Prostate cancer Research International:

Active Surveillance

(PRIAS)

Guideline and study for the expectant management of localized prostate cancer with curative intent

Study protocol

Version 6.0

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Index

Abstract

Introduction

This protocol aims to provide an evidence-based guideline for the management of prostate cancer by Active Surveillance. This page holds its definition, several goals, and the hypothesis, which will be tested in this study, as well as the endpoints and the study design. The following two pages show the inclusion and exclusion criteria, the follow-up criteria and the biopsy protocol. The pages thereafter give the evidence on which these criteria are based.

Definition

Active Surveillance manages selected men with prostate cancer expectantly with curative intent. This means men are carefully selected and subsequently actively observed in order to have the possibility to offer them curative treatment if/when tumor reclassification or progression is detected. Therewith, Active Surveillance fundamentally differs from watchful waiting. Watchful waiting is a rather confusing term due to the various intents of its participants. Not only men who can be managed with Active Surveillance can be watchful waiters, but those managed with palliative intent as well; for example because they are too sick or too old for curative treatment. Active Surveillance aims to reduce the overtreatment of tumors that are very unlikely to cause symptoms if left untreated.

Study goals

The goal of this study is to validate the treatment option Active Surveillance in men with localized, well differentiated prostate cancer, in order to limit the amount of overtreatment (i.e. treatments in men who are diagnosed with prostate cancer and would not have developed symptoms in the absence of screening). A number of subjects will be studied, such as PSA velocity (i.e. the absolute increase of PSA in a one-year time period), the pathological findings in radical prostatectomy specimens, and the effect of expectancy on the quality of life.

Update January 2020

Above the original goal of the study is described. Anno 2019 Active Surveillance is incorporated into many national and international guidelines as an equal treatment option for men with low-risk prostate cancer next to radical prostatectomy and radiotherapy. Therefore, the goal of this study shifts from validating Active Surveillance as a realistic treatment option to refinement of the inclusion and exclusion criteria of Active Surveillance and improving the follow-up schedule.

Hypothesis

Less than 5% of men managed by Active Surveillance will develop clinical progression (evidenced by a positive bone-scan) during their lifetimes.

Update January 2020

Evidence from the PRIAS study, amongst others, has shown that Active Surveillance can prevent unnecessary definite treatment in men diagnosed with low-grade prostate cancer. At the same time

the PRIAS protocol provides a safe method to detect tumor progression before losing the window of curability. PRIAS will provide evidence to further improve both the inclusion and exclusion criteria of Active Surveillance as well as the follow-up schedule.

Endpoint

The primary endpoint of this study is clinical progression, evidenced by metastasis (M1) on a bone scan. Secondary endpoints will be the number of men changing therapy, the behavior of PSA over time and the prostate cancer mortality.

Update January 2020

The primary endpoint of this is study is metastatic free survival, evidenced by imaging. The initiation of non-curatively intended systematic treatments is considered to be metastatic disease even without radiological confirmation. We want, therefore, to emphazise the importance to continue data collection even after discontinuation of active surveillance.

Secondary outcomes are prostate cancer specific survival, reclassification and discontinuation of active surveillance. End of study for participants is defined as lost to follow-up or death of any reason.

Design

This is a prospective, observational study. Fixed criteria are used for inclusion and follow-up.

I. Criteria for inclusion:

1) Histologically proven adenocarcinoma of the prostate.
2) Men should be fit for curative treatment.
3) PSA level at diagnosis ≤ 10 ng/mL, or ≤ 20 ng/mL if MRI is used at diagnosis or during follow up.
4) PSA density (PSA D) less than 0.2, or if MRI is used and negative or if targeted biopsies show no more than Gleason score 3+3 or 3+4 without invasive cribriform and intraductal carcinoma (CR/IDC) PSA D of less than 0.25 is acceptable. Patients with a PSA D ≥ 0.25 at inclusion can be followed outside the actual PRIAS protocol.
5) Clinical stage T1C or T2.
6) Gleason score 3+3=6 or Gleason score 3+4 without invasive CR/IDC. Total number of positive cores allowed:
    a. If an MRI, including targeted biopsies on positive lesions, is done at inclusion, there is no limit in the number of positive cores (that is, more than two, and no limit in the % of cancer present in the cores).
    b. If saturation biopsies (either transperineal or transrectal) are done 15% of the cores can be positive with a maximum of 4. (i.e. <20 cores 2 cores can be positive (standard), 20-26 cores 3 cores can be positive, >26 cores 4 cores can be positive) (all other inclusion criteria still apply).

   c. If more than 2 TRUS-guided biopsy cores are positive (Gleason score 3+3 or 3+4 without CR/IDC) an MRI is indicated. If the MRI is negative or if targeted biopsies show no more than Gleason score 3+3=6 or 3+4=7 without invasive CR/IDC, inclusion is possible.
   d. For patients with adenocarcinoma Gleason score 3+4 without invasive CR/IDC, the maximum number of positive cores should be ≤ 50%, where multiple positive cores from the same lesion on MRI count for one positive core.
7) Participants must be willing to attend the follow-up visits.
8) Signed informed consent.

II. Exclusion-criteria:

1) Men who can not or do not want to be radiated or operated.
2) A former therapy for prostate cancer.
3) For patients with a life expectancy of <10yr, watchful waiting is preferred above Active Surveillance.

III. Follow-up criteria for continuation of Active Surveillance:

1) Clinical:
   a. Clinical stage (cT) < 3
2) Histological:
   a. Gleason score 3+3=6 or Gleason score 3+4=7 without invasive CR/IDC.
   b. The allowed number of positive biopsies remains the same as at time of inclusion.
3) Biochemical:
   a. If the PSA-DT is <10 years a yearly mpMRI is advised in the years no standard repeat biopsy is recommended. Extra targeted biopsies are only taken if the mpMRI shows progression (progression is defined as a higher overall PIRADS score of one or more lesions, more/new lesions with PIRADS ≥ 3 and/or growth of lesions as assessed by the radiologist. Only leasions that showed progression are biopsied with approximately 2 biopsies per lesion. If no prior MRI is available to assess progression, targeted biopsies are taken from a maximum of 3 lesions with a PIRADS score ≥ 3).
   b. If the PSA-DT is <10 years and MRI is not available, it is advised the repeat the systematic biopsies yearly.
4) Patient is content with active surveillance.

Update January 2020

IV. Measurement of quality of life

An important outcome of active surveillance is the quality of life (QoL). As long-term QoL data is still scarce, this remains an important topic. We would like to introduce the EPIC-26 questionnaire into the protocol. Important moments to obtain EPIC-26 from patients are; before inclusion (or if not possible right after inclusion), six months after inclusion and every year thereafter.

V. Biopsy guideline for inclusion and repeat biopsy

Table 1 shows the recommended minimal number of systematic biopsies according to prostate volume. If the number of obtained biopsy cores is lower than the number stated in the table it is advised, but not obligatory, to perform a repeat biopsy within 8 weeks after inclusion in this study.

Table 1 – recommended minimal number of systematic biopsies according to prostate volume

Prostatic volume (cc)	Minimal number of systematic biopsies
0-40	8
40-60	10
> 60	12

Update January 2020

If the number of obtained biopsy cores is lower than the number stated in the table it is advised, but not obligatory, to perform an MRI after 3 months with possible targeted biopsies. If only targeted biopsies are performed during inclusion, it is advised, but not obligatory to perform systematic biopsies within eight weeks after inclusion of the study. It is strongly recommended to obtain systematic biopsies during the first year of active surveillance, possible together with targeted biopsies on month 12.

VI. Time table

The different follow-up schedule, i.e. time tables are given in Table 2, 3 and 4.

Table 2 – If MRI is available and not used at inclusion

Year	*1*					*2*				*3*		*4*		*5*		*6*		*7*	
Month	*0****	*3*	*6*	*9*	*12*	*15*	*18*	*21*	*24*	*30*	*36*	*42*	*48*	*54*	*60*	*66*	*72*	*78*	*84*
PSA-test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DRE	✓		✓		✓				✓		✓		✓		✓		✓		✓
Standard Biopsy*	✓				✓								✓						✓
Evaluation	✓	✓	✓		✓				✓		✓		✓		✓		✓		✓
MRI + targeted biopsies**		✓			✓				✓				✓		✓		✓		✓

** MRI 3 months after diagnosis: only targeted biopsies if lesion is visible on MRI (maximum of 3 lesions (2 biopsies per lesion)), no standard TRUS guided biopsies.*

*** If PSA-doubling time <10 years: An MRI is recommended every year (only in the years no standard biopsy is taken). Additional biopsies are indicated if MRI shows progression.*

**** Time of diagnosis*

Table 3 – if MRI is available and used at inclusion

Year	*1*					*2*				*3*		*4*		*5*		*6*		*7*	
Month	*0***	*3*	*6*	*9*	*12*	*15*	*18*	*21*	*24*	*30*	*36*	*42*	*48*	*54*	*60*	*66*	*72*	*78*	*84*
PSA-test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DRE	✓		✓		✓				✓		✓		✓		✓		✓		✓
Standard Biopsy*	✓				✓								✓						✓
Evaluation	✓		✓		✓				✓		✓		✓		✓		✓		✓
MRI + targeted biopsies*	✓				✓								✓						✓
Evaluation	✓				✓				✓		✓		✓		✓		✓		✓

** If PSA-doubling time <10 years: An MRI is recommended every year (only in the years no standard biopsy is taken). Additional biopsies are indicated if MRI shows PIRADS progression, more lesions or growth of currently known lesion(s).*

*** Time of diagnosis*

Table 4 – If MRI is not available

Year	*1*					*2*				*3*		*4*		*5*		*6*		*7*	
Month	*0***	*3*	*6*	*9*	*12*	*15*	*18*	*21*	*24*	*30*	*36*	*42*	*48*	*54*	*60*	*66*	*72*	*78*	*84*
PSA-test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DRE	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Biopsy*	✓				✓								✓						✓
Evaluation	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓

* Repeat biopsy:

a) Standard after 1, 4, 7 en 10 year and subsequently every 5 years.

b) If PSA–DT is 0-10 years repeat biopsy every year is advised.

No more than 1 biopsy per year should be performed

** Time of diagnosis

Introduction/Rationale

The increasing use of PSA as a screen test, the increasing number of biopsies, the increasing number of cores per biopsy and the increasing life expectancy has resulted in a more frequent diagnosis of prostate cancers, which are of lower grade and stage.[1-3] The majority of these (screen-detected) prostate cancers have a good long-term survival, especially when only a small number of cores with well-differentiated prostate cancer is diagnosed.[4, 5] Screening diagnoses prostate cancers which would not have been diagnosed in the absence of screening (i.e. overdiagnosis).[6] The amount of overdiagnosis is subject to discussion; a proportion of 53% was calculated by a computer model, using data from the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC).[1] In this study, men aged 55-75 are screened with a PSA threshold of 3.0 ng/mL (4.0 ng/mL before 1997). In essence, two types of curative treatment are, besides new minimally invasive treatments such as brachytherapy, HIFU and cryotherapy, available for men with localized prostate cancer, namely radical prostatectomy and radiotherapy. The therapy of choice is not only dependent on demographic and pathological aspects, such as PSA-level at diagnosis, biopsy Gleason score, clinical stage, age and comorbidity, but is also dependent on the preference of the patient. The goal of both treatments is to delete all vital tumor tissue. Unfortunately, both treatments can have toxic side-effects, which occur rather frequently and can be invalidating for the patient.[7, 8]

The combination of these side-effects, the slow natural course of minimal prostate cancer, the frequent overdiagnosis, ethical aspects and costs have led to the understanding that it is essential to find out which men can be managed with Active Surveillance with possible deferred treatment and whom need immediate definitive treatment in order to prevent transition of overdiagnosis into overtreatment. The expectation is that a large number of men will not need any treatment; they will die of other causes. The strategy has failed if metastases developed despite stringent control and no curative treatment can be applied. The strategy can also be regarded as a failure if waiting with treatment leads to a dramatic decrease in the quality of life. However, the application of deferred curative treatment should not be regarded as a strategy failure.

Update January 2020

Active Surveillance is nowadays an accepted treatment strategyfor low-risk prostate cancer and according to the international guidelines the preferred treatment strategy for men diagnosed with low-risk prostate cancer. [9], [10]

The biopsy protocol

The TRUS systematic biopsy approach

Prostate cancer is generally diagnosed by an ultrasound (TRUS) guided prostatic biopsy.[9] The current literature has not reached agreement about the optimal number of cores which should be taken. Therefore, the pros and cons of the different biopsy-protocols are discussed. The majority of the recent publications on this subject indicate that a higher number of cores per biopsy results in better cancer detection.[11-15] There is just one study which was not able to show a significant difference in cancer detection between 6 and 12 core biopsies.[16] With a sextant biopsy, Presti et al. found a detection rate of 73% in men who had a previously negative biopsy.[15] The lateralized sextant biopsy is widely used nowadays.[11] The detection rate increases to 85% with this technique. A further increase in detection rate to 95% can be achieved by taking an additional core midlobarly. Adding two extra cores to the octant biopsy does not result in a significant increase in detection rate. Chon et al. therefore recommend an octant biopsy.[17]

The size of the prostate also influences the probability of finding a tumor. Vashi et al. have constructed a mathematical model to calculate the amount of cores needed to diagnose a tumor of certain size with 90% certainty (Table 5).[14] For example: to diagnose a tumor with a volume of 1cc in a prostate of 20 grams with a probability of 90%, a sextant biopsy would be sufficient, while 15 cores are needed to diagnose the same tumor in a prostate of 50 grams.

Table 5 – Number op biopsies needed according to tumor volume and prostate volume

Prostate Size (cc)	Tumor Vol. (cc)									
	0.1	0.3	0.5	0.75	1	1.5	2.0	3.0	5.0	8
10	10	6	5	4	3	3	2	2		
20	20	12	9	7	6	5	4	3	2	2
30		18	14	11	9	7	6	5	3	2
40			18	14	12	9	8	6	4	3
50				17	15	11	9	7	5	4
60					17	13	11	9	6	4
80						18	15	11	8	6

With the increase of the size of the prostate, the detection rate of both the standard and the lateralized sextant biopsy decreases significantly. A paper shows the additional value of 10 over 8 cores per biopsy in prostates larger than 35 grams.[18]

Biopsy protocol Active Surveillance study

Mainly based on the literature, but partly based on arbitrary decisions as well, we have chosen the prostate size dependent protocol shown in Table 1.

Repeat biopsy

A repeat biopsy is not advised if the number of obtained cores already matches the number of corresponding cores in the table. If not, it is advised, but not obligatory to perform a repeat biopsy within 8 weeks after diagnosis to obtain adequate sampling and thereby to prevent missing an aggressive Gleason pattern or a larger than expected tumor volume. If a higher Gleason pattern is found, this is likely not due to progression of disease, but more probable due to a sampling error in the first biopsy.[19]

Update January 2020

The MRI-targeted biopsy approach

An MRI can be used to identify areas (regions of interest) in the prostate suspected to harbor clinically significant PCa. Targeted biopsies can be used to sample these areas. There are three methods to perform targeted biopsies: (1) Cognitive targeted biopsies are performed when the practitioner views the regions of interest on the MRI and then estimates where the biopsy should be taken. (2) Fusion software targeted biopsies are performed when through specialized software the MRI images are fused with the ultrasound images to determine where the region of interest is. (3) In-bore MRI-guided biopsies are performed when an MRI is performed simultaneously with biopsy to determine the right location of the biopsy. The Future trial showed no difference between these 3 approaches.[20]
If the MRI is positive e.g. a region of interest is identified, a minimum of 2 biopsies should be taken to obtain an adequate sampling of the area. If an MRI is available, it is preferred to perform an MRI with targeted biopsies if indicated instead of repeat biopsy alone.

Criteria for inclusion

Selection on the basis of survival

The definition of Active Surveillance implies that included men should be able to receive curative treatment at any time during their disease. This implies that men should have an organ confined (clinical stage T1C or T2) prostate cancer at the time of inclusion. The Albertsen tables (addendum) give an idea of the survival of men with organ confined prostate cancer who were managed conservatively.[21] The 20-year prostate cancer specific mortality for men with a Gleason score smaller than 6 varies from 4% to 15%, according to age at diagnosis. Although this proportion is 20% to 30% in men with a Gleason score 6 tumor, in men with Gleason score 7 disease already 40-75% decease as a result of prostate cancer. Moreover are these men less likely to die from other causes. The population that Albertsen et al. described was diagnosed before PSA was introduced. Therefore, 60% of men were diagnosed by transurethral resection of the prostate (TURP). As mentioned before, screening diagnoses prostate cancers earlier in their course, thus at younger age, and as a result the survival of men is likely to be longer.[1-3]

The Partin tables give an estimation of the findings of the pathological specimen, based on the preoperative PSA-level and the biopsy Gleason score.[22] Although it doesn't give survival rates, men who are operated on and have a pathologically organ confined tumor with negative margins have a favorable survival chance.[23, 24] According to the Partin tables, the probability of having an organ confined tumor is much higher in men with biopsy Gleason score 3+3 than in those with a primary or secondary pattern 4 in the biopsy. Besides Gleason score, other predictors for organ confined disease are PSA level and clinical stage. The inclusion criteria for clinical stage and Gleason score we have chosen are mainly based on these data.

Update January 2020

Due to multiple prospective Active Surveillance cohorts, we now know that patients on Active Surveillance for low-risk prostate cancer have excellent long-term outcomes. Klotz et al[25] reported a cancer-specific survival of 98.5% at a median follow-up time from biopsy of 6.4 years. 2.8% of patients developed metastatic disease. In this cohort patients with low-risk and intermediate-risk prostate cancer were included. Bokhorst et al[26] reported long-term outcomes from this study. Only low-risk prostate cancer patients were initialy included. Prostate-cancer mortality was less than 1% at 10 years of follow-up. These excellent outcomes made Active Surveillance a preferred treatment modality for patients with low-risk prostate cancer. Therefore Active Surveillance is incorporated in national and international guidelines, next to radical prostatectomy and radiotherapy. [9, 26, 27]

Biopsy Gleason score

The Gleason score is based on the two most prevalent architectural patterns of malignant prostatic tissue.[28] The Gleason patterns range from 1 to 5, being 5 the least differentiated pattern. Nowadays, most men diagnosed within the ERSPC have a Gleason score 3+3=6. A Gleason score of 4+3=7 is

essentially different from 3+4=7, and has a different prognosis as well. It is therefore more informative to give both patterns, than just providing the sum of those (i.e. the Gleason-score).

Update January 2020

During the 2014 International Society of Urological Pathology (ISUP) concensus meeting, the grading of prostate cancer was updated. It was recognized that there were some deficiencies with the Gleason score. A new grading system was discussed called Grade Groups. This classification should be used in conjunction with the Gleason system. The new Grade Groups are displayed in Table 6.

Table 6 – Grade Group and equivalent Gleason score

Grade Group	Gleason score
1	≤6
2	3+4=7
3	4+3=7
4	4+4=8, 3+5=8 and 5+3=8
5	9-10

Invasive cribriform and intraductal carcinoma are associated with adverse clinical outcome. Therefore, the presence of the secondary growth patterns is an exclusion criteria for Active Surveillance.[29]

Biopsy results

With the assumption that the invasion of tumor in the biopsy cores is a reflection of the total tumor volume in the prostate, a prediction of the tumor volume in the prostate can be made. Not only the proportion of cancer invasion in the biopsies, but also the number of cores invaded with prostate cancer can be of help in the decision which treatment should be applied.[30-33] The criteria of Epstein et al. use the proportion of prostate cancer in the biopsy as well; they postulated that men with a Gleason score ≤ 6, with two biopsies positive for prostate cancer with less than 50% invasion have a high probability (79%) to have a minimal focus of prostate cancer (≤ 0.5 mL).[34, 35] Therefore, every core of a biopsy should be handled and judged separately by the pathologist.

PSA density (PSA D)

The PSA D can easily be calculated by dividing the PSA level by the total volume of the prostate. A prostate larger than 40 cc. with a PSA level of 4.0 ng/mL has a PSA D of 4.0/40=0.10. A PSA D < 0.15 is correlated with a favorable biochemical progression free survival after radical prostatectomy. The mean PSA D of 120 watchful waiters, who were screen detected in the ERSPC with a PSA at diagnosis of < 10 ng/mL was 0.11 ng/mL/cc. (mean follow-up: 40 months, range 13-100). [36] The PSA D is dependent on the way of measuring the prostatic volume. The most reliable way to do this is a planimetric volume measurement. Research from Rotterdam has shown that the interobserver variability of these measurements is only 13%.[37] If planimetric volume measurement is not available, the volume can be calculated with the formula: volume = width * height * length * 0,52.[37]

Update January 2020

Life expectancy

The average life expectancy of men with an age over 60 is 19.0 years worldwide. The average life expectance at birth and at age 60 around the world is displayed in Table 7.

Table 7 – life expentancy around the world.

WHO region	Life expectancy at birth	Life expectancy at age 60
Africa	59.6	15.9
Americas	73.8	21.1
South-East Asia	67.9	17.2
Europe	74.2	20.2
Eastern Mediterranean	67.7	17.5
Western Pacific	75.0	19.5
Global	69.8	19.0

In summary

Inclusion criteria for the Active Surveillance study

1) Histologically proven adenocarcinoma of the prostate.
2) Men should be fit for curative treatment.
3) PSA level at diagnosis ≤ 10 ng/mL, or ≤ 20 mg/mL if MRI is used at diagnosis or during follow up.
4) PSA density (PSA D) less than 0.2, or if MRI is used and negative or if targeted biopsies show no more than Gleason score 3+3 or 3+4 without CR/IDC a PSA density (PSA D) less than 0.25 is acceptable.
5) Clinical stage T1C or T2.
6) Gleason score 3+3=6 or Gleason 3+4 without invasive CR/IDC.One or 2 biopsy cores invaded with prostate cancer.
    a. If an MRI, including targeted biopsies on positive lesions, is done at inclusion, there is no limit in the number of positive cores (that is, more than two, and no limit in the % of cancer present in the cores).
    b. If saturation biopsies (either transperineal or transrectal) are done 15% of the cores can be positive with a maximum of 4. (i.e. <20 cores 2 cores can be positive (standard), 20-26 cores 3 cores can be positive, >26 cores 4 cores can be positive) (all other inclusion criteria still apply).
    c. If more than 2 TRUS guided biopsy cores are positive (Gleason score 3+3 or 3+4 without CR/IDC) an MRI is indicated. If the MRI is negative or if targeted biopsies show no more than Gleason score 3+3=6 or 3+4=7 without CR/IDC, inclusion is possible.
    d. For patients with adenocarcinoma Gleason score 3+4, the maximum number of positive cores should be ≤ 50%, where multiple positive cores from the same lesion on MRI count for one positive core.

7) Participants must be willing to attend the follow-up visits.
8) Signed informed consent.

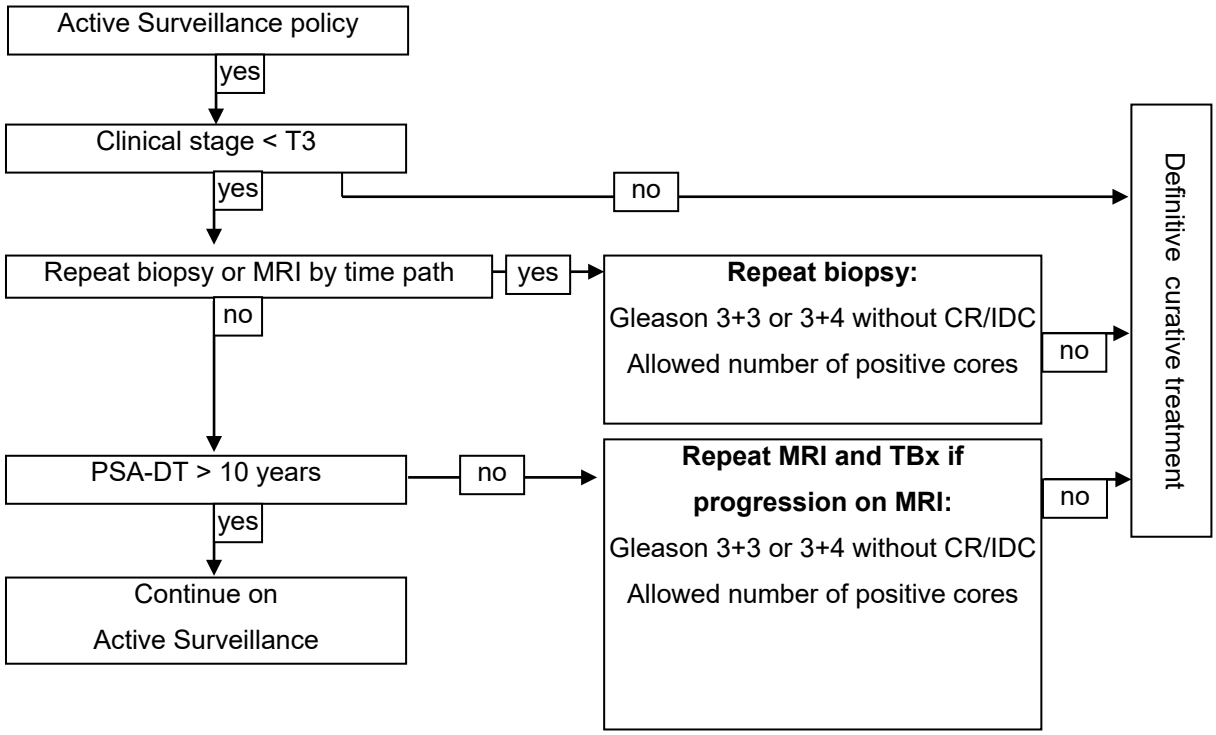
Exclusion-criteria:

1) Men who can not or do not want to be radiated or operated.
2) A former therapy for prostate cancer.
3) For patients with a life expectancy of <10yr, watchful waiting is preferred above active surveillance.

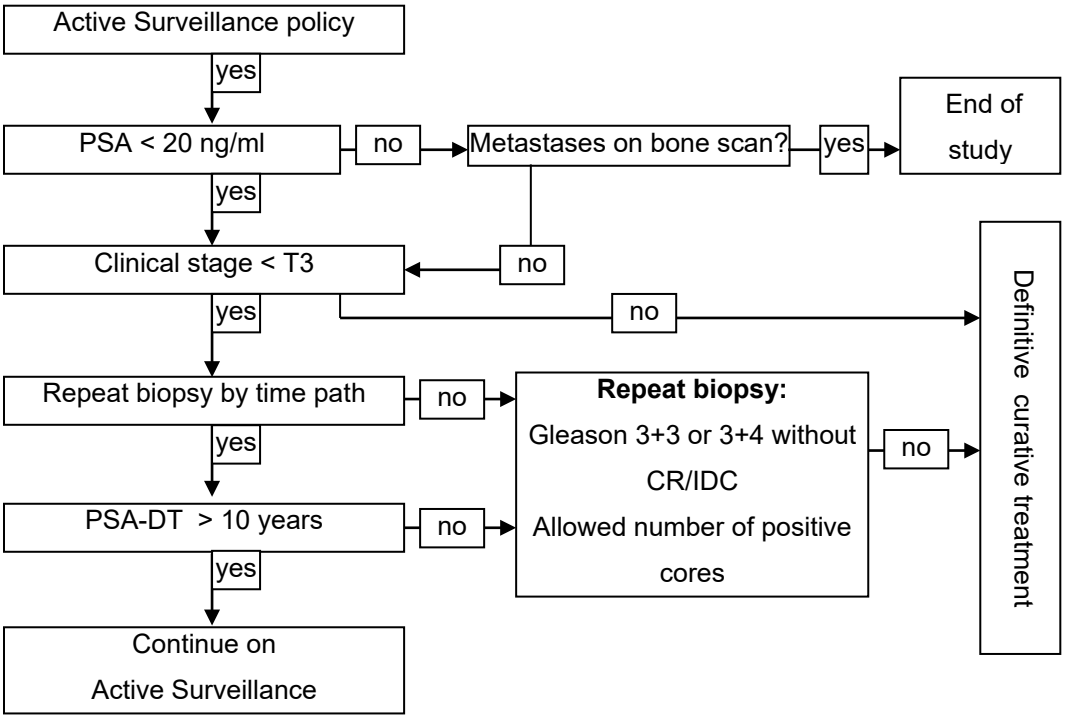
Follow-up criteria for Active Surveillance

1. **Clinical:**
    a. Clinical stage (cT) < 3
2. **Histological:**
    b. Gleason score 3+3=6 or Gleason score 3+4=7 without CR/IDC.
    c. The allowed positive biopsies remains the same during the follow up as a time of inclusion.
3. **Biochemical:**
    d. PSA doubling time (PSA DT) > 10 years
    e. If PSA DT 0-10 years: if the PSA-DT is <10 years a yearly mpMRI is advised in the years no standard repeat biopsy is done. Extra targeted biopsies are only taken if the mpMRI shows progression (progression is defined as a higher overall PIRADS score of one or more lesions, more/new lesions with PIRADS ≥ 3 and/or growth of lesions as assessed by the radiologist. Only lesions that showed progression are biopsied with a maximum of 2 biopsies per lesion. If no prior MRI is available to assess progression, targeted biopsies are taken from a maximum of 3 lesions with a PIRADS score ≥ 3).
4. **Patient is content with active surveillance**

When MRI is available:



When MRI is not available:



Time table

Year	*1*					*2*				*3*		*4*		*5*		*6*		*7*	
Month	*0***	*3*	*6*	*9*	*12*	*15*	*18*	*21*	*24*	*30*	*36*	*42*	*48*	*54*	*60*	*66*	*72*	*78*	*84*
PSA-test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DRE	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Biopsy*	✓				✓								✓						✓
Evaluation	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓

* repeat biopsy:

Standard after 1, 4, 7 en 10 year and subsequently every 5 years.

If PSA–DT is 0-10 years repeat biopsy every year is advised.

No more than 1 biopsy per year should be performed

** Time of diagnosis

Time table as of November 2018

	Year	**1**					**2**				**3**		**4**		**5**		**6**		**7**	
	Month	*0*	*3*	*6*	*9*	*12*	*15*	*18*	*21*	*24*	*30*	*36*	*42*	*48*	*54*	*60*	*66*	*72*	*78*	*84*
PRIAS-study	*PSA*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	DRE	X		X		X		X		X		X		X		X		X		X
	*Standard Biopsy**	X				X								X						X
	Evaluation	X		X		X		X		X		X		X		X		X		X
	*MRI + targeted biopsies***		*X**			*X*								*X*						*X*
	Evaluation		*X**			X				X		X		X		X		X		X

* *MRI 3 months after diagnosis: only targeted biopsies if lesion is visible on MRI (maximum of 3 lesions (2 biopsies per lesion)), no standard TRUS guided biopsies.*

** *If PSA-doubling time <10 years: A MRI is recommended every year (only in the years no standard biopsy is taken). Additional biopsies are indicated if MRI shows PIRADS progression, more lesions or growth of currently known lesion(s).*

Ad 1 Clinical progression

Digital rectal examination

The DRE has a high interobserver variability.[38] In the different Active Surveillance studies, different thresholds for the clinical stage are used.[4, 19, 38] In this study, a DRE is not obligatory at every visit, but only at evaluation visits. Clinical progression is defined as stage T3 or more (penetration of the capsule), irrespective of the initial clinical stage.

Ad 2 Histological progression

The proposed pattern for repeat biopsies is a one, four, seven, ten, fifteen and twenty years biopsy scheme. These moments are arbitrary. The number of biopsy cores is again indicated by the biopsy protocol. Besides the standard biopsies, a repeat biopsy is necessary if the PSA DT is between three and ten years. No more than one biopsy per year should be obtained.

Update January 2020

Due to the use of MRI in patients on active surveillance, the proposed pattern for repeat biopsy is slightly altered. If an MRI has not been obtained at diagnoses, an MRI should be performed 3 months after diagnosis. Targeted biopsies should be performed if a lesion (PI-RADS ≥ 3) is identified at the MRI. Before the subsequent repeat biopsies at one, four, seven, ten, fifteen and twenty years an MRI should be performed to make targeted together with systematic biopsies possible.

Ad 3 Biochemical progression

PSA doubling time (PSA DT)

PSA DT is defined as the time PSA needs to double its start-value. To preserve a difference in men who for example have a PSA of 2 and 10, the 2logPSA should be used. The PSA DT can subsequently be calculated by 1/slope. The slope denotes the slope through all 2log PSA values.

The use of PSA DT as a decision tool in this study is based on the observation that preoperative PSA levels are significantly correlated with the tumor volume in radical prostatectomy specimens.[39] It is furthermore based on the knowledge that PSA values have an exponential course in individual non-treated patients.[40] The PSA DT should therefore be linear.[41] It is intuitively correct that the PSA DT is a good indicator for tumor growth, and this assumption is supported by studies which show that PSA DT is a strong predictor for the risk of metastases[42] and death[43] due to prostate cancer after radical prostatectomy or radiotherapy. McLaren et al. have shown that the PSA DT was the strongest predictor of clinical progression in conservatively treated men.[44] Klotz described that in his Active Surveillance cohort the metastases free survival was 99% after 8 years. Initially, a PSA DT of less than two years led to curative treatment.[41]

If the PSA-DT is <10 years a yearly mpMRI is advised in the years no standard repeat biopsy is done. Extra targeted biopsies are only taken if the mpMRI shows progression (progression is defined as a higher overall PIRADS score of one or more lesions, more/new lesions with PIRADS ≥ 3 and/or growth of lesions as assessed by the radiologist. Only leasions that showed progression are biopsied with a maximum of 2 biopsies per lesion. If no prior MRI is available to assess progression, targeted biopsies are taken from a maximum of 3 lesions with a PIRADS score ≥ 3).

Ad 4 Motivation of the patient

It is known from the scarcely available studies that anxiety in patients is an important reason for choosing deferred curative treatment. This study provides the possibility of investigating this topic further by adding a quality of life component.

Update January 2020

As long-term quality of life data is still scarce, this remains an important topic.

Moments of evaluation

It is unnecessary to calculate the PSA DT with every new PSA recording. The biological variation in serum PSA necessitates that calculation of PSA DT is based on several measurements. For this reason the annual moments of evaluation were invented. At the end of the first year, an evaluation on biochemical, clinical and histological progression can be made. By the end of the second year, the evaluation is based at least at the DRE and the PSA DT.

Frequency of visits

The argument for choosing a 3-monthly visit-schedule in the first two years and a semi-annual schedule thereafter is to recognize and filter out the fast growing tumors, which are not corresponding with the definition of clinically irrelevant tumors. Those are likely the tumors that were undersampled at diagnosis. By means of intensive control by repeat biopsy, 4 PSA recordings in the first year and a DRE, men should be identified as not having irrelevant cancer. They would then have a therapy delay of a year. The literature which is available for such patients does not show a negative effect for this delay. Different follow-up schedules of different cohorts are given in Table 8.

Update January 2020

Increasing knowledge of the risk of progression of low-risk prostate cancer during prostate biopsies motivated the development of personalized schemes to schedule next prostate biopsy for patients on active surveillance. Personalized schedules aim to prevent unnecessary biopsies, in comparison to fixed patterns, and minimalize delay in detection of progression of the prostate cancer using historical data as prostate-specific antigen level en repeat biopsy result.[45]

Table 8 - follow-up parameters of published Active Surveillance studies

Cohort	PSA (mo)	Confirmatory biopsy (mo)	Repeat biopsies (yr from previous)	Triggers for biopsy
Canary-PASS	3	0–12	2	–
Johns Hopkins	6	<12	1	–
MSKCC	6	3	First 1–1.5, then 2–3	DRE change or sustained PSA increase
PRIAS	3 (for 2 yr), then 6	≤12	3	PSA-DT 3–10 yr
Toronto	3 (for 2 yr), then 6	≤12	3–4	PSA-DT <3 yr[b]
UCSF	3	<12	1–2	–

Study focus

PSA velocity (PSA V)

PSA V is the absolute increase of PSA values in one year. A minimum of three measurements should be available with at least 3 months in between. A start PSA of 4 ng/mL, with values of 4.2 and 4.3 after three and six months has a PSA V of 0.3 in six months and thus a PSA V of 0.6 in one year. Carter et al. showed that 70% of men with prostate cancer and only 5% without prostate cancer had a PSA V less than 0.75 ng/mL/year.[46] In ERSPC, this value is 0.62 ng/mL. A recent NEJM publication shows that a PSAV > 2.0 in the year before operation is a strong predictor for clinical progression and death due to prostate cancer.[47] The results of this study are convincing. The reason we have not included PSA V as a decision tool is that only one study has proven this effect so far. It has to be validated in cohort studies and clinical trials before it can be used in clinical settings. We have included the PSA V as a subject of study.

PSA D

The value of PSA D as a decision parameter in the follow-up was not evident in published studies. Therefore, PSA D is a subject of study in this protocol and not a decision parameter.

Quality of Life

It is known from the scarcely available studies that anxiety in patients is an important reason for choosing definitive curative treatment. This study provides the possibility of investigating this topic further by adding a quality of life component.

Long term quality of life of men on Active Surveillance

Although there is a growing body of knowledge about active surveillance, long term follow-up is scarce, as are long term quality of life data. This study provides the possibility to investigate, amongst others, long term quality of life of men on Active Surveillance.

Update January 2020

MRI

The value of MRI and subsequent targeted prostate biopsies has been studied in the MRI PRIAS side study (METC 2013-434). Since the start of the MRI PRIAS side study in 2013, the use of MRI in daily clinical practice has increased enormously[48]. MRI has been implemented in national[49] and international guidelines[50, 51] and has become standard of care. The performance of MRI and targeted biopsies at suspicious lesions before the start of active surveillance and/or at confirmatory biopsy is strongly recommended. The evidence for performing repeat MRI with biopsy during follow-up on active surveillance is less strong, but still considered beneficial. The evidence to use MRI only – without biopsy – as a monitoring tool during follow-up is not recommended yet but is being investigated (for instance in other large active surveillance studies in the USA and Canada). The negative predictive value of MRI reaches 98% for the presence of clinically significant PCa and improves the ability to predict reclassification and upstaging up to 90% in some studies[52]. Other active surveillance studies

have included MRI as a standard inclusion and follow-up tool [52, 53]. On February 12, 2019 the MRI PRIAS side study was closed for inclusion as MRI for the inclusion and follow-up in active surveillance has become standard of care.

Practical aspects

Website (www.prias-project.org)

Active surveillance patients will be managed on a website, which will give project documentation, store the inserted data at a central secured place, calculates parameters such as PSA DT and PSA D, gives protocolized advice to the physician and provides a printed documentation for the patient chart each time the patient attends the outward patient clinic for an evaluation visit. The information handling of patients is such that might the data become public, the information is useless and anonymized.

Questions and remarks

See www.prias-project.org for contact information.

List of abbreviations

ERSPC	European Randomized study of Screening for Prostate Cancer
MRI	Magnetic Resonance Imaging
PSA	Prostate-Specific Antigen
PSA D	PSA Density
PSA DT	PSA Doubling Time
QoL	Quality of Life
TRUS	TransRectal UltraSound

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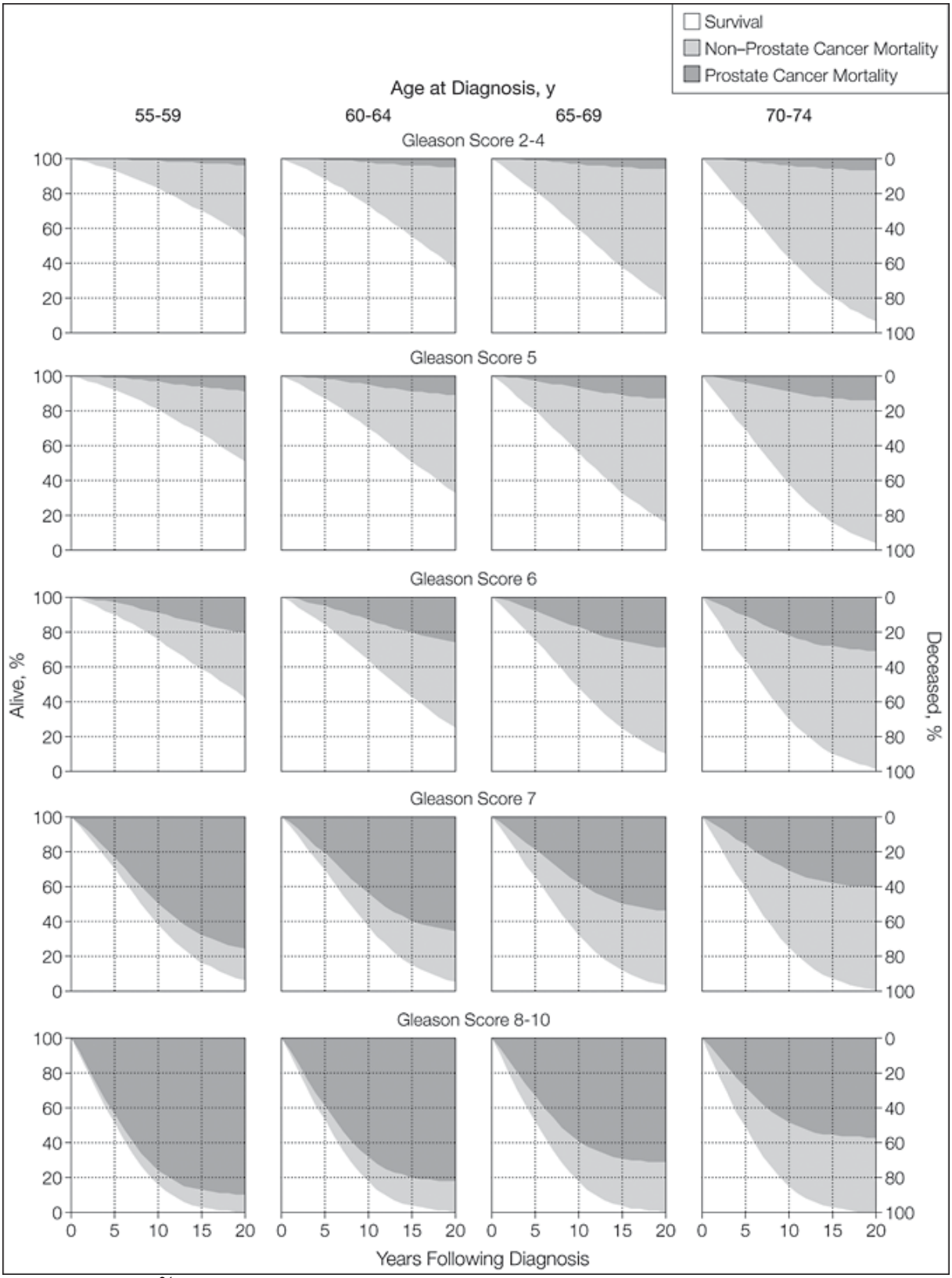
Albertsen tables



Albertsen tables[21]