Understanding Active Surveillance. A new treatment option for PSA positive low risk prostate cancer

Chris H. Bangma[1], Roderick C. N. van den Bergh[1], Louis Denis[2], Monique J. Roobol[1]

[1]Department of Urology, Erasmus MC Rotterdam, The Netherlands
[2]Oncology Center Antwerp, Belgium

KEY WORDS

active surveillance ◗ prostate cancer ◗ quality of life

ABSTRACT

Active Surveillance (AS) is a treatment option for newly discovered prostate cancer (PCa) that offers the possibility to delay or completely withdraw radical treatment in men with low risk tumors that likely remain silent during follow-up. Deferred active curative therapy can be applied when signs of tumor progression occur.
In this review article the arguments raised on the safety and efficacy of AS against the background of alternative treatment options are discussed. Frequently asked questions from forum discussions and published opinions were clustered into four categories: 1. the criteria for tumor and patient selection, 2. the methods for follow-up and for progression, 3. the observations made on surrogate endpoints, 4. the effects on quality of life (QOL). Information from recent peer reviewed articles on AS and related issues was used for the discussion.
A combination of strict criteria for indolent cancer, including volume dependent numbers of prostate biopsies are used to select candidates for AS. Cut-off values for probability scores on indolence are prospectively being evaluated. Follow-up parameters, based on expert opinion, should include PSA-kinetics and rebiopsy information. While not validated prospectively, these parameters so far missed curable cancers in 1% over 10 years. Surrogate endpoints for AS are multiple and need continuous evaluation. The patient-dependent balance between anxiety and distress being on AS and the benefit of deferring radical treatment is studied prospectively. The debate on active surveillance is ongoing. However in the present era of PCa screening, the question no longer seems to be if it is a justified strategy, but rather how to improve the current protocols. Current data suggests that data Active Surveillance for prostate cancer seems to be a safe initial treatment option for men with a high probability of having indolent disease selected by clinical parameters.

INTRODUCTION

Active Surveillance (AS) is a treatment option for newly discovered prostate cancer (PCa) that is regarded indolent. AS offers initial expectant management with deferred curative treatment for tumors that show signs of progression during follow-up. The standards of selection criteria for AS, as well as the methods for follow-up and the triggers for shifting towards radical treatment are currently non evidence based and are currently being evaluated by various prospective observational studies.

In this article we discuss AS along the arguments that are commonly raised in public and professional discussions. As AS differs from Watchful Waiting, in which patients are not candidates for curative treatment because of severe co-morbidity or high age, this review does not discuss the effects and outcomes of Watchful Waiting.

Indolent cancers

Various definitions for the small, localized, well-differentiated tumors have appeared in literature [1]. We use 'indolent' for those tumors that are defined by the pathological Epstein criteria for insignificant disease upfront, and that therefore are likely to follow a beneficial clinical course and outcome [2]. The Epstein criteria are based on the retrospective histological evaluation of tumors obtained by radical prostatectomy that showed long-term disease-free survival. The term 'Low risk tumors' indicates primarily a favorable (asymptomatic) clinical outcome, and this definition might also include tumors with less strict histological criteria. Though genetic analysis of minute tissue volumes from needle biopsies is feasible, there still is no clinically validated set of genomic (or proteomic) markers for the identification of indolent disease.

We are currently unaware of the exact incidence and relevance of micrometastases at the time of diagnosis linked with indolent tumors. As PSA recurrence after radical prostatectomy of pathological organ confined disease after 20 years is between 25% and 50% [3], the incidence of micrometastases at the time of surgery has to be substantial. Autopsy studies in men with PCa confirm the presence of predominantly asymptomatic bone metastases at death in 25 to 50% [4].

Current AS studies

The number of studies that are observing men with PCa on expectant management with the intention to initiate active therapy on signs of progression is limited [5-10]. Some of these studies analyze (partly) retrospective cohorts of men on AS, without following a consistent protocol. Overall, nearly 20-30 % of men on AS shift towards invasive therapy during the first three years of follow-up (Table 1), and half of those do so based on psychological factors like anxiety, instead of due to objective signs of biological tumor progression [11]. Ongoing studies analyze the role of the psychological profile of the patient as a selection criteria for AS, as well as of the treating physician.

Current public arguments used against AS

The current arguments used to critically review AS can be divided into those dealing with 1. the criteria for patient and tumor selection, 2. the methods and criteria for follow-up and progression, 3. the observations made on surrogate endpoints, and 4. the effects on QOL. Discussions on AS are often illustrated by case re-

Table 1. Surrogate endpoints for AS in relation to current AS-series.

Study, number of participants, mean follow-up time	Survival percentage over follow-up time	Metastases analyzed	Percentage of pT3 in case of radical prostatectomy	Percentage of men with PSADT > 10 years	Conversion to invasive therapy
Klotz 2006 N = 299, 8 years	99.3% PCa specific	2/299% (N+)	58% (14/24)	42%	35%
Parker 2005 N = 80, 3.5 years	100% PCa specific, 94% overall	–	50% (1/2)	45%	20%
Carter 2007 N = 405, 2.8 years (range 0.4 – 12.5)	98% overall	0.5% (2)	20% (10/49)	–	25% after 2.2 years (PSADT no trigger)
Roemeling 2007 N = 278, 3.4 years	100% PCa specific, 90% overall	–	1/13 (8%)	44%	29% after 2.5 years
Soloway 2008 N = 157, 4 years	100% PCa specific	0%	0/2 (0%)	Mean 13.1 years in no treatment group, 3.6 in treatment group	8%

ports supportive of any argument, against a variable cultural and legal context of our societies.

1. the selection of tumors and patients for AS

'...the incidence of indolent tumors is low...'

It is well appreciated by autopsy studies and studies on prostate cancers in radical cystoprostatectomy series that the frequency of histological asymptomatic small and well differentiated tumors is considerable [12] and age dependent. The diagnosis of these low risk cancers, as defined by the pathologic criteria of Epstein, is increasingly made, mainly due to enhanced wild screening for PCa (CapSure database [13]). It has been reported that at the population level, the incidence of overdiagnosed tumors might be as high as 54% in a screening cohort [14], while this is much lower in clinical series (Table 2).

'...Indolent cancers can not be predicted accurately ...'

Various nomograms have been constructed to calculate the probability of the presence of an indolent cancer. These nomograms differ in their outcome, as they are based on different clinical or screening populations [15]. Validation of individual nomograms in relevant independent patient cohorts appears pivotal, and perhaps even more important cut-off values of probability need to be tested in prospective treatment studies.

'...Small tumors may be dangerous...

Some series on radical prostatectomy specimens have reported on incidental small tumors with portions of Gleason 4 or 5 in it. An identical clinical long term outcome was reported in men with small cancers versus those with relevant cancers after radical prostatectomy [16].

'...Prostate biopsies underestimate grade and tumor volume...'

Prostate biopsies underestimate Gleason grading by about 30% especially in large prostates. Repeating the biopsies with saturation biopsies in men on AS increased the Gleason score overall in 38% of patients; a second saturation biopsy once again increased Gleason score in 11% [17]. Upgrading occurs also in one third of men using a limited set of biopsies, but rarely to Gleason 8 or higher [18]. At the same time, in 30% of men no cancer is found in the repeat biopsies. This underlines the value of regular directed biopsies, and this information should be used to optimize current protocols.

The accuracy to assess tumor size was attempted in a prostatectomy simulation model in which the minimal number of biopsies needed to detect a 1 ml tumor with 95% certainty was calculated for any prostate volume, and varied between 12 and 18 [19]. In an autopsy study, the sensitivity of detecting relevant tumors with Gleason >6 was 80% by the well directed (lateralized) 12-core biopsy scheme, and 18-cores (6 extra cores from the central zone) could not improve this [20]. So it appears to be justified to advise a size dependent 12-to-18 core biopsy to determine the size and grade of tumors.

Which age?

'...Younger men have more aggressive cancers...'

Tumors detected between the age of 30 to 40 actually appear less aggressive with respect to 5-year biochemical recurrence [21] and histology, compared to those detected later in life.

'...Younger men have a longer life expectancy, so active surveillance is too risky...'

In men after radical prostatectomy for locally confined disease, more than 50% have recurrent systemic disease after 22 years [3]. The spread of tumor cells into the circulation is presumably an early event in a large proportion of tumors, as PSA positive cells were detected in men undergoing radical prostatectomy circulating systemically, and in 44% in the bone marrow, unrelated to stage, grade, or age [22]. The biological mechanism why these

Table 2. Radical prostatectomy series reporting on the incidence of indolent cancers.

Series	Noguchi J Urol 2001	Kattan J Urol 2003	Huland Eur Urol 2003	Steyerberg J Urol 2007	Catalona J Urol 2006
Number of patients	222	409	1254	247	2196
Origin/setting	clinical	clinical	clinical	screening	screening
Percentage of indolent disease	10	20	6	48	10

Criteria for indolent prostate cancer = PSA<10 ng/ml, tumor volume <0.5 ml, Gleason <7

cells remain dormant and start to regrow later in life is subject to intense studies. The biologic fate of micrometastases rather than the management of the primary tumor may be the pivotal determinant of disease outcome in a large proportion of men.

From the patient perspective, asymptomatic survival is of relevance, with or without the presence of asymptomatic micrometastases and biochemical recurrence. Even when detected later in life, cancers have plenty of time to grow.

'...Delaying surgery gives the tumor time to grow...'

In active surveillance protocols typically patients with slow growing tumors are selected for surveillance, using PSA doubling times of more than 10 years as the surrogate indication for slow biologic growth. The question is which trade off can be made against a higher likelihood of biochemical progression against the benefits of delay. In screen-detected tumors, the effect of delay may be favorable as well because of the long leadtime of more than10 years [14] , however prospective studies with longer follow-up time are missing to draw definite conclusions.

'...By delaying therapy men might become inoperable due to new comorbidity...'

Comorbidity, like cardiovascular and pulmonary conditions, occurs independent of a prostate cancer. Early surgery would not have improved the outcome of these conditions, also when they emerge later in life. The potential initiation or deterioration of comorbid diseases therefore cannot be a valid argument to offer unnecessary surgery early in life. Treatment choices might however change over time.

2. the follow-up of tumors during AS

'...PSA variation and PSADT do not indicate tumor progression in time...'

Changes of PSA level over time, most often expressed as PSA Doubling Time or PSA velocity, have been advocated by various experts as the best available biologic parameter to monitor tumor growth [23]. Due to the biologic variation of PSA, a number of PSA values within a limited timeframe has to be collected to obtain an optimal impression of PSADT. A number of online tools is available for this purpose (www.prias-project.org).

So far, sparsely available clinical experience shows that with PSADT <3 years as a trigger point for deferred invasive treatment for men on AS there is a very small fraction that escapes the window of 'curability' over a time period of 10 years [24]. This number, currently estimated to be 1% (Table 1), is still far smaller than the number of recurrences at radical prostatectomy (10-year 15-20% PSA-recurrence in pT2).

In AS series, about 30-50% of changes towards invasive therapy are made on biopsy information, likely due to correction of a previous sampling error. PSADT might lack this kind of sampling error, but still has to be validated as a monitoring parameter. Evaluations of MRI or ultrasonography as imaging tools for tumor size and monitoring are ongoing.

'...Repeated biopsies are inadequate to show dedifferentiation...'

The primary arguments for repeating biopsies are for correcting initial understaging and for identifying tumor dedifferentiation. The process of dedifferentiation has never been observed adequately in patients. Statistically, dedifferentiation has been illustrated by modelling over time.

3. observations made on (surrogate) endpoints

"...There is no randomized study with survival as an endpoint..."

As the biological course of the tumors selected for AS is generally slow and men have an ever increasing life expectancy, the overall or prostate cancer specific survival endpoints of AS studies are not easily reached. Medical progress on (adjuvant) treatment of PCa may interfere with AS protocols over time. It can be disputed whether an overall or cancer specific endpoint is the most relevant, if at all feasible. Rather, surrogate endpoints like the progression to symptomatic disease, and the quality of life appear to be important. Furthermore the pathologic characteristics of the tumors detected at the time of delayed invasive therapy can be compared to those of tumors treated immediately after diagnosis in historical series. All currently used parameters, like PSA-doubling time, but also novel clinical and biological parameters, like PSA isoforms in serum, or molecular markers in urine, need to be related to these surrogate endpoints.

Table 1 shows a number of potential surrogate endpoints that are discussed along the lines of this article. Comparison between studies is compromised by the variations in inclusion and follow-up regimens.

'...Patients have a 99.8% 5-year survival rate after surgery...'

5-year reports on survival are obsolete in an AS-setting. Realizing that the lead time for screen detected early cancers is about 10 years, that all AS studies also report a favorable short-term survival rate (Table 1), and that the effect on survival of high risk tumors are overshadowed by the abundancy of low risk tumors, the results of the various treatments (including AS) for early detected PCa are best compared with the natural course of the disease [25]. 15 year survival figures are needed in prostate cancer for a meaningful evaluation of any treatment efficacy.

'...AS studies show many pT3 cases on progression that could have been saved earlier by surgery...'

The number of pT3 tumors removed at the time of delayed therapy compared to historical series might illustrate whether AS is acceptable, although subjective to various selection biases. There are many other factors that determine the fate of the patient beyond the stage of the tumor removed, like grade, the surgical margins, the presence of lymphnode metastases, the extension of the node dissection, and comorbidity factors. Furthermore, we are insufficiently aware of the importance of molecular determinants.

The various studies on AS so far have reported variable results based on their inclusion and monitoring schemes, Table 1.

4. QOL

'...Active surveillance causes anxiety...'

85 – 90% of men (and their spouses) appear to feel safe under surveillance, while 10-15% of men turn to invasive therapy for psychological reasons independent of their changes in PSA. It is needed to provide physicians as well as patients with balanced information, and in the future identify those men upfront that are least likely to comply with AS in order to reduce the rate of treatment shift towards invasive therapy [11].

'...I do not have side-effects from my invasive treatment...'

Reviews on the side effects of invasive treatments based on individual series are widely available. In the Prostate Cancer Outcomes Study, a population-based study of 1,291 men who underwent radical prostatectomy, 30% of men reported increased impairment of urinary control after surgery, and at least 20% noted a decline in sexual performance [26].

Over-treatment: please call my lawyer...

A defensive attitude in medicine has dictated that professionals want to eradicate all forms of cancer at any price. The lack of adequate prognostic factors and treatment protocols justified re-

moval of all cancers (including the indolent). With the possibility to determine the pre-treatment probability of indolent cancers, and with protocols for active surveillance, the urologist and radiotherapist will have to justify radical treatment, balancing prevention of potential cancer related symptoms later in life against the immediate and continuous side effects of invasive therapies. Delaying these side effects that may decrease quality of life, and interfere with daily professional and social activities is essential for most patients. Some men might even want to translate this into economical terms.

Professionals have to prevent being blamed for the effects of invasive treatment of minimal lesions. Patients, on the other hand, need to consent for active surveillance, like illustrated on www.prias-project.org. Patient support groups in Europe are very aware of these issues [27].

Conclusion: AS, is it safe?

Retrospective evidence justifies the inclusion of men in current prospective observational studies in various institutions that evaluate and improve the protocols used. AS should do better than the previously reported natural history of cancer with a cancer specific survival for Gleason 6 disease estimated after 20 years of 85-96% [25]. For men on AS it can be concluded that, with only 10 years follow-up, 99% survived their tumor, but up to 1% had metastases. Men need to know that it is still safe to follow AS until signs of tumor progression occur, but that there is a risk of 1% that their tumor is beyond cure at the time when invasive therapy is being indicated by current monitoring modalities.

It is questionable whether in the absence of mature data the balance between those overtreated having indolent disease versus those undertreated by AS having relevant cancers is the optimal argument. The ethical, economical, and political discussion is fed by estimates that 60-70% men with asymptomatic PCa have to be treated invasively to prevent one cancer death [28]. As a randomized trial between treatment options is difficult to perform, a registration trial for AS was started in Europe [www.prias-project.org]. Only the finding of the perfect prognostic tumor marker or a treatment without side effects will render the discussion on AS redundant.

REFERENCES

1. Schroder FH: *Biomarkers and screening for prostate cancer.* Ann Oncol 2006; 17 Suppl 10: 201-206.
2. Epstein JI, Carmichael M, Partin AW, Walsh PC: *Is tumor volume an independent predictor of progression following radical prostatectomy? A multivariate analysis of 185 clinical stage B adenocarcinomas of the prostate with 5 years of followup.* J Urol 1993; 149: 1478-1481.
3. Swanson GP, Riggs MW, Earle JD, Haddock MG: *Long-term follow-up of radical retropubic prostatectomy for prostate cancer.* Eur Urol 2202; 42: 212-216.
4. Abrams HL, Spiro R, Goldstein N: *Metastases in carcinoma; analysis of 1000 autopsied cases.* Cancer 1950; 3: 74-85.
5. Carter HB, Kettermann A, Warlick C et al: *Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience.* J Urol 2007; 178: 2359-2364; discussion 2364-2355.
6. Hardie C, Parker C, Norman et al: *Early outcomes of active surveillance for localized prostate cancer.* BJU Int 2005; 95: 956-960.
7. Dall'era M.A., Konety, B.R., Cowan, J.E., Shinohara, K., Stauf, F., Cooperberg, M.R., Meng, MV, Kane CJ, Perez N et al: *Active surveillance for the management of prostate cancer in a contemporary cohort.* Cancer 2008; 112: 2664-2670.
8. van den Bergh RC, Roemeling S, Roobol MJ et al: *Prospective validation of active surveillance in prostate cancer: the PRIAS study.* Eur Urol 2007; 52: 1560-1563.
9. oloway MS, Soloway CT, Williams S et al: *Active surveillance; a reasonable management alternative for patients with prostate cancer: the Miami experience.* BJU Int 2008; 101: 165-169.
10. Klotz L: *Active surveillance with selective delayed intervention for favorable risk prostate cancer.* Urol Oncol 2006; 24; 46-50.
11. Latini DM, Hart SL, Knight SJ et al: *The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance.* J Urol 2007; 178: 826-831; discussion 831-822.
12. Gosselaar C, Roobol MJ, Roemeling S et al: *The value of an additional hypoechoic lesion-directed biopsy core for detecting prostate cancer.* BJU Int 2008; 101: 685-690.
13. Miller DC, Gruber SB, Hollenbeck et al: *Incidence of initial local therapy among men with lower-risk prostate cancer in the United States.* J Natl Cancer Inst 2006; 98: 1134-1141.
14. Draisma G, Boer R, Otto SJ et al: *Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer.* J Natl Cancer Inst 2003; 95: 868-878.
15. Schroder F, Kattan MW: *The Comparability of Models for Predicting the Risk of a Positive Prostate Biopsy with Prostate-Specific Antigen Alone: A Systematic Review.* Eur Urol 2008; 54: 274-290.
16. Sengupta S, Blute ML, Bagniewski SM et al: *After radical retropubic prostatectomy 'insignificant' prostate cancer has a risk of progression similar to low-risk 'significant' cancer.* BJU Int 2008; 101: 170-174.
17. Abouassaly R, Lane BR, Jones JS et al: *Staging saturation biopsy in patients with prostate cancer on active surveillance protocol.* Urology 2008; 71: 573-577.
18. Choo R, Danjoux C, Morton G et al: *How much does Gleason grade of follow-up biopsy differ from that of initial biopsy in untreated, Gleason score 4-7, clinically localized prostate cancer?* Prostate 2007; 67: 1614-1620.
19. Vashi AR, Wojno KJ, Gillespie B, Oesterling JE: *A model for the number of cores per prostate biopsy based on patient age and prostate gland volume.* J Urol 1998; 159: 920-924.
20. Haas GP, Delongchamps NB, Jones RF et al: *Needle biopsies on autopsy prostates: sensitivity of cancer detection based on true prevalence.* J Natl Cancer Inst 2007; 99: 1484-1489.
21. Loeb S, Hernandez DJ, Mangold LA et al: *Progression after radical prostatectomy for men in their thirties compared to older men.* BJU Int 2008, 101, 1503-1506.
22. Gao CL, Dean RC, Pinto A et al: *Detection of circulating prostate specific antigen expressing prostatic cells in the bone marrow of radical prostatectomy patients by sensitive reverse transcriptase polymerase chain reaction.* J Urol 1999; 161: 1070-1076.
23. Arlen PM, Bianco F, Dahut WL et al: *Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time.* J Urol 2008; 179: 2181-2185; discussion 2185-2186.
24. Klotz L: *Point: active surveillance for favorable risk prostate cancer.* J Natl Compr Canc Netw 2007; 5: 693-698.
25. Albertsen PC, Hanley JA, Fine J: *20-year outcomes following conservative management of clinically localized prostate cancer.* Jama 2005; 293, 2095-2101.
26. Stanford JL, Feng Z, Hamilton AS et al: *Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study.* Jama 2000; 283: 354-360.
27. Hudson T, Denis LJ: *Europa Uomo: the European Prostate Cancer Coalition.* Recent Results Cancer Res 2007; 175: 267-271.
28. Klotz L: *Active surveillance versus radical treatment for favorable-risk localized prostate cancer.* Curr Treat Options Oncol 2006, 7: 355-362.

Correspondence

Chris H. Bangma
PO Box 2040
3000 CA Rotterdam, The Netherlands
phone: +31 10 704 36 07
c.h.bangma@erasmusmc.nl