in our case and the data from other center in our country, which show that in the year 2011 only 17% of the possible candidates for AS chose active treatment, are irrefutable data regarding the increase in patients who also choose AS in our environment.

The analysis of our RPs performed in possible candidates for AS showed a 14% infrastaging and a 31.4% infragradation; nevertheless, over half had a significant volume taking into consideration the cut-off point of 0.5 cc. The criteria for insignificant PCa were established by Stamey in 1993, in incidental PCas, in specimens from 139 cysto-prostatectomies

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Anatomopathological results of the radical prostatectomy specimens that met the criteria selected for AS (n = 86).</th>
</tr>
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<tbody>
<tr>
<td>pT</td>
<td>pT0 = 5 (5.8%)</td>
</tr>
<tr>
<td>Gleason</td>
<td>≤6 = 59 (68.6%)</td>
</tr>
<tr>
<td>Tumor volume</td>
<td>Not recorded = 25 ≤0.5 cc = 27 (44.3%)</td>
</tr>
<tr>
<td>Perineural inf.</td>
<td>Not recorded = 27 Yes = 22</td>
</tr>
</tbody>
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<tr>
<th>Table 2</th>
<th>Clinicopathological variables with differences between the study (insignificant PCa in RP specimen) and control (not insignificant PCa in RP specimen) groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group (n = 69)</td>
<td>Control group (n = 466)</td>
</tr>
<tr>
<td>Preoperative PSA</td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>57 (14.5%)</td>
</tr>
<tr>
<td>10–20</td>
<td>12 (11.7%)</td>
</tr>
<tr>
<td>≥20</td>
<td>0</td>
</tr>
<tr>
<td>Gleason biopsy</td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>54 (15.4%)</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>≥8</td>
<td>0</td>
</tr>
<tr>
<td>cT</td>
<td></td>
</tr>
<tr>
<td>≤T2a</td>
<td>49 (10.8%)</td>
</tr>
<tr>
<td>≥T2b</td>
<td>0</td>
</tr>
<tr>
<td>Prostate volume</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>52.4 (25.64)</td>
</tr>
<tr>
<td>Median (min–max)</td>
<td>47.5 (20–143)</td>
</tr>
<tr>
<td>PSA density</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.1 (0.12)</td>
</tr>
<tr>
<td>Median (min–max)</td>
<td>0.1 (0–0.6)</td>
</tr>
<tr>
<td>Percentage of affected cylinders</td>
<td></td>
</tr>
<tr>
<td>≤33%</td>
<td>55 (19.1%)</td>
</tr>
<tr>
<td>&gt;33%</td>
<td>3 (2.2%)</td>
</tr>
</tbody>
</table>
and in patients who therefore had not been derived from screening programs. Thereby, the cutoff point of 0.5 cc has been recently questioned and other authors have increased this point to 1.3 cc for the index lesion and to 2.5 cc of total tumor volume as a reference for clinically insignificant PAs in patients coming from screening programs, which without any doubt would substantially increase the number of insignificant tumors in our series and would force us to remake many nomograms using a tumor volume of 0.5 cc as a cutoff point. In a review carried out by SEARCH of 2062 RPs, among which 398 (19%) were cT1c-2a, PSA ≤10 ng/mL, Gleason ≤6 with no more than one or 2 positive cylinders in a Bx as a minimum sextant, 8% of them showed a Gleason score of 4 + 3, 28% had a Gleason score of 3 + 4, 16% were pT3a and 2% were pT3b. We deem it important to highlight that less than 7% of our patients had the 3 poor prognosis factors and none had a Gleason score ≥4 + 4 in the specimen (Table 1). Logically, these data depend on the criteria with which AS is contemplated; in an exhaustive revision work of 1070 RPs and of 16 selection criteria for patients candidates for AS, a range between 10.9% and 33.5% of adverse pathology was detected which was dependent on the thoroughness or on the laxness regarding inclusion criteria.

With regard to the analysis of clinical factors which may enable us to predict an insignificant PA in a RP specimen, we ratify the importance of prostate volume and therefore of PSAD and the number of affected cylinders as independent prognostic factors to that end (Table 2); this has made us consider a maximum of 2 positive cylinders and a PSAD <0.2, this latter variable being of importance in those prostate -60 cc where PSA is frequently higher than 10 ng/mL. Both PSAD and the fact of having 2 affected cylinders versus only one cylinder have also been independently associated in many series with progression and the need for active treatment. With regard to the relevance of the number of affected cylinders, this will directly depend on the number of cylinders taken; we currently consider a minimum of 10-12 cylinders in the first Bx and in the confirmation biopsy we took 18 (transrectal) or 24–32 (transperineal), since it has been proven that in RP specimens the percentage of adverse pathology with 2 positive cylinders is approximately half of that if, instead of 12, 21 cylinders would have been taken, so this fact should be taken into account along with the patient due to the consequences it entails (continue with or quit the AS program) if for instance there are 3 cylinders with a Gleason score of 3 + 3 in the confirmation or follow-up Bxs.

With the same intention to select good candidates for AS, it is well known the importance of the pathologist’s sub-specialization in the analysis of prostate Bxs, with a better prognosis for Gleason ≤3 + 3 having been proven when following the recommendations made by the ISUP-2005 when compared to those same pre ISUP-2005 tumors. The results of the AS series with a greater follow-up can only be improved with the best interpretation of the Gleason score recognized from such a consensus, which forces any center to demand its implementation by a uropathologist.

Finally, from the first analysis performed on our patients under AS we are able to inform future patients who follow the statistics from series published in the literature with a greater follow-up, perhaps with some slightly lower percentages of ATFS influenced by including approximately half of the series with induced AS criteria. We have not observed any case of metastatic progression in the true AS group so far and the percentages of biochemical progression in the group of patients who were crossed over to active treatment was similar to that observed when the latter was applied as the first strategy at our center, as observed in series with a follow-up greater than ours.

Conclusions

We believe that the percentage of patients candidates for AS who choose it is going to be increased as urologists and patients are better informed on the potential of the PAs they are confronting. We think that a review of the casuality at every center should be compulsory in order to be able to truthfully inform patients about the profitability of Bx at the center and of whether the infragradation, infrastaging, of insignificant PAs are in line with those in the literature, as a kind of internal audit enabling an AS program with some kind of guarantees. Once these data have been revised, and with standard criteria (PSA ≤10 ng/mL, a PSAD ≤0.2), particularly in voluminous prostates, a maximum number of 2 positive cylinders, a Gleason score of ≤3 + 3 and 3 + 4 in patients over 70 years of age and tumors cT1-2a), an AS protocol can be started with certain guarantees for the patient choosing it. With a mean follow-up of around 3 years, we detected a parallel with the most extensive series on AS, so we think that the AS program can continue to be implemented and can include a growing number of patients.

Funding

This work has been supported by the grants PI061619, PI101206 from the Instituto Carlos III (Madrid, Spain), ACOMP/2009/176 from the Generalitat Valenciana, and by the Aid to Research from Astra Zéneca, Spain.

Authorship

All signatory authors of the article claim that they have complied with the ethical responsibilities required and have actively participated in the completion of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

This work would not have been possible without the technical assistance of the Data Manager of the Department of Urology of the IVO, Vanessa Pérez and the administrative assistance of Amparo Alcina and Martina Alcyade. We thank the Instituto Carlos III de Madrid for their support (PI061619, PI101206) for various studies on prostate cancer which this work has benefited from.

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