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# Active surveillance criteria for prostate cancer amongst Dutch urologists

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**Abstract:** Introduction: This survey amongst Dutch urologists aimed to investigate their criteria before enrolling patients to active surveillance (AS) and managing follow-up. Materials and Methods: An online survey was distributed to 421 Dutch urologists. Demographics, enrollment criteria, intervention criteria and the role of magnetic resonance imaging (MRI) in AS were questioned. Results: 15% responded and completed the survey. A major 98% see AS as an alternative treatment for low-risk prostate cancer (PCa). 79% felt that patients with a PSA  $\leq 10$  ng/ml were eligible for AS and 74% felt that patients required a Gleason score  $\leq 6$  for admitting to AS. There was agreement on the timing of second biopsies but, not for subsequent biopsies. 58% see a role for MRI in AS. Conclusions: Dutch urologists are accepting AS. They were in agreement regarding enrollment criteria, the best time for second biopsy, but there was no agreement on the timing of follow-up biopsies.

**Keywords:** Active Surveillance, Survey, Watchful Waiting, Prostate Cancer

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## 1. Introduction

In the Netherlands, the use of PSA screening is widespread. This has led to a rise in the detection of low-risk prostate cancers (PCa). Treatment of PCa may induce morbidity and this is not always acceptable since low-grade prostate cancers may be insignificant to patient survival and morbidity [1].

Active surveillance (AS) is nowadays worldwide accepted as a valid option for postponing potential morbidity of treatment for all patients suitable for radical treatment whilst containing a curative setting.

This survey, sent to all "Nederlandse Vereniging voor Urologie" (NVU) members, aimed to survey knowledge, acceptance and criteria on active surveillance criteria for low-risk prostate cancer amongst Dutch urologists.

Guidelines from the European Association of Urology (EAU) [2] propose AS as an option for men with low-risk PCa, however there are no uniform criteria for patient selection, no criteria for triggers for delayed treatment and no criteria for follow-up of these patients in published data. There is also no data available comparing varying AS protocols.

## 2. Materials and Methods

We distributed an email-based survey, anonymously, to 421 practicing urologists in the NVU membership directory of practicing urologists. This happened only after approval of the NVU institutional board. The email circulated only once. And urologists in training were not addressed.

Demographics of respondents were queried and respondents were surveyed with the Gorin et al. Questionnaire [3], for their knowledge, acceptance and personal criteria of AS. Only practicing urologists were included and they were asked if they completed training. Also their specialty of training was surveyed, the years served in practice, the context of their practice (university, community or mixed), the percentage of their practice dedicated to patient care and the percentage of practice dedicated to the care of PCa patients.

Only urologists who Completed fellowship training could complete the survey.

The urologists who felt AS was a reasonable strategy in the management of their patients with low-grade PCa, before primary treatment, were queried on the criteria for AS enrollment (patient age, Gleason score on biopsy, PSA level, core volume in positive biopsy) and the details of their

management of AS (time to second biopsy, triggers for early second biopsy or treatment).

Those urologists who felt AS was not an alternative were queried as to the reasons why. Respondents were also asked if they see a role for magnetic resonance imaging (MRI) in following patients under AS. The survey was designed and distributed using FluidSurveys.com.

### 3. Result

Of the 421 urologists who were invited to participate, 64 (15%) responded and completed the survey. This is 6% more responding urologists than Gorin *et al.* [3] received.

Median post training years of the responding urologists was 12 (range 1–30). Table 1 lists the demographics of the responders. Most urologists had a community-based practice (81%) dedicated to patient care. All of the respondents were familiar with AS and 59 (92%) acknowledge a meaningful difference between AS and Watchful Waiting (WAWA).

*Table 1. Demographics of studied respondents:*

Parameter	n=64 (%)
Type of practice:	
University-based	8 (13)
Community-based	52 (81)
Mixed	4 (6)
Specialty of fellowship training:	
Oncology	28 (44)
Endo-urology/MIS/robotics	27 (43)
Infertility/sexual medicine/andrology	5 (8)
Female urology/neuro-urology	12 (18)
Transplant	0 (0)
Reconstruction	5 (8)
Research	3 (5)
Paediatrics	2 (3)
Other	8 (13)
Percentage of time dedicated to patient care:	
<10	2 (3)
10–25	0 (0)
26–50	2 (3)
51–75	6 (9)
>75	54 (84)
Percentage of practice dedicated to PCa patients:	
<10	4 (6)
10–25	35 (55)
26–50	23 (36)
51–75	0 (0)
>75	2 (3)

Of those who acknowledge a meaningful difference, 58 responders or a vast majority of 98% see AS as an alternative for treating low-risk PCa. Only one participant (2%) did not see AS as a reasonable alternative. He gave “fear for missing an opportunity to cure” and “fear for legal liability” as the reasons why he would never enroll a patient for AS.

34 respondents (58%), see a role for MRI in following patients in an AS protocol.

Most respondents (79%) felt that patients with a PSA  $\leq 10$  ng/ml were eligible for AS and 74% of respondents felt that patients required a Gleason score no higher than 6 for admitting to AS follow up. Criteria for patient enrollment in AS, felt reasonable by the respondents, are to be found in

table 2. There was great agreement on the timing of second biopsies (88% at twelve months) but, strikingly, not for subsequent biopsies. Repeat biopsy and intervention criteria of respondents are listed in table 3. Urologists most commonly (100%) felt that a rise in PSA should trigger an earlier than scheduled biopsy.

*Table 2. Criteria felt reasonable for patient enrollment in AS:*

Variable	n=58 (%)
Age no less than:	
No minimum	36 (62)
40–50	5 (9)
55–65	13(22)
<b>Variable</b>	<b>n=58 (%)</b>
PSA no greater than:	
2–9	7 (12)
10	39 (67)
11–15	9 (16)
<b>Variable</b>	<b>n=58 (%)</b>
Maximum number of core biopsies for prostate cancer:	
1	3 (5)
2	44 (76)
3	9 (16)
4	1 (2)
5	0 (0)
<b>Variable</b>	<b>n=58 (%)</b>
Gleason sum no higher than:	
3+3=6	43 (74)
3+4=7	14 (25)
4+3=7	1 (2)
<b>Variable</b>	<b>n=58 (%)</b>
% of core biopsy invaded by tumour no greater than:	
5–15	34 (59)
20–30	14 (24)
35–50	4 (7)
>50	6 (10)

*Table 3. Repeat biopsy and intervention criteria of respondents:*

Variable	n=58 (%)
Number of months before second biopsy:	
1–3	0 (0)
6–9	5 (9)
12	51 (88)
15–36	2 (3)
Number of months between subsequent scheduled biopsies:	
6–9	1 (2)
12	17 (29)
15–18	2 (3)
24	16 (28)
36	22 (38)
Triggers for an earlier than scheduled biopsy:	
Rise in PSA	58 (100)
Change in clinical exam	39 (67)
Patient wishes	33 (57)
Change on imaging (US or MRI)	19 (33)
New symptoms	16 (28)
Triggers for treatment:	
Increase in tumour grade	58 (100)
Patient wishes	55 (95)
Rise in PSA	54 (93)
Increase in tumour volume	44 (76)
Change in clinical exam	41 (71)
Change on imaging (US or MRI)	29 (50)
New symptoms	19 (33)
Age related	4 (7)

## 4. Discussion

All of the respondents were familiar with AS, but of course, when not knowing of AS, one is not likely to respond to an email survey concerning AS, so the population may be biased. 92% of respondents acknowledge a meaningful difference with (WAWA).

The difference between AS and WAWA is clearly described in the last updates of current guidelines [2].

Most urologists incorporate low PSA values ( $\leq 10$ ) and maximum number of core biopsies of two in their acceptance of patients for AS. Although some like R.C. van den Bergh et al. describe results of surveying a series of men with Gleason 7 (3+4) tumours [4], most limit AS for men with Gleason 6 or better differentiated tumours. Monitoring of PSA for men on AS is based on the correlation between high PSA velocity in the year before diagnosis and PCa mortality after treatment with radical prostatectomy or external beam radiotherapy [5, 6].

Most series describe PSA testing every 3 months. There was great agreement on the timing of second biopsies (88% at twelve months) but, strikingly, not for subsequent biopsies. In the query of Gorin et al. there wasn't even agreement on timing of the second biopsies. In the Netherlands, the PRIAS-project is generally known amongst Dutch urologists and advises second biopsies at twelve months [7]. Subsequent biopsies are planned after 48 months according to the PRIAS-Protocol. We cannot reproduce the application of this advice by urologists from our gathered data. Having no histological feedback from the patients tumour for 36 months seems to be uncomfortable for the clinician.

As described in literature, increase in tumour grade and PSA for the clinician, anxiety over the uncertainty of the future for the patient or fear of losing the opportunity for a cure are for patient and clinician important triggers for initializing treatment [8].

Despite the fact that entry criteria differ between studies, the disease-specific and all-cause survival over the short term is high for men in AS [9].

34 respondents (58%), see a role for MRI in following patients in an AS protocol. Imaging as a potential screening tool for AS candidates would greatly reduce the burden of prostate biopsies for the patient under AS or could be an extra factor in determining the risk of the PCa before admitting a patient to AS. Most of the patients with low-risk PCa have no abnormalities on ultrasound (US), and serial trans rectal US does not prove to be beneficial for tumour characterization or monitoring for disease progression [10]. When trying to predict high-risk PCa features at the time of radical prostatectomy, for men with presumed low-risk PCa on MRI, there was no independent predictive value found, leaving the role of MRI for AS unclear [11].

Prostate imaging will likely become more important and will have a greater role for selecting and monitoring men with PCa for AS.

## 5. Conclusions

Dutch, practicing urologists are knowledgeable of AS and are accepting AS as an option before treating low-grade PCa.

They were in relative agreement regarding low PSA  $\leq 10$  ng/ml and Gleason score no higher than 6, for enrollment of men in AS. The best time for second biopsy was preferred at 12 months.

However, there was a lack of agreement on the timing of follow-up biopsies. Dutch urologist seem to be following the PRIAS-protocol [7] when referring to criteria for follow-up.

Future studies regarding AS should determine the role of imaging before admitting patients to AS and in the follow up regiment. Also the optimal enrollment criteria and follow-up protocol should be unanimously determined in guidelines since particularly the long term follow-up protocol seems to be a matter of debate.

In general more work is needed to identify triggers who can tip the balance between recommending treatment for patients at high risk for progression and minimizing treatment for those at low risk for progression. In the future, epigenetic testing could become more important in determining the risk of the tumour characteristics in patients with PCa.

## Abbreviations

AS: active surveillance, Pca: Prostate Cancer, MRI: magnetic resonance imaging, NVU: Nederlandse Vereniging voor Urologie, WAWA: watchful waiting, US: ultrasound

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