Active surveillance for prostate cancer

quality of life and risk stratification

Lionne Venderbos

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Colofon

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Active Surveillance for Prostate Cancer: quality of life and risk stratification

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Chapter 1

General introduction

1.1 Prostate cancer

Prostate cancer is the second most common cancer and the fifth leading cause of cancer death among men worldwide. In 2012 an estimated 1.1 million men were diagnosed with prostate cancer and 307,000 men died of their disease [1]. The highest incidence rates are to be found in Australia/New Zealand, Northern America and Western and Northern Europe. In the Netherlands 10,897 men were diagnosed with prostate cancer in 2013 and 2,535 died of their disease [2].

The incidence of prostate cancer in the Netherlands has been rising since the early 1990's. This is most probably due to increased prostate cancer awareness, diagnostic improvements, early detection through prostate-specific antigen (PSA) testing and the ageing of the male population [3]. Prostate cancer mortality slightly decreased [2].

The difference seen between the incidence and mortality rate indicates that many more men die with prostate cancer than from prostate cancer which brings us to the natural history of the disease. Some prostate cancers grow and spread quickly; most prostate cancers, however, have a slow growing nature. Autopsy studies have shown that many older men who died of other causes also had prostate cancer [4].

1.2 PSA based prostate cancer screening

PSA is a protein produced by cells of the prostate gland. The PSA test was first described in the 1960's after which it became an approved biomarker in 1986 and a potential screening tool for prostate cancer in the early 1990's [5-7]. Before the introduction of the PSA-test, approximately half of the prostate cancers detected were lethal [3,8].

With increasing evidence that PSA could be used for the early detection of prostate cancer [7] three randomized controlled trials, aiming to evaluate whether population-based screening could reduce prostate cancer mortality, were initiated in the early 1990's; the European Randomized study of Screening for Prostate Cancer (ERSPC) and the Göteborg Randomized Population-based Prostate Cancer Screening trial in Europe and the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial in the United States [9]. Screening refers to the active search for diseases, precancerous or risk factors in order to discover them at the earliest possible stage so that early treatment is possible [10]. Ideally, screening should lead to an increased, but not excessive rate of early-stage detected cancers, a decrease in metastatic disease and a reduction in disease-specific mortality [10].

1.2.1 The European Randomized study of Screening for Prostate Cancer

The ERSPC is a randomized controlled, multicenter trial, which was initiated in the early 1990's [11]. Men from eight European countries, i.e. Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden and Switzerland, aged 50-74 years, were identified from population registries and, after signing informed consent, randomized into a screening (n=72,890) or control arm (n=89,353). Men in the screening arm received PSA testing, followed by a lateralized sextant biopsy in case the PSA value was ≥ 4.0 ng/ml, or later in case the PSA was ≥ 3.0 ng/ml. Men in the control arm received usual care. In 2009, with a median follow-up of nine years, the ERSPC group reported that prostate cancer was detected in 5,990 men (8.2%) in the screening arm and in 4,307 men (4.8%) in the control arm. 214 and 326 men died of prostate cancer, respectively, corresponding to a 20% reduction (p=0.04) in men dying from prostate cancer in the screening arm [11]. The corresponding number of men that needed to be screened (NNS) and needed to be treated (NNT) amounted to 1410 and 48 [11]. Since 2009, two analyses with 11- and 13-year follow-up outcome data have been published [12,13] both confirming the 21% substantial relative reduction in prostate cancer mortality due to screening. In the 13-year follow-up publication the absolute risk reduction of death from prostate cancer amounted to 0.11 per 1,000 person years or 1.28 per 1,000 men randomized. This translates into averting one prostate cancer death per 781 men invited for screening (NNI) or one per 27 additional prostate cancers detected (NND) [13].

Screening for prostate cancer did not only reduce disease-specific mortality, it also decreased the rate of metastatic disease [14]. Schröder et al. assessed the effect of screening for prostate cancer on the incidence of metastatic disease in four ERSPC centers (Finland, the Netherlands, Sweden and Switzerland). Among 76,813 men (n = 36,270 for the screening arm, n = 40,543 for the control arm) aged 55-69 years, 666 men (256 in the screening arm and 410 in the control arm) with metastatic prostate cancer were detected at a median follow-up of 12 years. In an intention-to-screen analysis a relative reduction of 30% (RR 0.70, 95%CI 0.60-0.82, p=0.001) was found. When adjusted for those men actually screened the relative reduction amounted to 42% (RR 0.58, 95%CI 0.45-0.74, p<0.001) [14].

1.2.2 The Göteborg Randomized Population-based Prostate Cancer Screening trial

Shortly after the 2009 publication of the ERSPC, the results of the Göteborg Randomized Population-based Prostate Cancer Screening trial were published [15]. The Göteborg screening trial was initiated in 1994 as an independent study, but joined the ERSPC study shortly thereafter. With a follow-up of 14 years, the researchers found a prostate cancer mortality reduction in favor of the screening arm of 44% (rate ratio 0.56, 95%

CI 0.39-0.82, p=0.002). When adjusted for non-compliance, prostate cancer mortality was reduced by 56% (rate ratio 0.44, 95% CI 0.28-0.68, p=0.002). This translated into a NNS of 293 and a NNT of 12; for attendees after adjustment for non-compliance a NNS of 234 and a NNT of 15 was found [15]. In 2014, with a follow-up of 18 years, the study group reported a relative risk reduction of 42% (rate ratio 0.58, 95% CI 28-54%) and a NNI and NND of 139 and 13 [16]. Main differences between the Göteborg screening trial and the ERSPC trial as a whole are the type of randomization, the younger age of the participants, a shorter screening interval (2 years vs. 4 years in ERSPC as a whole), and the longer follow-up available due to the simultaneous randomization of all participants in 1994 in Sweden [17].

1.2.3 The Prostate, Lung, Colorectal, and Ovarian cancer screening trial

The prostate component of the PLCO trial included a total of 76,685 men, aged 55-74 years. These men were enrolled in ten centers and randomly assigned to an intervention or control arm. The intervention arm entailed organized screening, consisting of PSA testing for 6 years and annual digital rectal examination (DRE) for 4 years. Men included in the control arm received usual care, which included opportunistic screening. After nine years of follow-up, contrary to the findings of the ERSPC and the Göteborg screening trial, the PLCO trial found no evidence of a mortality benefit [18]. The lack of a mortality benefit was confirmed in later publications where longer follow-up data were presented [19,20]. The results of the PLCO trial were influenced by issues in the design and execution of the study, which affected the power of the study. Men included into the trial were allowed to have undergone one screening within the three years before enrollment and an unlimited number of PSA screens. The results were furthermore influenced by the 52% contamination rate in the control arm and the low biopsy compliance rate (40%) in the screening arm. Al together this led to an identical stage distribution of the detected cancers in the screen and control arm, making the occurrence of a difference in prostate cancer mortality between the two arms difficult, also with longer follow-up [18,19,21].

1.2.4 Harms of screening for prostate cancer

The benefits of screening for prostate cancer are, as shown above, the reduced risk of advanced disease and the reduced risk of dying from the disease. Screening, however, is also associated with downsides. Adverse effects of screening are the overdiagnosis and subsequent overtreatment. Overdiagnosis is referred to as the detection of cancers that would not have been diagnosed during the patients' lifetime had he not been screened [22]. In the ERSPC trial the rate of overdiagnosis was estimated to be no less than 50% in the screening arm [22]. If such overdiagnosed cancers are treated, we speak of overtreatment. 'Overdiagnosed' men have to live longer with the knowledge of having

prostate cancer, or, for those who opt for curative treatment, with the side-effects of treatment [23] while these years might otherwise have been symptom-free.

1.3 Active surveillance

During the last decade active surveillance has emerged as an alternative strategy for immediate active therapy in the management of potentially overdiagnosed prostate cancers. The aim of active surveillance is to delay or completely avoid unnecessary treatment of a potentially indolent tumor, i.e. a tumor that has little or no lethal potential, and therewith avert side-effects of treatment and preserving quality of life [24,25]. Patients who choose active surveillance are offered a monitoring program that includes PSA measurements, rectal examinations, repeat prostate biopsies and (only recently added) the option of undergoing an MRI. If risk classification towards a higher risk or disease progression is suspected, men can switch to active therapy with curative intent [24,25].

The difficulty when selecting patients for active surveillance is to identify only patients with indolent prostate cancer. Up to now, there is no marker available that distinguishes indolent perfectly from aggressive prostate cancer. The inclusion of patients on active surveillance is currently based on a combination of clinical and pathological markers like Digital Rectal Examination (DRE), Gleason score and PSA-density which are gained at diagnosis. Frequent follow-up of these patients should warrant early detection of potential misclassification of low-risk disease or true progression in order not to miss the window of curability.

Several studies assessing the value of active surveillance have been initiated worldwide during the last ten years. Examples are the active surveillance cohorts at Johns Hopkins in Baltimore, USA [26]; University of California, San Francisco (UCSF), USA [27]; Miami, Florida, USA [28]; Klotz, Canada [29]; Royal Marsden Hospital, London, UK [30]; and the Prostate cancer Research International: Active Surveillance (PRIAS) study which operates worldwide [25,31]. All active surveillance cohorts use different sets of inclusion criteria, one set being more stringent than the other.

Results of these cohorts so far seem promising with respect to disease-specific survival, active-therapy free survival, rate of metastases and prostate cancer death [32]. Klotz et al. recently published data with a follow-up of 15 years [29]. The authors reported that 2.8% of men developed metastatic disease and that 1.5% died of prostate cancer. Because this mortality rate is consistent with expected mortality in favorable-risk patients with initial definitive intervention, Klotz et al. conclude that active surveillance seems

feasible and safe within a 15-year time frame [29]. More robust long-term follow-up outcomes are, however, warranted.

1.3.1 PRIAS

The Prostate cancer Research International: Active Surveillance (PRIAS) study, was set-up by investigators of the Rotterdam section of ERSPC and the department of Urology, Erasmus University Medical Center, Rotterdam, the Netherlands [25]. PRIAS is a protocol- and web-based, multicenter, worldwide observational study. It started including patients in 2006. PRIAS was designed to validate an active surveillance protocol based on the then available knowledge. If deemed necessary, the PRIAS protocol would be adapted to more current scientific evidence on the management of low-risk prostate cancer [25]. To date, PRIAS includes more than 5,000 patients from 17 countries.

In 2013 Bul et al. published results on 2,494 patients that were included in the PRIAS study and were followed for a median of 1.6 years. In 1,480 men one or more repeat biopsies were performed; 415 (28%) showed reclassification meaning Gleason upgrading, reclassification based on the number of positive cores or a combination of both. The 2-year active therapy free survival amounted to 77.3% and the disease-specific survival rate was 100% [31].

1.3.2 Quality of Life

With the initiation of an active surveillance management strategy, also the question on how active surveillance might influence quality of life of men came up. Men who choose active surveillance have to deal with living with their 'untreated' prostate cancer. Although being closely monitored, active surveillance may cause distress and anxiety because of the continuous uncertainty that men might experience. Several studies have been carried out assessing the effect of active surveillance on quality of life of men. It has been shown that in the short run, anxiety and depression scores of men on active surveillance are favorably low [33-35]. The overall health related quality of life scores of men on active surveillance were good and therewith comparable or even slightly better than for those post radical treatment [35]. While these results yield optimism for those choosing active surveillance, longer follow-up is needed as well as studies that investigate the characteristics of patients that do not choose active surveillance to begin with or switch to curative therapy in a very early stage due to anxiety.

When localized prostate cancer is treated radically with surgery (radical prostatectomy) or radiotherapy (brachytherapy or external beam radiation therapy) side-effects of treatment, like impotence, erectile dysfunction, or urinary problems, could occur which can impact quality of life. Five years after radical prostatectomy for localized prostate

cancer 71-88% of patients reported erectile dysfunction and 14-31% reported urinary incontinence. After radiotherapy 64% of patients reported erectile dysfunction and 11% experienced problems with their bowel functions [23,36]. With active surveillance treatment is delayed, or even completely avoided. The biopsies performed when on active surveillance are, however, not without risk. Glass et al. assessed whether repeated biopsies affect urinary function of men on active surveillance. They concluded that the repeated biopsies independently do not pose an additional risk of lower urinary tract symptoms in men on active surveillance [37]. Braun et al. assessed whether serial repeat biopsies affect erectile functioning of men on active surveillance. The authors found a small decrease in erectile functioning of men. They, however, could not separate the effect of aging and multiple biopsies. They therefore suggested that active surveillance-related biopsies do not seem to have a large impact on erectile function [38]. In both studies, the follow-up was rather short. Studies with longer-term follow-up data would therefore be warranted.

1.4 This thesis

Part I – Screening for prostate cancer

The main endpoint of prostate cancer screening studies is to determine whether PSA-based screening can reduce prostate cancer mortality. The ERSPC and the Göteborg Cancer Screening Trial have shown such an effect of screening on disease-specific mortality. Screening programs furthermore, have secondary endpoints; one of them being the development of tumor characteristics and applied treatments in both the screening and control arm over time. Such an assessment can give insight into the rate of opportunistic testing within the screening and control arm of the study. This is needed to investigate whether a shift over time towards more favorable tumor characteristics at diagnosis due to opportunistic screening, possibly followed by a change in therapy choices, influences the main endpoint of the trial due to the potential diminished differences between the screening and control arm.

Research question 1: How do tumor characteristics and treatment patterns change in the course of a screening trial for prostate cancer?

It has been shown that screening has both advantages and disadvantages. Due to the conflicting situation that arose after the publications of the ERSPC, the Göteborg Cancer Screening Trial and the PLCO study, some professionals strongly recommend against PSA testing, while others strongly advise in favor of PSA testing.

Research question 2: How to advice patients who consult their general practitioner or urologist with a screening request?

Part II – Active surveillance for low-risk prostate cancer

Overdiagnosis and overtreatment are two main concerns that have been acknowledged by all three prostate cancer screening trials. Currently, research is being done on how to reduce the overdiagnosis of prostate cancer. As no marker is available yet that distinguishes indolent disease perfectly from aggressive prostate cancer, an alternative management strategy has come up with which to reduce the rate of overtreatment. Active surveillance was introduced almost a decade ago alternatively to direct invasive therapy and aims to prevent, or delay, invasive therapy and its associated potential side-effects in selected patients with latent low-risk prostate cancer. Part two of this thesis will focus on the development of active surveillance as a management strategy, in particular by assessing quality of life and patient selection through risk stratification. To achieve these goals, several research questions will be addressed.

Research question 3: As active surveillance cohorts mature, how do the related clinical outcomes develop?

Research question 4: In the light of personalized medicine, what is the best way to select patients for active surveillance?

In the short run, men on active surveillance do not seem to experience much anxiety or depressive feelings. Longer follow-up data are, however, lacking.

Research question 5: How does quality of life develop in men who follow an active surveillance management strategy for a longer period of time? How does their quality of life compare to that of men who underwent direct curative therapy?

Research question 6: With the increasing clinical acceptance of active surveillance as a feasible alternative to immediate active therapy, how do urologists value active surveillance and what should they be aware of in such a fast moving area of expertise?

1.5 Outline of this thesis

In part one, **chapter 2**, of this thesis the results of an prospective, observational study on the change of tumor characteristics and treatment patterns in the screening and control arm of the ERSPC study are presented. **Chapter 3** reviews options on how to advice patients that come to their general practitioner or urologist with a screening request.

In part two, **chapter 4**, the results of a review on oncologic outcomes for men on active surveillance are presented. In **chapter 5**, it is assessed whether probabilistic-based selection by applying a nomogram will improve patient selection for active surveillance as compared to the currently used rule-based criteria. Chapter 6 and 7 discuss patient reported outcome measures (PROMS) for men on active surveillance. **Chapter 6** describes quality of life of men who followed an active surveillance strategy for an 18-month period. **Chapter 7** reports on quality of life of men who followed an active surveillance strategy for 5-years. These results are compared to quality of life results of men who were treated curatively ≥5 years ago and to a reference group of men who do not have prostate cancer. In chapters 8 and 9 active surveillance is looked upon from two different perspectives. **Chapter 8** discusses how urologists value active surveillance as a management strategy and alternative to direct curative treatment. **Chapter 9** is written from a legal perspective and reports on the elements that urologists should be aware of when offering active surveillance to patients. Finally, in **chapter 10**, the key findings of the studies will be discussed and placed into perspective after which directions for future research will be proposed.

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Part I

Screening for prostate cancer

Chapter 2

Change of tumor characteristics and treatment over time in both arms of the European Randomized study of Screening for Prostate Cancer

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Eur J Cancer. 2010 Nov;46(17):3082-9.

Abstract

Objective. To evaluate a change in tumor characteristics and applied treatments over time in the control arm of all centers of the European Randomized study of Screening for Prostate Cancer (ERSPC) and to compare this with similar data of the screening arm.

Methods. Between 1993 and 2003, 182,160 men, aged 50-74 years, were randomized to the screening arm (N=82,186) and the control arm (N=99,184). Men in the screening arm were offered Prostate Specific Antigen (PSA) testing every four years whilst men in the control arm received usual care. Tumor characteristics and treatment were evaluated in all men diagnosed with prostate cancer up to December 2006 or the third screening round. Data on the control arm were divided into three periods: 1994-1998, 1999-2002 and 2003-2006.

Results. Tumor characteristics were more favorable over time in both the control and the screening arm, with especially increasing proportions of T1C tumors with 29% in 1994-1998 vs. 50% in 2003-2006 and 48% at the initial screening round vs. 75% at the third screening round, respectively. Tumor characteristics observed in the last period of the control arm were comparable to tumor characteristics in the initial screening round. In the control arm, treatment changed over time with surgery as the most common treatment in the entire observed period, but almost doubling of expectant management and the combination of hormone therapy and radiotherapy over time. In the initial screening round, surgery was the most common treatment (42%), changing over time to expectant management as the most frequently applied treatment in the third screening round (33%).

Conclusion. Tumor characteristics in the control arm became more favorable over time and show similarity with prostate cancer cases detected at the initial screening round. The most prominent change in treatment over time was an increase of application of expectant management in both arms of the ERSPC. These observations reflect an increasing rate of opportunistic testing over time in men randomized to the control arm.

Introduction

The European Randomized study of Screening for Prostate Cancer (ERSPC) was initiated in 1994 to assess whether screening for prostate cancer is effective in decreasing prostate cancer mortality at an acceptable cost, both in terms of quality of life and finance [1].

After a mean follow-up of 9 years the third interim intention to screen analysis resulted in a significant 20% reduction in prostate cancer mortality in favor of screening [2]. This reduction was 30% when corrected for non-compliance and contamination [3]. The study is still ongoing, continued follow-up will provide further information needed for the decision on whether prostate cancer screening should become a population-based program.

Next to the main endpoint, disease specific mortality, studies on the so-called secondary endpoints (i.e. stage and grade shift of tumors detected in both intervention and control arm) are of great value. Earlier studies comparing the tumor characteristics between the screening and the control arm showed that prostate cancer patients in the control arm had significantly higher PSA levels at diagnosis and had more advanced clinical stage as compared to prostate cancer patients in the screening arm. The distribution of Gleason score of the sextant prostate biopsies showed a similar pattern, the prostate cancers detected in men in the control arm had a significantly higher proportion of cancers with Gleason >7. All data point towards a shift towards more favorable tumor characteristics at diagnosis in the screening arm [4-6]. This was also confirmed when comparing tumor characteristics between two subsequent screening rounds [5-8].

Therapy choices reflect stage and grade distribution at diagnosis and hence were different between the screening arm and the control arm. Men in the screening arm were offered curative therapy more often, whilst men in the control arm received endocrine therapy more often [4]. A similar pattern was seen between prostate cancers detected at initial and repeat screening. The proportion of men managed by active surveillance increased drastically and more than doubled, reflecting the more favorable tumor characteristics at diagnosis [8]. It must be noted however, that within ERSPC there was no imbalance in treatments applied between the two study arms after correcting for differences in tumor characteristics at diagnosis [9].

Meanwhile, PSA testing in asymptomatic men occurs in the control arm, and if the contamination is effective: i.e. opportunistic PSA testing followed by a prostate biopsy and early diagnosis it may have an effect on the characteristics of the prostate cancers

detected and thus therapy. This so-called opportunistic PSA testing or contamination testing occurs also in men randomized to the screening arm but to a lesser extent [10].

The aim of the study presented here was to inventory the tumor characteristics and applied treatments over time in the control arm of the different ERSPC centers and to compare this with similar data from the screening arm in order to (a) assess the effect of contamination (i.e. opportunistic screening) in the control arm over time and (b) to further explore the earlier reported favorable grade and stage shift and subsequent treatment changes as a result of PSA based screening.

Materials and methods

Study population

Between 1993 and 2003, a total of 182,160 men, aged 50-74 years, were included in the screen and control arm of the ERSPC. Participating centers were located in Finland, the Netherlands, Sweden, Belgium, Italy, Switzerland and Spain. Men who were randomized to the intervention arm (N=82,816) received systematic screening every 2 or 4 years and men who were randomized to the control arm (N=99,184) received usual care [11]. Follow-up for mortality analyses began at randomization and ended at death, emigration or a uniform censoring date (December 31, 2006) with identical follow-up in the two study arms [2]. The mean follow-up for both arms is 9 years. In the current study, all men diagnosed with prostate cancer in the control arm between January 1994 and December 2006 and all men diagnosed with prostate cancer in the intervention arm from the initial screening round up to the third screening round are included (for Sweden, men are included up to the 6^{th} screening round because of a 2-year screening interval). Cancers diagnosed in men who did never attend screening, and cancers diagnosed between the two screening intervals clinical or due to opportunistic screening, transurethral resection of the prostate (TURP) for benign disease, and cystoprostatectomy specimens, were considered as well and defined as interval cancers.

Men with prostate cancer in the control group were identified through a linkage with national cancer registries. These men received standard medical care consisting of symptom evaluation as well as prostate cancer diagnosing and treatment by a general practitioner and a local urologist. Screening methodology was reviewed for all centers by Schröder et al. In most centers a PSA cut-off value of 3.0 ng/ml was used as an indication for prostate biopsy. In Finland a PSA value of ≥4.0 ng/ml was defined as a biopsy indication. Men with a PSA value of 3.0-3.9 ng/ml underwent an ancillary test. Up to 1998 this meant that men underwent a digital rectal examination (DRE). In 1999 the Finnish center

started to calculate the ratio of the free PSA value to the total PSA value. If the ancillary test was positive, men were referred for biopsy. In Italy, men with a PSA value of 2.5-3.9 ng/ml underwent ancillary tests (i.e. DRE and transrectal ultrasonography (TRUS)). A PSA of ≥4.0 ng/ml was defined positive to refer men for prostate biopsy. In both the Dutch and the Belgium centers, a combination of DRE, TRUS and PSA testing with a cut-off value of 4.0 ng/ml was used for screening up to February 1997. After February 1997 this combination was replaced by PSA testing only with the cut-off value of 3.0 ng/ml. In Belgium, they initially used a PSA cut-off value of 10.0 ng/ml since the results of a pilot were included in the dataset. Most centers used sextant biopsies guided by TRUS. From June 1996 on, lateralized sextant biopsies were recommended. In Italy they have used transperineal sextant biopsies, whilst in Finland a biopsy procedure with 10-12 biopsy cores was adopted as the general policy in 2002. Most centers adopted a screening interval of 4 years; whilst Sweden used a 2-year interval [2,11].

Screening rounds 1 and 2, 3 and 4, and 5 and 6 in Sweden were added to screening rounds 1,2 and 3 of the centers with a 4-year interval, respectively.

Cancers were classified according to the 1992 TNM classification. Grading of the cancers was done using the Gleason grading system. Organ confined disease was considered as T1 and T2 disease, advanced disease as T3 and T4 disease and metastatic disease as N1, N2, N3 and M1. Incidence data of the control arm were subdivided according to year of diagnosis. The periods were: 1994-1998, 1999-2002 and 2003-2006 and compared to the initial, repeat and third screening round. Prostate cancers diagnosed before randomization were excluded, both in the control and the screening arm. Missing data on stage and grade were filled in taking into account the stage and grade distribution in the available data, assuming that there is no bias in this respect in obtaining follow-up data.

Statistical analysis

The statistics are mainly descriptive. Cumulative incidence was calculated for tumour characteristics per 10,000 men at risk. We used the men at risk at the start of the predefined periods of the control arm for both arms. Tumour characteristics, i.e. stage and grade, and treatment were compared amongst the predefined successive periods. Furthermore, we compared the change in tumour characteristics over time in the control arm with the tumour characteristics in subsequent screening rounds of the screening arm. The Statistical Package for Social Sciences (SPSS) for Windows, version 15.0, software was used. T-test for independent samples and the Mann-Whitney-U test were used to compare between groups.

ERSPC is registered under the Current Controlled Trials number ISRCTN49127736.

Results

Patient characteristics and incidence data

A total of 4,782 prostate cancers (4.8%) were diagnosed between January 1994 and December 2006 in the control arm (N=99,184). In the screening arm (N=82,816) a total of 6,567 prostate cancers (7.9%) were detected in subsequent screening rounds.

Median PSA at diagnosis decreased in the successive periods in the control arm; 12.7 ng/ml (1994-1998), 10.9 ng/ml (1999-2002) and 9.4 ng/ml in the period 2003-2006. Median PSA at diagnosis in subsequent screening rounds was quite stable; 5.3 ng/ml (initial screening), 4.7 ng/ml (repeat screening) and 5.4 ng/ml at the third screening round (4 year interval). Men diagnosed with prostate cancer in the control arm had significantly ($P<0.01$) higher PSA levels at diagnosis as compared to men in the screening arm. Mean age at diagnosis was 67.7 years in the control arm and 66.2 in the screening arm and differed significantly ($P<0.001$).

Tumor characteristics

Clinical TNM classification

The clinical T stage distribution showed a favorable shift over time, in both the control arm and the screening arm (table 1). The proportion of T1c tumors in the control arm increased from 29% (95% CI 28.2-28.8) in 1994-1998 to 37% (36.7-37.3) in 1999-2002 and to 50% (49.7-50.3) in 2003-2006. The percentage of screen detected T1c prostate cancers increased from 48% (47.4-48.2) in the initial screening round, 65% (64.8-65.4) in the repeat screening round to 75% (74.6-75.2) in the third screening round. The opposite was seen in T3 prostate cancers. In the control arm T3 tumors decreased from 23% in 1994-1998 to 13% in 2003-2006. At the initial screening round T3 tumors accounted for 14% of all tumors detected. This proportion decreased to 4% in the third screening round. This positive effect was also reflected by cumulative incidence in the screening arm, particularly between the initial screening round and the second screening round where advanced disease decreased (61.6 to 14.8 per 10,000 men at risk) and T1c cancers increased (204.9 to 214.1 per 10,000 men at risk).

Prostate cancers in the control arm showed in the last period (2003-2006) a similar clinical T stage distribution as compared to prostate cancers detected at the initial screening round. In 2003-2006 in the control arm, T1c and T3 accounted for 50% and 13% of the tumors, respectively. At the initial screening round T1c and T3 tumors had similar proportions of 48% and 14%, respectively.

Table 1: Tumor characteristics in the control and screening arm of ERSPC

	Control arm				Screening arm			
	1994-1998	1999-2002	2003-2006	Total	Initial round	2nd round	3rd round	Total
	Cum.Inc.* (%)	Cum.Inc.* (%)	Cum.Inc.* (%)	No.	Cum.Inc.* (%)	Cum.Inc.* (%)	Cum.Inc.* (%)	No.
Clinical T stage								
T1a-T1b	4.8 (6.2)	11.5 (6.2)	20.6 (7.2)	322	5.8 (1.3)	11.6 (3.5)	7.7 (3.7)	178
T1c	21.9 (28.5)	68.3 (37.0)	142.9 (50.0)	2044	204.9 (47.8)	214.1 (65.1)	155.0 (74.9)	3968
T2	29.5 (38.4)	63.3 (34.3)	75.7 (26.5)	1468	156.5 (36.5)	88.0 (26.8)	34.7 (16.7)	1867
T3	17.5 (22.8)	34.9 (18.9)	37.7 (13.2)	783	59.8 (13.9)	13.6 (4.1)	9.0 (4.4)	530
T4	3.2 (4.1)	6.6 (3.6)	9.2 (3.2)	165	1.8 (0.4)	1.2 (0.4)	0.6 (0.3)	24
Total	76.9 (100)	184.6 (100)	286.2 (100)	4782	428.8 (100)	328.4 (100)	207.0 (100)	6567
Metastasis								
Lymph node	2.5 (3.2)	4.9 (2.6)	4.7 (1.6)	105	5.6 (1.3)	3.3 (1.0)	1.9 (0.9)	72
Distant	8.0 (10.4)	13.0 (7.0)	12.4 (4.3)	288	9.6 (2.2)	8.0 (2.4)	4.3 (2.1)	149
Biopsy Gleason score								
Gleason 2-6	44.5 (57.9)	105.7 (57.2)	145.6 (50.9)	2583	300.9 (70.2)	249.3 (75.9)	141.4 (68.3)	4726
Gleason 7	16.0 (20.8)	51.3 (27.8)	92.6 (32.4)	1404	93.9 (21.9)	56.1 (17.1)	46.7 (22.6)	1326
Gleason 8-10	16.4 (21.3)	27.5 (14.9)	48.0 (16.8)	795	33.9 (7.9)	23.1 (7.0)	18.9 (9.2)	515
Total	76.9 (100)	184.6 (100)	286.2 (100)	4782	428.8 (100)	328.4 (100)	207.0 (100)	6567
Men at risk	72,549	94,094	86,894		60,711	76,698	69,796	

A favorable shift over time was seen in metastasis status in the control arm (3.2 to 1.6% in lymph node metastasis and 10 to 4% in distant metastasis), whilst in the screening arm the proportion of lymph node metastasis was slightly decreasing (1.3 to 0.9%) and distant metastasis were quite stable over time (2%).

Gleason score

Gleason score distribution showed no explicit shift over time in both trial arms (table 1). Only low-grade tumors, i.e. Gleason scores 2-6, decreased over time (58 to 51%) and moderate Gleason grade tumors (Gleason score 7) increased over time (21 to 32%) in the control arm. A decreasing trend was however seen in high Gleason grade tumors (Gleason 8-10) in the control arm. In the first study period the proportion was 21% (21.0-21.6), decreasing to 17% (16.6-17.0) in the last study period. In the screening arm these proportions were 7.9% (7.7-8.1), 7.0% (6.8-7.2) and 9.2% (9.0-9.4) at 1st, 2nd, and 3rd screening, respectively.

The comparison of Gleason score distributions between the control arm and the screening arm showed that in the control arm only Gleason scores 8-10 reached a comparable proportion with that of the initial screening round in 2003-2006 (17% versus 8%, respectively). A substantial difference remained in Gleason scores 2-6 (51% in 2003-2006 versus >70% in the initial screening round).

Treatment

Table 2 shows the distribution of initial treatment over time in both the control and the screening arm. The category "Other treatments" consists of therapies rarely applied in at most 9 prostate cancer cases per arm and comprised surgery with gene therapy, surgery with radiotherapy and hormone therapy, expectant management followed by surgery, expectant management followed by radiotherapy and expectant management followed by hormone therapy.

In the control arm surgery was the most frequently applied treatment in 1994-1998, in 31% of the patients. This was followed by hormone therapy and radiotherapy, accounting for 24% and 21% of treatments, respectively. At the initial screening round surgery was the most frequently applied treatment in 42% of the cases, followed by radiotherapy, applied in 29% of the cases.

In the last period of the control arm surgery was still the most common treatment, but had decreased to 25% of all treatments applied. Surgery was now closely followed by hormone therapy (22%) and the increased proportion of expectant management

Table 2: Treatment in the screening and control arm of the ERSPC

Treatment	Control arm				Screening round			
	1994-1998	1999-2002	2003-2006	Total	Initial round	2nd round	3rd round	Total
	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)
Hormone and radiotherapy	9.0 (50)	17.9 (310)	18.3 (455)	16.7 (815)	4.0 (104)	8.6 (218)	11.2 (162)	7.2 (484)
Hormone therapy alone	23.9 (133)	20.3 (353)	21.8 (542)	21.5 (1028)	7.4 (192)	8.0 (201)	8.7 (126)	7.9 (519)
Radiotherapy alone	21.1 (118)	18.4 (319)	14.1 (351)	17.0 (788)	29.4 (766)	24.1 (607)	15.7 (227)	24.8 (1600)
Surgery and hormone therapy	3.2 (18)	1.0 (17)	0.8 (21)	1.3 (56)	2.1 (54)	1.1 (27)	0.7 (11)	1.4 (92)
Surgery and radiotherapy	0.4 (2)	0.3 (5)	0.6 (15)	0.4 (22)	0.3 (8)	0.2 (5)	0.0 (0)	0.2 (13)
Surgery alone	30.8 (172)	29.8 (518)	24.9 (618)	27.9 (1309)	42.3 (1101)	34.7 (875)	30.1 (435)	37.1 (2413)
Expectant management	10.8 (60)	12.1 (211)	19.3 (480)	15.0 (751)	14.2 (370)	23.1 (581)	33.1 (479)	21.2 (1431)
Other treatments	0.8 (5)	0.2 (4)	0.2 (5)	0.2 (13)	0.3 (8)	0.2 (5)	0.5 (5)	0.2 (18)
Total	100 (558)	100 (1737)	100 (2487)	100 (4782)	100 (2603)	100 (2519)	100 (1445)	100 (6567)
Mean age at diagnosis (range)	65.8 (50.8-78.1)	66.8 (54.4-82.8)	68.8 (54.3-86.0)		64.8 (50.9-78.2)	66.6 (53.1-82.5)	68.1 (56.5-83.2)	

Table 2a: Treatment broken down by stage for the control arm of ERSPC

Treatment	Control arm								
	Organ confined disease			Advanced disease			Metastatic disease		
	1994-1998	1999-2002	2003-2006	1994-1998	1999-2002	2003-2006	1994-1998	1999-2002	2003-2006
	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)
Hormone and radiotherapy	8.2 (31)	14.8 (174)	16.1 (218)	12.4 (17)	31.2 (106)	29.9 (79)	1.5 (1)	2.1 (3)	2.4 (3)
Hormone therapy alone	13.1 (49)	12.0 (142)	14.8 (200)	51.1 (71)	49.1 (168)	57.8 (153)	92.6 (64)	86.6 (131)	84.9 (115)
Radiotherapy alone	21.6 (81)	20.9 (246)	16.0 (216)	24.8 (34)	12.7 (43)	6.1 (16)	2.9 (2)	1.4 (2)	1.6 (2)
Surgery and hormone therapy	3.3 (12)	1.0 (11)	0.9 (12)	2.2 (3)	0.3 (1)	0.4 (1)	1.5 (1)	0.7 (1)	-
Surgery and radiotherapy	0.3 (1)	0.4 (4)	0.7 (10)	-	-	-	-	-	0.8 (1)
Surgery alone	37.7 (141)	35.1 (413)	28.8 (388)	8.0 (11)	4.8 (17)	2.5 (7)	1.5 (1)	6.3 (10)	6.3 (9)
Expectant management	14.8 (55)	15.5 (182)	22.6 (306)	1.5 (2)	1.8 (6)	3.3 (9)	-	2.8 (4)	4.0 (5)
Other treatments	1.0 (5)	0.4 (5)	0.2 (2)	-	-	-	-	-	-
Total	100.0 (375)	100.0 (1177)	100.0 (1352)	100.0 (138)	100.0 (341)	100.0 (265)	100.0 (69)	100.0 (151)	100.0 (135)

Table 2b: Treatment broken down by stage for the screening arm of ERSPC

Treatment	Screening arm								
	Organ confined disease			Advanced disease			Metastatic disease		
	Initial round	2nd round	3rd round	Initial round	2nd round	3rd round	Initial round	2nd round	3rd round
	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)	% (No.)
Hormone and radiotherapy	3.3 (65)	7.1 (150)	9.1 (96)	6.9 (23)	32.7 (33)	45.8 (24)	4.7 (4)	9.0 (8)	2.8 (1)
Hormone therapy alone	3.8 (76)	5.5 (116)	6.1 (64)	15.9 (53)	25.5 (25)	22.9 (12)	81.2 (70)	70.5 (58)	80.6 (32)
Radiotherapy alone	26.0 (518)	24.9 (524)	17.2 (180)	56.2 (188)	26.5 (26)	8.3 (4)	4.7 (4)	5.1 (4)	-
Surgery and hormone therapy	1.9 (38)	0.9 (20)	0.3 (3)	0.6 (2)	1.0 (1)	6.3 (3)	-	1.3 (1)	5.6 (2)
Surgery and radiotherapy	0.1 (1)	0.1 (3)	-	0.3 (1)	-	-	-	1.3 (1)	-
Surgery alone	47.6 (947)	36.1 (757)	31.1 (326)	18.3 (61)	12.2 (12)	8.3 (4)	4.7 (4)	7.7 (6)	5.6 (2)
Expectant management	17.0 (337)	25.0 (526)	35.9 (376)	1.8 (6)	2.0 (2)	8.3 (4)	4.7 (4)	5.1 (4)	2.8 (1)
Other treatments	0.3 (7)	0.3 (5)	0.3 (3)	-	-	-	-	-	2.8 (2)
Total	100.0 (1989)	100.0 (2101)	100.0 (1048)	100.0 (334)	100.0 (99)	100.0 (51)	100.0 (86)	100.0 (82)	100.0 (40)

(19%). In the screening arm, at the third screening round, expectant management was most commonly applied (33%) and followed by surgery (30%) and radiotherapy (16%).

The comparison of treatments applied between the control and the screening arm showed that the changes over time regarding expectant management (increasing) and the combination of hormone therapy and radiotherapy (increasing) and the decreasing proportion of surgery and radiotherapy were similar. A difference was seen in the frequency of the combination of hormone and radiotherapy and hormone therapy. These therapies are being more frequently applied in the control arm during the study period. The proportion of men treated with hormone therapy was on average 22% in the control arm versus 8% in the screening arm. The combination of hormone therapy and radiotherapy was chosen in 17% of cases in the control arm versus 7% of cases in the screening arm on average.

Tables 2a and 2b show treatment broken down by stage for the screening arm and the control arm, respectively. Both trial arms showed an increase over time of expectant management and the combination of hormone therapy and radiotherapy in both organ confined and advanced disease.

First, surgery was the most applied treatment in organ confined disease for both trial arms. Surgery remained the most applied treatment for the control arm, but changed into expectant management for the screening arm in the third screening round.

In advanced disease radiotherapy was the most common treatment at initial screening and the combination of hormone therapy and radiotherapy in the third screening round. In the control arm hormone therapy was the most applied treatment during the whole observation period.

Hormone therapy was the most common applied treatment in metastatic disease during the whole observation period in both trial arms.

Discussion

In this report based on data of the ERSPC, tumor characteristics (stage and grade) at diagnosis and applied treatments of prostate cancers detected in men randomized to the screening or control arm were inventoried over a period covering the years 1994-2006.

During the study period especially the clinical T stage of prostate cancers detected in the control arm showed a more favorable distribution over time. This is most likely a direct consequence of the increasing rate of opportunistic PSA screening in the control arm of ERSPC. Beemsterboer et al. found an opportunistic testing rate in the control arm of 7.6% per year in the first 1.5 years after randomization (ERSPC, Rotterdam section) [12]. Otto et al., also using ERSPC Rotterdam data, found that after 3 years of follow-up, 20.2% of men in the control arm had had at least one PSA test as compared to 14.1% opportunistic PSA testing in the screening arm [10]. In other ERSPC centers the rate of opportunistic screening in men randomized to the control arm varied from 6.7% up to 36% [13].

At the beginning of the study period surgery and endocrine therapy were most frequently applied in prostate cancers detected in the control arm. At the end of the study period the combination of endocrine therapy and radiotherapy and expectant management were seen relatively more, but surgery and endocrine therapy remained the most common treatments. These changes in treatment are most likely due to (a) the observed change in tumor characteristics, (b) ageing of the cohort (more expectant management), mean age at diagnosis (table 2) and (c) positive results for adjuvant or neoadjuvant hormone therapy in addition to radiotherapy in locally advanced prostate cancer [14]. Cooperberg et al. found that in the U.S. the majority of patients younger than 60 years with low-risk cancers (i.e. PSA at diagnosis $\leq$10.0 ng/ml, biopsy Gleason <7 and clinical stage T1 or T2a) received radical prostatectomy. With increasing age, like in our study cohort, this proportion dropped rapidly, whilst endocrine therapy and expectant management increased with advancing age [15]. In older patients (>65 years) diagnosed with these low-risk tumors diagnosed in the years 1989-2001, expectant management was relatively uncommon. Most patients received radiotherapy or endocrine therapy [16]. Wolters et al. compared all treatments applied in both arms of the ERSPC during the median follow-up period of 9 years and found that PSA at diagnosis, age and clinical T stage are the most important factors in treatment choice [9]. But whereas that study focused on differences in treatment in screening and control arm, our aim was to describe change of treatment over time taking into account stage at time of diagnosis.

Men diagnosed with prostate cancer in the screening arm had more favorable prognostic factors than those cases in the control arm when comparing time periods side by side. During the total observation period, mean age at diagnosis was 66.2 years for those men randomized to the screening arm versus 67.7 years for men in the control arm. In the screening arm organ confined disease was more frequent (92% versus 80% in the control arm) and also a larger proportion of low-grade tumors (72% versus 54%

in the control arm) were observed. Endocrine therapy was offered much more often in the control arm (22% versus 8% in the screening arm) and surgery and expectant management more often in the screening arm 37% versus 28% in the control arm for surgery and 21% versus 15% in the control arm for expectant management. These observations are in line with other studies comparing the tumor features and applied treatments of screen detected and clinically diagnosed prostate cancer [4,5,17-19].

However, when comparing tumor characteristics of the last period (2003-2006) in the control arm with tumor characteristics of cancers detected at the initial screening round we observed similarities. The proportion of T1c tumors in the control arm was 50% in the last period whilst 48% of the cancers detected at the initial screening round were staged as T1c, pointing to more screening activities in the control arm over time.

Despite the fact that the ERSPC cohort is a closed and thus ageing cohort, prostate cancer was detected more often in an early stage in the control arm. Our data showed that the proportions of organ confined disease in the control arm were 73.1% in 1994-1998 and 83.7% in 2003-2006. Advanced disease reduced from 26.9% to 16.4%. This is in line with the study of Cremer et al. [20] describing the situation in the Dutch population, using incidence data. They also report an increase in detection of early stage disease, leading to a decrease of metastatic prostate cancer and a lower mortality rate and increased survival [20].

The decrease of Gleason >7 prostate cancers in the control arm (from 21.3% towards 16.8%) should be interpreted with caution due to the so-called Will Rogers Phenomenon. However, the statistical artefact of Gleason score reclassification results in higher Gleason score readings between 1992 and 2002; strengthening our observation of decreasing high grade tumors in the control arm over time [21].

The comparison of prostate cancers detected at the initial screening round with those cases detected at repeat screening rounds showed a remarkable stage and grade shift in favor of the repeat screening rounds. These observations were reported earlier. In two subsequent screening rounds, advanced disease reduced from 19% to 4% and tumors with Gleason scores >7 decreased from 8% to 3% in the Dutch center [8]. Sweden also reported that PSA screening rapidly cause a stage shift, which leads to only detecting low-stage and also low-grade malignancies [19].

In conclusion, the earlier reported favorable stage and grade shift as a result of screening is confirmed with longer follow-up data. Also, the tumor characteristics of prostate cancers found in the control arm of the ERSPC showed a favorable shift over time. The

stage and grade shift coincided with a change of treatment reflected in an increasing occurrence of expectant management as initial treatment. The tumor characteristics of prostate cancers detected in men in the control arm become, with advancing time, more comparable to prostate cancers detected in the initial screening round. These observations point towards an increasing rate of opportunistic testing in men randomized to the control arm. We propose that future studies perform a survival analysis in different time periods after randomization in the control arm of the ERSPC.

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Conflicts of interest statement

None declared.

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Chapter 3

PSA-based prostate cancer screening: the role of active surveillance and informed and shared decision making

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Abstract

Since the first publication describing the identification of prostate-specific antigen (PSA) in the 1960s, much progress has been made. The PSA test changed from being initially a monitoring tool to being also used as a diagnostic tool. Over time, the test has been heavily debated due to its lack of sensitivity and specificity. However, up to now the PSA test is still the only biomarker for the detection and monitoring of prostate cancer. PSA-based screening for prostate cancer is associated with a high proportion of unnecessary testing and overdiagnosis with subsequent overtreatment. In the early years of screening for prostate cancer, high rates of uptake were very important. However, over time the opinion on PSA-based screening has shifted towards the notion of informed choice. Nowadays, it is thought to be unethical to screen men without them being aware of the pros and cons of PSA testing, as well as the fact that an informed choice is related to better patient outcomes. Now, as the results of three major screening studies have been presented and the downsides of screening are becoming better understood, informed choice is becoming more relevant.

Introduction

The incidence of prostate cancer (PC) is rising in most Eastern and Western countries. In Europe the disease affects approximately 225.000 men each year [1]. The increase can be explained by the increasing overall life expectancy of men, the increasing number of biopsies and cores per biopsy, and most importantly, the increasing use of prostate-specific antigen (PSA) measurements as a screening test [2].

The first publication describing PSA appeared in 1960 [3]. Difference of opinion exists as to who should be credited for its discovery, as different groups isolated the same protein simultaneously [4]. In 1986, the American Food and Drug Association approved the PSA as a test to aid in the management of patients diagnosed with PC. In 1994, the PSA test was approved by the American Food and Drug Association as a diagnostic tool which can be used, for instance, for the early detection of PC [4]. Throughout the years, it became clear that the use of the PSA test in a screening setting has both advantages and disadvantages. The published results of the European Randomized study of Screening for Prostate Cancer (ERSPC) [5], the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial [6], and the Göteborg randomized population-based PC screening trial [7], all initiated in the early 1990s, provide evidence on whether PSA testing is beneficial. The data from the three studies point towards a disease-specific mortality reduction due to screening , as well as the fact that screening by using a PSA test leads to overdiagnosis and therefore overtreatment [5-7]. The apparent controversial outcomes – with on the one hand a mortality reduction and on the other hand overdiagnosis and overtreatment – have motivated some professionals (i.e. primary care providers and/or urologists) to strongly recommend against PSA testing and some to strongly advise in favor of testing. Very few professionals truly inform men about the pros and cons of the PSA test [8]. Because more specific biomarkers are still lacking, the most commonly used screening test remains the serum PSA test. Disadvantages of the PSA test are the false-positive and false-negative results. A false-negative result can create uncertainty, while false-positive tests may lead to unnecessary additional testing [9,10]. At the same time, men feel pressured or even encouraged by family members, friends or media to consider PSA testing [8,11,12]. In the light of the confusing situation that has occurred, informed decision making about whether a man should or should not get tested seems more needed than ever.

Incidence and mortality of PC

Different incidence and mortality rates for PC are found around the world (table 1). It appears that Asia has the lowest incidence and mortality rates, while the highest rates are nowadays found in the United States [13]. After the introduction of the PSA test, the incidence of PC increased drastically. Recent data from the US Surveillance, Epidemiology and End Results program confirm this; new cases of PC have increased substantially in 1975-2005. The introduction of the PSA test led to a steep increase in PC incidence. Over time incidence declined; however, incidence rates did not retain to the level that was seen before the introduction of the PSA test. If this would reflect a true increase of the disease, it should be accompanied by an increase in disease-specific death rates, which is not the case. In fact, the mortality rates for PC declined during this period [14]. As the increase in incidence and mortality rates does not appear simultaneously, another explanation has to be found. According to Murphy et al. [15], the trend can be explained by the large stage shift from palpable and locally advanced disease to impalpable and localized disease. Due to PSA-based screening for PC, increasing numbers of patients with low-risk tumors (with low risk for both metastasis and mortality) are being detected [1]. These potentially clinically insignificant PCs (PSA < 10 ng/ml, stage ≤T2a disease and Gleason ≤6) [16,17] would not have been diagnosed without screening and may not lead to symptoms or death during the patient's lifetime. Within the screening arm of the ERSPC (section Rotterdam, the Netherlands), 27-56% of all cancers detected in men aged 55-75 years can be classified as potentially overdiagnosed [18].

Table 1: Age-standardized incidence (world standard population) and mortality rates for prostate cancer in Asia, Europe and America, 2002 estimates.

World region	Incidence per 100,000	Mortality per 100,000
Eastern Asia	3.8	1.9
South Central Asia	4.4	2.8
South-Eastern Asia	7	4.5
Western Asia	10.9	6
Eastern Europe	17.3	9.7
Southern Europe	35.5	13.2
Northern Europe	57.4	19.7
Western Europe	61.6	17.5
Central America	30.6	15.5
South America	47	18
Northern America	119.9	15.8

Data source: Globocan – Cancer incidence, mortality and prevalence worldwide, 2002 [13].

Overtreatment

The ERSPC reported in March 2009 that PSA-based screening reduced the rate of death from PC by 20% in the intention to screen analysis. However, this mortality reduction was associated with a high risk of overdiagnosis and overtreatment [5]. Overtreatment means that men with overdiagnosed tumors, which would not have caused any symptoms during a man's lifetime if they had remained undiagnosed, are subject to unnecessary costly and invasive treatment [2]. Despite their indolent character, these low-risk tumors are often actively treated, resulting in so-called overtreatment [19]. Within the first round of the ERSPC (section Rotterdam), e.g. 293 out of 1014 men with detected PC could be classified as potentially overdiagnosed or 'indolent' and were eligible for active surveillance (AS). It turned out that in only 64 out of the 293 men an initial AS strategy was chosen [20]. The question thus arises how to deal with overdiagnosis and overtreatment more effectively. A specific biomarker for potentially life-threatening disease would probably solve a large part of the problem; however, no such biomarker is currently available. It is claimed that AS provides a realistic strategy to avoid overtreatment by surgery or radiation therapy. AS starts with a selection process in which men with favourable disease-specific prognoses are included. The age of a patient and his estimated life expectancy play an important role. Radical treatment is withheld and replaced by closely monitoring the disease [21]. If progression occurs, curative treatment is indicated. The criteria for switching from AS to delayed curative treatment are based on both medical and non-medical aspects. A benefit of AS can be the delay of active treatment, including avoidance of possible side effects and the delay of complications for a few years [22]. However, the psychological aspects of AS should not be ignored during the period of close monitoring. These include the anxiety of being too late for curative treatment.

Active surveillance

AS is subject of ongoing studies since the 1990s. Klotz et al. [23], Carter et al. [24,25], and Kakehi et al. [26] have all initiated studies regarding the value of AS (table 2). Klotz et al. [23] reported on the long-term clinical results of a large, AS cohort with localized PC at the beginning of 2010. The cohort consisted of 450 patients with a median age of 70.3 years and a median follow-up of 6.8 years. Klotz et al. [23] reported that among the 450 patients, 97 patients died (21.6%) and 353 were alive (78.4%). The 10-year overall survival was 68% (95% CI, 62-74%). There was no difference in overall survival between the patients who remained on surveillance and those who were reclassified and treated radically. The reported 5- and 10-year cancer-specific survival rates were

99.7% and 97.2% for AS and active treatment respectively. In the study period, five PC-related mortalities occurred; all in men who had been reclassified as higher risk and who were offered radical treatment. Radical intervention was undertaken in three of the five patients (radiation n=2, prostatectomy n=1). The two other patients refused treatment. Klotz et al. [23] conclude that after a mean follow-up of 6.8 years only a single patient died after a relatively prolonged period of observation (>2 years) and subsequently experienced progression. Main reasons for discontinuing AS involve: short PSA doubling time (65/135, 14% of men of the total cohort) and grade progression (36/135, 8% of men of the total cohort). Carter et al. [25] reported in 2007 that out of the 407 men included in the program on expectant management (i.e. the careful selection and monitoring of older men considered to have low-risk disease with the intention to cure if the disease progresses [25]), 239 (59%) men remained on AS at a median follow-up of 3.4 years (0.43-12.5). A total of 103 (25%) men underwent curative intervention at a median of 2.2 years after diagnosis (0.96-7.39), 45 (11%) men withdraw from the program, 12 (2%) men were lost to follow-up and 8 (3%) men died of causes other than PC. Reasons for withdrawal of the 45 men are not mentioned. Regarding the men who underwent curative intervention, older age at diagnosis (p=0.011) as well as an earlier date of diagnosis (p=0.001) was significantly associated with curative intervention. It should be noted that the Johns Hopkins approach for selecting and monitoring men differs from that reported by Klotz et al. [23] and can be considered to be more conservative, i.e. a smaller amount of T2 cancers are included in the Johns Hopkins program. Kakehi et al. [26] reported the first prospective study on AS in Japanese patients where PC was detected using only a PSA elevation. The study included 134 men;

Table 2: Criteria for active surveillance

Klotz et al [23]
1. Gleason ≤ 6
2. PSA ≤ 10 ng/mL
3. Stage T1b to T2b N0M0
4. Patients older than 70 years with PSA ≤ 15 ng/mL or Gleason ≤ 3 + 4
Carter et al [24,25]
1. PSAD* ≤ 0.15 ng/ml/cm³
2. Stage T1c
3. Favourable biopsy characteristics, i.e. Gleason ≤ 6 with no Gleason pattern grade 4 or 5, no more than 2 cores positive for cancer, and no more than 50% of any 1 core involved with cancer
Kakehi et al [26]
1. Age ranging between 50-80
2. Initial serum PSA of ≤ 20 ng/ml
3. Number of positive core being one or two per 6-12 systematic biopsy cores
4. Gleason score ≤ 6
5. ≤ 50% cancer involvement in any of the positive cores

* PSAD – PSA before diagnosis divided by prostate volume determined by transrectal ultrasound measurement

of whom 118 chose the AS program and 16 chose immediate curative treatment at enrolment. Up to 31 October 2006, no manifestation of metastasis or cancer death was observed in any of the participants. Three men died due to other disease, while five men were lost to follow-up [26]. Of the 118 patients who chose AS as initial treatment, 54 (46%) remained on AS for the maximal observation period of 54 months. Reasons for discontinuing AS were: a PSA doubling time $\leq$ 2 years (17/65), pathology progression (16/65), change in T-stage (1/65), patient's preference (15/65) and comorbidities (8/65). For seven men who discontinued AS, reasons are unknown. Kakehi et al. [26] reported that during the observation period, no serious adverse events were observed: not in the AS program group and not in those men who chose immediate treatment.

Prostate cancer Research International: Active Surveillance (PRIAS) study

Within the ERSPC (section Rotterdam, the prospective, observational PRIAS study has been initiated as a decision aid for the urologists managing their patients with AS and at the same time with the aim of validating this management [2]. It is an entirely web-based study. Potential patients can retrieve study information from the website (www.prias-project.org). Inclusion and follow-up data of patients can be entered in on the website after an urologist has gained access to the secured parts of the web tool. When data of a follow-up visit are entered, the website presents a graph survey of the PSA measurements and the PSA doubling time. On the basis of the follow-up criteria, a recommendation will be presented to the urologist on whether the patient should continue on AS or whether to discontinue and opt for active treatment. So, besides being a helpful tool for urologists in daily clinical practice, the website supports in clinical practice by providing decision points during AS.

By defining inclusion and follow-up criteria (table 3), the PRIAS study is attempting to select men with insignificant, organ-confined tumors who have a favorable prognosis. Other arguments in choosing AS include age, quality of life issues, ethical aspects and costs associated with treatment [27]. Currently, the PRIAS study is applied in several medical centers across the Netherlands, as well as in other European countries, the United States, Canada, Japan and Australia. The initiators and participating centers of the PRIAS study hope to provide a highly needed evidence-based guideline for AS in PC to prevent overtreatment [2].

Table 3: Inclusion and follow-up criteria for the PRIAS study [19]

Inclusion
1. Men should:
• have histologically proven adenocarcinoma of the prostate
• be fit for curative treatment
• be willing to attend the follow-up visits
• not have received former therapy for prostate cancer
2. Clinical stage is T1C or T2
3. Gleason score is ≤6 and ≤2 biopsy cores are invaded with prostate cancer
4. PSA is ≤10 ng/ml and PSA density is ≤0.2 ng/ml/ml
Follow-up
1. The patient is content with active surveillance
2. Clinical stage remains <T3
3. Gleason score remains ≤6 and ≤2 of the repeat biopsy cores are invaded with prostate cancer
4. PSA doubling time is favorable and remains longer than 3 years

PRIAS: Prostate cancer Research International: Active Surveillance study
PSA: prostate-specific antigen

PRIAS – results so far

Currently, worldwide over 1500 patients are included in the PRIAS study. The first study interim analysis is based on the initial 500 study inclusions. These patients were included between December 2006 and July 2008 with a median follow-up time of 1.02 year (IQR (interquartile range) 0.6-1.5 years) [19]. The 2-year active therapy-free survival rate accounted for 73%. Eighty-two men changed to active therapy during follow-up; 83% (68/82) did so on protocol basis. The other 17% of the men who switched to active therapy did so because of anxiety and/or upon request. Two hundred and sixty-one repeat biopsies were available for analysis of which 34% showed no cancer, while 22% showed a Gleason score >6 or >2 positive biopsy cores. In 53% (102/194) of men with favorable biopsy results, a relatively unfavorable PSA doubling time of 0-10 years was seen. For men with an unfavorable biopsy result this percentage amounted to 62% (33/53). Seventeen percent (4/24) showed T3 disease after radical prostatectomy and 50% showed a Gleason score of >6. This compares favorably to the results of Klotz et al. [23]. Overall, the authors stated that AS is a feasible strategy in avoiding overtreatment on the short term. When applying the strict PRIAS inclusion and follow-up protocol the result is that one out of four men who start on AS switch to active therapy within 2 years after diagnosis [19].

The PRIAS study is still young and further follow-up data need to be obtained and analyzed. However, the first results look promising.

Several studies show that a program of careful selection and monitoring of men who are likely to harbor clinically insignificant cancers is a rational alternative to active treatment.

The value of AS alone is still under study; however, it is not clear how AS performs in a combined approach (i.e. which treatment can be best chosen if a man with a clinically insignificant PC presents). The Surveillance Therapy Against Radical Treatment trial is aiming at answering such a question. It is a large randomized controlled trial in which standard treatment with surgery or radiation will be compared against AS [28]. The trial is currently recruiting participants.

Quality of life aspects with AS

As the clinical features of AS studies look hopeful, the quality of life aspect should definitely be taken into account. Due to screening, low-risk cancers are diagnosed that would not have been detected during the man's lifetime in the absence of screening. Men who underwent screening are confronted with having cancer. By offering AS they could feel like no treatment is offered at all and they have to face the fact that they are living with cancer. This thought, but also the fear of disease progression, can cause psychological problems.

Results from the PRIAS trial

Van den Bergh et al. [29-31] assessed the impact of AS on the quality of life of men participating in PRIAS. Van den Bergh firstly looked at the level of knowledge of PC and the perception of AS in men on AS [29]. It could be that patients perceive AS as a complex or contradictory treatment strategy, especially if these men are lower educated. Perception of the disease is an important aspect of treatment satisfaction. If men have a wrong perception of AS, treatment will most probably not be satisfactory. Hundred and fifty men who were recently diagnosed with PC received a questionnaire containing a 15-item measure on general knowledge of PC, an open-ended question on the most important advantages and disadvantages of AS and questions on the specific perception of AS. It was hypothesized that younger and higher-educated men showed higher knowledge scores. Van den Bergh et al. [29] reported that the patients included in the cohort had an adequate knowledge of PC and realistic expectations of AS. No true misconceptions on AS were identified.

Van den Bergh et al. [30] initiated a study regarding the levels of anxiety and distress among men on AS who were living with 'untreated' cancer. These possible feelings of anxiety and distress were quantified in a questionnaire using the decisional conflict scale (DCS), a measure for generic anxiety (STAI-6), depression (CES-D), PC-specific anxiety (MAX-PC), physical health (SF-12 PCS), personality (EPQ) and shared decision making. Hundred and fifty men received a questionnaire, of which 129 men responded by send-

ing the questionnaire back (response rate of 86%). The majority of men included in this protocol-based program for AS showed favorable anxiety and distress scores in comparison with reference values and to groups of patients with PC who underwent other types of treatment [30]. It turned out that some aspects, such as a poor physical health, high PSA levels and a high neuroticism score, were associated with one or more of the CES-D, STAI-6, DCS and MAX-PC scores. A neurotic personality is therefore associated with unfavorable scores. After 9 months, the 129 men who filled in the first questionnaire received a second questionnaire. The aim was to investigate whether the levels of anxiety and distress among patients on AS changed over time. The response rate regarding the second questionnaire amounted to 90%. Men with low-risk PC who started and remained on AS during 9 months, remain to have favorable levels of anxiety and distress. Only 2/129 men (2.6%) discontinued AS because of non-medical reasons.

Other results

Whereas Van den Bergh et al. [30,31] reported very favorable levels of anxiety and distress among men under AS, Wallace [32] reported that men undergoing watchful waiting (i.e. initial surveillance followed by active treatment if and when tumour progression produces symptoms [32]) were uncertain. This uncertainty results in or from their perception of danger and therefore influences men's quality of life. Latini et al. [33] reported that treatment decisions were influenced by cancer anxiety and that more psychological support should be provided to men. Patel et al. [34] found, in an evaluation of men undergoing AS, that 8% of men with no evidence of cancer progression were given active treatment because they had significant anxiety about the possibility of progression and about living with cancer. These results point towards the need of appropriate teaching and management interventions to alleviate anxiety.

Van den Berg et al. [29] reported that men on AS had adequate knowledge of PC. Avery et al. [35] reported that while most men found PSA testing and biopsy acceptable, their perception of risk were not always accurate. It should be stressed to men that the lack of relationship between the risk of PC and urinary symptoms is essential; urinary symptoms are more likely to indicate benign rather than malignant prostate disease. Next to that a two-stage information process may also be necessary to overcome barriers at both PSA testing and prostate biopsy. The provision of more tailored information on the one hand improves PC knowledge, while on the other hand it helps to facilitate informed decision making.

Furthermore, few studies regarding quality of life in men undergoing AS have been performed. Even fewer studies have measured utilities for AS health states. Utilities derived from Dale et al. [36] were used by Hayes et al. [16] in a modeling study. They

concluded that under a wide range of assumptions AS is a reasonable approach for a 65-year-old man with low-risk PC. Hayes et al. [16] performed a decision analysis to assess the quality-adjusted life expectancy of AS compared with initial definitive treatment with radical prostatectomy, intensity-modulated radiation therapy or brachytherapy. The authors reported that AS was the most effective strategy, with intensity-modulated radiation therapy for progression. The most effective strategy was defined as the strategy that was associated with the highest quality-adjusted life expectancy. AS provided 6 additional months of quality-adjusted life expectancy as compared to brachytherapy, i.e. the most effective initial treatment. However, it should be taken into account that the model is based on individual patient utilities and that the decision analysis only modeled outcomes for 65-year-old men.

Shared decision making

In the light of the above and taking into account that PSA is still the most important pillar for diagnosing PC, it is important to enhance informed and shared decision making [37-39]. According to Marteau, an informed choice can be described as 'a choice that is based on relevant knowledge, consistent with the decision maker's value and behaviorally implemented' [40]. Marteau [40] describes that at the beginning of the twenty-first century screening was largely viewed as a public health activity which was aimed at reducing disease prevalence. To achieve this, the emphasis has been upon high rates of uptake, and not upon an informed choice. Throughout the years, a shift in emphasis towards informed choice has occurred [40]. Several considerations reflect this shift. First, it reflects an increasing recognition of the fact that it is unethical for individuals not to be informed of the consequences of medical interventions. Men undergoing a PSA test should be made aware of the consequences that the PSA test could have on their lives. It is not just the pros and cons of the PSA test that should be weighted. Second, it reflects a belief that an informed choice is associated with better patient outcomes, as compared to an uninformed choice. Finally, the concern that failure to appreciate the consequences of screening may result in litigation has also resulted in the emphasis towards an informed choice. As PC screening is available to more men nowadays, it is important to raise awareness around an informed choice. Earlier it was already described that the PSA test is currently the most commonly used screening tool for PC [41]. However, the PSA test has both strengths and weaknesses. Men deciding to undergo PSA testing should be aware of both, which enables them to make a choice that is consistent with their individual values. It is also important for men to be informed about further medical consequences. If a PSA of $\geq$3 ng/ml is measured, in most cases a prostate biopsy will be recommended [5]. Nijs et al. [42] reported that the idea of

undergoing a prostate biopsy already caused anticipated pain and discomfort. Zisman et al. [43] found that undergoing a prostate biopsy can have an impact on the patient's well-being due to causing pain and anxiety. Macefield et al. [44] reported that although most men coped well with undergoing a biopsy, a minority experienced elevated distress at the time of biopsy and after receiving a negative result. The authors stress that men should be informed of the risk of distress that is related to diagnostic uncertainty before consenting to PSA testing and possibly undergoing a biopsy.

While uncertainties persist around screening for PC using a PSA test, combining informed decision making with shared decision making seems a logical step. If patients are able to make an informed choice, it is certain that their choice balances their personal values. By also recommending shared decision making, the professional and the patient will share information, jointly participate in the decision making and agree in a course of action that incorporates the patient's personal preferences [45].

In general, decision aids help men make an informed decision about a number of preventive measures and treatments [8]. Throughout the years, several aids have been developed specifically to address PSA testing [8,46-52]; all showing a positive effect on informed decision making. O'Connor et al. [51] lists several elements which should be enhanced in a good decision aid: (i) improve knowledge of the problem, options and outcomes; (ii) create realistic expectations of outcomes; (iii) clarify personal values for outcomes; (iv) promote congruence between values and choice; (v) reduce decisional conflict; (vi) promote implementation of choices; and (vii) improve satisfaction with decision making.

In an evaluation study of decision points provided with the paper version of a risk indicator the value of informed decision making has been assessed [41]. Two questionnaires were sent to a random sample of 2000 men, age 55-65 years. An informed choice in this study was defined as 'relevant knowledge about the PSA test, a positive attitude towards a PSA test, and undergoing a PSA test'. A man also makes an informed choice if he has relevant knowledge about the PSA test, has negative attitude towards the test and does not undergo it. Other combinations reflected an uninformed choice. Van Vugt et al. [41] reported that significantly more men met the requirements of an informed choice after receiving information on PC and after receiving an individualized risk estimate made possible with a PC risk calculator: 81/535 men (15%) at the first versus 174/522 (33%) at the second assessment ($p<0.001$).

Volk et al. [53] reported that decision aids, focused on PC screening, showed a long-term effect on screening behavior and also promoted informed decision making.

As shared decision making is being engaged in several major guidelines (American Urological Association, American Cancer Society and the US Preventive Services Task Force) [45], the question rises whether shared decision making is applied effectively in practice. Several studies confirm that shared decision making is applied in practice [45,53-55]; however, it appears that discrepancies exist between the preferred role and the actual role of patients in the decision-making process [56]. Men are becoming more active in the decision-making process, as the study by Davison and Degner [57,58] (32% of men wanting their physician to make the final decision, versus 58% of men in a similar conducted study 5 years earlier) shows. However, in general it is still the doctor who sets the agenda and who decides how much information is presented to the patient [56]. Whether effective shared decision making is reached, is affected by the willingness of the urologist to involve the patient in the decision-making process.

Conclusions

Throughout the years, the knowledge on PSA and the PSA test has increased. However, that has not led to an unambiguous trust in the PSA test. The sensitivity and specificity of the PSA test are not optimal. Since no other prostate-specific biomarker is currently available, the PSA test will stay the most important diagnostic tool in both clinical and screening settings. Several screening studies, all using the PSA test as a diagnostic tool, have provided evidence regarding the efficacy of screening. Screening can lead to a disease-specific mortality reduction; however, it is currently also associated with overdiagnosis and overtreatment. AS seems a realistic strategy in avoiding overtreatment. AS is the subject of several ongoing studies, of which the results look promising.

It is important to enhance shared and informed decision making, because on the one hand the pros and cons of PSA testing should be clear to men who wish to be screened. On the other hand, informed and shared decision making can play a role when choosing a treatment strategy, especially when there are more options.

Suggestions for the future

Since Steginga et al. [59] reported that an informed choice about PSA testing was the exception rather than the rule, and since the advantages for patients have been documented by now, more urologists should enhance informed and shared decision making in clinical practice. Many men are tested without a preceding discussion or even because PSA is included in routine lists of laboratory tests. In the United States current guidelines

recommend that PC screening should be discussed with patients and that a PSA test should be provided to those men who decide to be tested [60-62]. However, if a man is not aware of the pros and cons of the test, as well as the consequences the result of the test can have, the doctor deciding for them does not seem justifiable, since decision making should balance personal values. A doctor can help in making such a decision; however, he should not make the decision himself unless asked.

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Part II

Active surveillance for low-risk prostate cancer

Chapter 4

Active surveillance: oncologic outcome

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Abstract

Purpose of review. To give insight into recent literature (during the past 12-18 months) reporting on oncologic outcomes of men on active surveillance.

Recent findings. From recent published trials comparing radical prostatectomy vs. watchful waiting we learn that radical treatment only benefits a small proportion of men and that a substantial part of men is overtreated. Therefore, active surveillance should aim at postponing treatment for most, but still generate the same disease-specific mortality as radical prostatectomy by treating only those who benefit. In this review some recent published data on prostate cancer-specific mortality under active surveillance as well as intermediate outcomes are described.

Summary. Prostate cancer-specific mortality under active surveillance is very low, however, longer follow-up is warranted. When deferred radical treatment and immediate radical treatment are compared, results seem to be quite similar, suggesting that postponing treatment does not affect the outcomes of men under active surveillance. Furthermore, in the majority of men active treatment could be avoided completely, without compromising oncologic outcome.

Introduction

Since the introduction of prostate-specific antigen (PSA) in the mid-1980s, a lot has changed in the world of prostate cancer. As a result of the embracement of PSA as a biomarker for the early detection of prostate cancer, a sharp increase in the incidence of prostate cancer was seen. Later on in time, after the prevalent cases were diagnosed and treated and the median volume of prostate cancer in newly diagnosed patients began to fall, a dramatic increase in the number of patients with low-risk disease, that is a prostate cancer never leading to symptoms or death irrespective of patients' comorbidities or expected life span, was seen [1]. Here lies one of the key challenges in the management of prostate cancer; low-risk disease is very common [1-2]. Autopsy studies have shown that for men of age 60 years, cancerous cells can be found in 30-40% of the prostates [3], rising to 60-70% by the age of 80 years [4], although the eventual risk of death from prostate cancer is only about 3% [3]. Meanwhile randomized prostate cancer studies were initiated and have shown a positive effect of screening, with a reduction of the disease-specific mortality in the screening arm as compared with the control arm [5-6]. However, the related overdiagnosis and subsequent overtreatment evolving from PSA based prostate cancer screening have made that population-based screening is not (yet) a worldwide accepted strategy.

Up to now there are no biological or clinical parameters available that distinguish low risk from potentially aggressive prostate cancer. With the introduction of active surveillance as management strategy for low-risk prostate cancer, it is attempted to balance the risks of the disease vs. the risks of treatment. Active surveillance aims to avoid overtreatment by initially withholding radical therapy. The tumor is closely monitored with the possibility to switch to active therapy with curative intent when progression occurs [7]. Several active surveillance programs have been initiated worldwide, all with the aim to establish active surveillance as a proven treatment option and to determine the optimal selection and surveillance criteria for men on active surveillance. The purpose of this review is to give insight into oncologic outcomes of prostate cancers managed with active surveillance.

Differences in mortality between radical prostatectomy vs. watchful waiting

In 2011 and 2012 the results of the randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4 trial) and the Prostate Cancer Intervention versus Observation Trial (PIVOT trial) were published [8*-9*]. Bill-Axelson et al. [9*] reported that radical

prostatectomy was associated with a reduction in prostate cancer death of 38% as compared to watchful waiting (i.e. receiving no immediate treatment apart from transurethral resection in case of local progression [10]), after a median follow-up of 12.8 years. In the radical prostatectomy group 55 of 347 men (16%) died because of prostate cancer. In the watchful waiting group 81 of 348 men (23%) died because of prostate cancer. In contrast, Wilt et al. [11] reported on the PIVOT trial that among men with localized prostate cancer, radical prostatectomy did not significantly reduce prostate cancer mortality as compared to observation (i.e. watchful waiting with delayed palliative intervention upon disease progression) through at least 12 years of follow-up [8*]. Radical treatment was beneficial only for subgroups of men with more aggressive tumor features.

If looked at low-risk patients, Bill-Axelson et al. [9*] reported a non-significant difference in prostate cancer death of 14% and 8% in the watchful waiting and radical prostatectomy group, respectively (low-risk defined as PSA < 10 ng/ml and Gleason score < 7 or WHO grade 1). Most men were, however, diagnosed in the pre-PSA era. Wilt et al. [8*] reported lower rates of prostate cancer death for men with low-risk prostate cancer according to the D'Amico criteria (PSA < 10 ng/ml, Gleason score < 7 and clinical stage < T2b) of 3% and 4% for the observation and radical prostatectomy groups, respectively.

Both studies seem to contradict in what they conclude, that is surgery being beneficial over watchful waiting in the SPCG-4 trial and radical prostatectomy not significantly reducing prostate cancer mortality as compared with observation in the PIVOT trial. What we can conclude from these studies is that radical treatment only benefits a small proportion of men with less favorable tumor characteristics and that a substantial part is overtreated. Therefore, active surveillance should aim at postponing treatment for most, but still generate the same disease-specific mortality as radical prostatectomy, by treating those who would benefit.

Prostate cancer mortality and active surveillance

Present studies on the value of active surveillance have reported low disease-specific mortality rates. In the Göteborg prostate cancer screening trial [12**] about half of all screen-detected prostate cancers were managed with active surveillance; a proportion that seemed to be stable throughout the entire study. The cohort of active surveillance patients consisted of 439 men with a median age at diagnosis of 65.4 years and a median follow-up of 6.0 years from diagnosis. Godtman et al. [12**] classified their

active surveillance patients according to the Epstein criteria as very-low-risk, low-risk, intermediate-risk and high-risk. Of all 439 men, 63% (277) continued on active surveillance throughout the entire study period. Of the 162 men who switched to deferred active treatment at some point during the study period; 106 were treated with radical prostatectomy, 32 with radiotherapy and 24 with hormonal therapy. During follow-up 60 men died; 59 from other causes than prostate cancer. One individual in the intermediate-risk group died after having received hormonal therapy 8.6 years after active surveillance. He developed distant metastases and died of prostate cancer 12.7 years after diagnosis [12**].

Klotz [1] reported on a Canadian study initiated in 1995. This prospective, single arm cohort study was initiated to assess the feasibility of an active surveillance protocol with selective delayed intervention. This cohort consists of 450 patients with a median age of 70.3 years and a median follow-up of 6.8 years. Among the 450 patients 97 died (21.6%). The 5-year and 10-year disease-specific survival was 99.7% and 97.2%, respectively. Five men died of prostate cancer, all of which had been reclassified as higher risk and were offered radical treatment.

Bul et al. [13**] reported on the outcomes of the Prostate cancer Research International: Active Surveillance (PRIAS) study. In this worldwide active surveillance cohort, 2494 men were followed prospectively with a median follow-up of 1.6 years. In 1480 men one or more biopsies were performed; 415 (28%) showed reclassification. Overall, 1885 patients continued on active surveillance and 527 patients (21%) underwent active therapy. Of these 527 men, 387 (73%) underwent active therapy because of protocol-based reasons, 47 men (9%) switched because of anxiety and 93 men (18%) of other reasons. The disease-specific survival rate was 100%, and during follow-up 18 men died of causes other than prostate cancer.

Tosoian et al. [14**] reported on the outcomes of the Johns Hopkins active surveillance study. In total 769 men were followed for a median of 2.7 years. Deferred active treatment was given to 255 men (33.2%), of which 192 men had a follow-up after treatment of more than one year. During follow-up no prostate cancer death or metastases were found.

If we compare the outcomes of these studies, the results in terms of disease-specific mortality are promising. However, longer follow-up is needed to be able to evaluate the potential of active surveillance as an acknowledged management strategy.

From the article by Xia et al. [15] we learn that, even though empiric data have a too short follow-up, modeling data on prostate cancer mortality show promising results. The authors used a model to project prostate cancer mortality among contemporary low-risk cases on active surveillance, followed by radical prostatectomy if the disease progresses, and compared these projections with prostate cancer mortality had the cases received immediate radical prostatectomy [15]. The model projected that 2.78% of men on active surveillance and 1.64% of men with immediate radical prostatectomy would die of their disease in 20 years. On average, the model projected that men on active surveillance would remain free of treatment for an additional 6.4 years relative to men treated immediately. This modeling experiment shows that the performance of active surveillance is comparable to radical prostatectomy in terms of disease-specific mortality.

Intermediate outcomes

As active surveillance studies have a relatively short follow-up to compare disease-specific mortality, it may be worthwhile to evaluate the intermediate outcomes. Intermediate outcomes can be defined as, among others, PSA progression, local progression and metastases. To make a comparison between active surveillance and radical treatment we have looked at outcomes of radical treatment after an initial active surveillance strategy as compared with immediate radical treatment. By evaluating these outcomes we can determine how many men on active surveillance had worse outcomes and should perhaps have been treated earlier.

Bul et al. [16**] presented data from the PRIAS study. Of the 189 radical prostatectomy cases, pathology results were available for 167. Pathology results showed 134 organ-confined cases and 32 cases (19%) with extracapsular extension. Gleason scores 6 or less, 3+4, 4+3 and 8 were found in 79, 64, 21 and 3 cases, respectively. Unfavorable radical prostatectomy results (pT3-4 and/or Gleason score $\geq$4+3) were found in 49 patients (29%), of whom 33 (70%) had a biopsy-related reason for deferred radical prostatectomy.

Tosoian et al. [14**] and Dall'Era et al. [17] reported on the biochemical recurrence rate after active treatment. Of the 192 men who were treated actively and had a follow-up of more than 1 year in the Johns Hopkins study, 9.4% showed biochemical recurrence after a median follow-up of 2.8 years for men who underwent radiotherapy and 2.0 years for men who underwent radical prostatectomy [14**]. Dall'Era et al. [17] compared outcomes of immediate treatment (within 6 months of diagnosis) vs.

an initial active surveillance strategy followed by active treatment. In total, 233 men with low-risk prostate cancer (defined as PSA < 10 ng/ml, Gleason sum ≤ 6, absence of Gleason grade 4 or 5, cancer involvement of ≤ 33% of biopsy cores and ≤ 50% of any single core, clinical stage T1/T2) were on active surveillance. A total of 65 men (28%) underwent deferred treatment, 33 of which received radical prostatectomy after a median time on active surveillance of 18 months. At radical prostatectomy, 30% of patients were upgraded to at least a Gleason score 7 and 21% of men on active surveillance followed by radical prostatectomy showed upstaging to pT3A. These rates did not differ significantly from the 278 men who received immediate radical prostatectomy. Biochemical disease-free survival for men with more than 4 years of follow-up after radical prostatectomy was 98% and 100% for immediate surgery and surgery after active surveillance, respectively [17].

Godtman et al. [12**] defined failures after active surveillance as prostate cancer death, metastatic disease (which were both reported above) as well as PSA recurrence after curative treatment and hormonal treatment. Fourteen of 167 men (8%) had a PSA recurrence after radical prostatectomy, radiotherapy or radical prostatectomy with salvage radiation [12**].

Ischia et al. [2] reported on the Australian experience. Men who chose active surveillance for their low-risk prostate cancer and were managed by one surgeon in Melbourne, Australia, were included in the study. This cohort consisted of 154 men with a median age of 63.0 years and a mean PSA of 6.5 ng/ml. The median time of active surveillance was 1.9 years (0.1-16.1). Active surveillance was ceased in 29 patients (19%) after a mean of 2.4 years (0.2-7.9). Of these 29 men, 26 were upstaged, one chose curative treatment despite stable disease, and two died of disease not related to prostate cancer. Of the 17 men who received radical prostatectomy, four had T3 disease (31%). Ischia et al. [2] concluded that no biochemical recurrences or prostate cancer deaths were seen in men treated for prostate cancer during the short follow-up period. In table 1 all information is summarized.

These intermediate outcomes of active surveillance are harder to interpret, with less unequivocal end-points used in different studies. Overall, results after deferred radical treatment seem to indicate a proportion of men with less favorable outcomes (8-31%). It could be argued that these men should have been treated earlier. However, if compared to immediate radical treatment, results seem to be quite similar, suggesting that postponing treatment does not affect the outcome of these men within the available follow-up. Active surveillance did, however, delay the side-effects of treatment and positively affects the patients' quality of life [18-19]. Furthermore, the majority of men

are still on active surveillance without the protocol indicating to switch to deferred active treatment. This suggests that the tumors in these men show very indolent growth patterns. Future active surveillance studies may compare immediate outcomes with outcomes of men receiving immediate radical treatment to demonstrate the safety of active surveillance.

Conclusion

Overall, it can be concluded that prostate cancer mortality under active surveillance is very low, which supports the suggestion of active surveillance being a safe management strategy for low-risk prostate cancer. However, longer follow-up is warranted as present studies on the value of active surveillance have rather short follow-up to assess mortality outcomes, considering the slow natural course of prostate cancer. With respect to intermediate outcomes of active surveillance, it is more difficult to draw conclusions, as less unequivocal end-points are used in ongoing active surveillance studies. After having reviewed the results published during the last 12-18 months, it seems that choosing an initial active surveillance strategy, if applicable looking at prostate cancer characteristics, does not affect the outcomes of these men compared with those men who choose immediate active treatment. Choosing active surveillance then has the advantage of delaying side-effects of treatment and preserving health-related quality of life.

Table 1: Summary of oncologic outcome for current active surveillance studies published in the last 12-18 months.

Institute	Inclusion criteria	Number participants	Median follow-up (months)	Switch to other treatment %	Unfavourable outcome after radical treatment %	OS	DSS
University of Göteborg (Godtman et al. [12**])	No strict inclusion criteria. 53% of men T1c; Gleason ≤ 6; PSA density <0.15 ng/ml; fewer than three cores with cancer; and ≤ 50% cancer in any core	439	72	37	8^{+}	87	99
Johns Hopkins (Tosoian et al. [14**])	Gleason ≤ 3+3; PSAD ≤ 0,15 ng/ml/ml; cT stage 1; ≤ two cores positive; ≤ 50% of any core positive	769	32	33	9″	98	100
University of California San Francisco (Dall'Era et al. [17])	Gleason ≤ 3+3; PSA ≤ 10 ng/mL; cT stage ≤ 2; ≤ 33% of cores positive; ≤ 20% of any core positive	233	30	28	30/21^	NR	100
University of Toronto (Klotz [1])	Gleason ≤ 6; PSA ≤ 10 ng/mL; cT stage 1 (until January 2000, for men age >70 years: Gleason ≤ 3+4; PSA ≤ 15 ng/ml)	450	82	30	NR	79	97*
PRIAS (Bul et al. [13**,16**])	Gleason ≤ 3+3; PSA ≤ 10 ng/ml; PSAD ≤ 0,2 ng/ml/ml; cT stage 1c to 2; ≤ two cores positive	2494	19	22	29′	99	100
Monash University and Southern Health, Australia (Ischia [2])	No strict inclusion criteria. All men Gleason ≤7, median PSA 6.5, 68% 1 or 2 cores positive	154	23	16	31#	99	100

PRIAS: Prostate cancer Research International: Active Surveillance; PSA: prostate specific antigen; PSAD: prostate specific antigen density OS: overall survival; DSS: disease specific survival; NR: not reported

*: 10 year disease specific survival, ′: defined as pT3-4 and/or Gleason score ≥4+3 ″: biochemical recurrence rate at 2.8 year follow-up. ^: 30% Gleason score ≥ 7 and 21% pT3a #: defined as T3 disease after radical prostatectomy, $^{+}$: biochemical recurrence rate

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Chapter 5

Rule-based versus probabilistic selection for active surveillance using three definitions of insignificant prostate cancer.

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Abstract

Purpose. To study whether probabilistic selection by the use of a nomogram could improve patient selection for active surveillance (AS) compared to the various sets of rule-based AS inclusion criteria currently used.

Methods. We studied Dutch and Swedish patients participating in the European Randomized study of Screening for Prostate Cancer (ERSPC). We explored which men who were initially diagnosed with cT1-2, Gleason 6 (Gleason pattern ≤3+3) had histopathological indolent PCa at RP [defined as pT2, Gleason pattern ≤3 and tumor volume (TV) ≤0.5 or TV ≤1.3 ml, and TV no part of criteria (NoTV)]. Rule-based selection was according to the Prostate cancer Research International: Active Surveillance (PRIAS), Klotz and Johns Hopkins criteria. An existing nomogram to define probability-based selection for AS was refitted for the TV1.3 and NoTV indolent PCa definitions.

Results. 619 of 864 men undergoing RP had cT1-2, Gleason 6 disease at diagnosis and were analyzed. Median follow-up was 8.9 years. 229 (37%), 356 (58%), and 410 (66%) fulfilled the TV0.5, TV1.3, and NoTV indolent PCa criteria at RP. Discriminating between indolent and significant disease according to area under the curve (AUC) was: TV0.5: 0.658 (PRIAS), 0.523 (Klotz), 0.642 (Hopkins), 0.685 (nomogram). TV1.3: 0.630 (PRIAS), 0.550 (Klotz), 0.615 (Hopkins), 0.646 (nomogram). NoTV: 0.603 (PRIAS), 0.530 (Klotz), 0.589 (Hopkins), 0.608 (nomogram).

Conclusions. The performance of a nomogram, the Johns Hopkins, and PRIAS rule-based criteria are comparable. Because the nomogram allows individual trade-offs, it could be a good alternative to rigid rule-based criteria.

Introduction

Early detection of prostate cancer (PCa) has led to increased prevalence of finding indolent tumors, i.e. tumors that are unlikely to become symptomatic during life. The ability to predict indolent PCa is needed to avoid overtreatment [1]. Active surveillance (AS) has emerged as a feasible strategy to decrease the overtreatment of low-risk PCa. With AS, men with low-risk PCa are strictly monitored over time, and if risk reclassification or disease progression occurs, they can opt for curative therapy. Hence, the aim of AS is to safely delay or completely avoid side effects of active therapy [2]. There are 16 unique world-wide AS cohorts which all have their highly variable own protocols [3]. So far, published results on AS study cohorts worldwide show encouraging results on biochemical recurrence (BCR) rates and disease-specific mortality [4]. Long-term effects are yet unknown. Research on how to improve the existing AS protocols is, however, needed as misclassification at diagnosis, and subsequent reclassification after one-year repeat biopsy is not uncommon [5]. For example, 28% of men within the Prostate cancer Research International: Active Surveillance (PRIAS) study were reclassified after one or more repeat biopsies [6].

Currently, all existing AS cohorts apply relatively simple combinations of inclusion criteria for patient selection ("rule-based selection"). More refined risk stratification through a nomogram may be preferable, especially in the light of individualized medicine and shared decision-making ("probability-based selection") [7]. We aimed to assess the performance of inclusion criteria as used in several prospective AS protocols in identifying indolent cancer at radical prostatectomy (RP) and follow-up outcomes of men who received immediate RP but were also suitable for AS. For comparison, we used a previously developed and externally validated nomogram that predicts indolent disease [8,9]. We hypothesize that the use of probabilistic selection by the use of a nomogram that incorporates multiple patient characteristics may be better for selection.

Materials and methods

Patients

Men included in this study were participants in the screening arm of the European Randomized study of Screening for Prostate Cancer (ERSPC). Data cohorts of the Swedish and Dutch sections of ERSPC were combined. All men were diagnosed with screen-detected PCa and underwent RP as primary treatment. Details on both Dutch and Swedish screening protocols were previously studied [10,11].

Methods

Men with T3-4, Gleason ≥7 PCa at diagnostic biopsy or an unknown tumor volume were excluded from this analysis, as well as men with positive lymph nodes or distant metastases at the time of diagnosis or at the time of surgery. A multiple imputation model was used to fill in missing data. We used the first imputation of a multiple imputation procedure with the impute function in SPSS software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0 Armonk, NY: IBM Corp). A total of 936 confounder values were missing, comprising 13.5% of all values. Filling in these values through imputation allowed us to include the 382 (44%) patients with any missing value in the analysis. All tumour characteristics were used for the multiple imputation.

We first assessed the frequency of indolent PCa at RP according to the classic definition of pT2, tumor volume <0.5 ml (TV0.5), and pathological Gleason pattern ≤3 [12]. Men not fulfilling these criteria for indolent PCa (TV >0.5 ml and/or pathological Gleason pattern >3) were categorized as having significant PCa.

Second, we selected men from our study cohort with low-risk PCa at diagnosis defined according to the PRIAS (T1c-T2, PSA ≤10 ng/ml, PSA density <0.20 ng/ml/cc, Gleason ≤3+3, ≤2 positive cores), Klotz (T1b-T2b, PSA ≤10 ng/ml, Gleason ≤6), and John Hopkins criteria (T1c, PSA density <0.15 ng/ml/cc, Gleason ≤6, ≤2 positive cores, ≤50% single core involvement). The frequencies of indolent PCa at RP in these groups were studied.

Third, we explored the use of a nomogram to estimate risk for indolent PCa at RP [13]. We assessed the effect of applying various eligibility criteria for the nomogram (T1c-T2a, PSA ≤20 ng/ml, Gleason ≤3+3, ≤50% positive cores, 20 mm PCa, 40 mm benign tissue in all cores) and of different thresholds in the predicted chance of harbouring indolent PCa (referred to as Pind) on the number of men remaining suitable for AS at diagnosis.

The classic definition of a pathologic indolent PCa (pT2, TV0.5 and Gleason pattern ≤3) might be too restrictive and not reflecting biology well [14]. Therefore, we repeated steps one to three with two updated and more recent definitions of indolent PCa: (1) pT2, tumor volume <1.3 ml (TV1.3) and Gleason pattern ≤3+3 [14-16]; (2) pT2, Gleason pattern ≤3+3 and tumor volume no part of definition (NoTV) [15]. For step three, the nomogram was refitted twice using the original data [13], to account for the adjusted definitions of an indolent PCa.

Having the availability of follow-up data, we were able to calculate BCR after RP. The criteria proposed by Freedland et al. [17] were used to define BCR, i.e. one PSA value

after RP >0.2 ng/ml. The different sets of rule-based selection criteria and Pind cut-off points were compared using the Kaplan-Meier method and log-rank test.

We finally applied decision curve analysis (DCA) [18] to evaluate the potential clinical usefulness of rule-based selection and probability-based selection models. We estimated a net benefit (NB) for the four models by summing the benefits (true-positive indolent PCa) and subtracting the harms (false-positive indolent PCa). The harms were weighted by a factor related to the relative harm of being unjustly included on AS versus being directly curatively treated while suitable for AS. This weighting was derived from the threshold probability at which a patient would opt for AS. This threshold varies between men and urologists. Clinical practice currently uses a threshold probability of 50-70% [19]. The interpretation of a decision curve is rather straightforward; the model with the highest NB at a particular threshold should be chosen over alternative models.

P-values (two-sided) <0.05 were considered statistically significant. For statistical analysis, we used the Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0 Armonk, NY: IBM Corp) and R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Our study cohort consisted of 864 men of whom 619 had cT1-2, Gleason 6 disease at diagnosis and were therefore eligible for analyses. Median follow-up time after diagnosis was 8.9 years. Table 1 presents the study cohort characteristics at diagnosis and outcomes after RP. With TV0.5 cut-off, a total of 229 (37%) tumors at RP could be defined as indolent versus 390 (63%) as significant. When applying the TV1.3 and NoTV indolent PCa definitions, the number of indolent PCa increases to 356 (58%) and 410 (66%), respectively. Pind could be calculated for 455 (74%) men meeting the nomogram inclusion criteria.

Table 2 presents the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for all three indolent PCa definitions (TV0.5, TV1.3, NoTV) at RP of the rule-based selection and nomogram-based selection approaches. The table also contains the effect of applying different thresholds of the nomogram calculated risk of harboring indolent PCa, i.e. Pind.

The area under the curve (AUC) for the TV0.5 indolent definition was 0.658 for PRIAS, 0.523 for Klotz, 0.642 for Johns Hopkins, and 0.685 for the nomogram. For the TV1.3

Table 1: Study cohort characteristics at diagnosis and outcomes after radical prostatectomy (n=619)

At diagnosis		
ERSPC study centre:		
The Netherlands (n, %)	336	54
Sweden (n, %)	283	46
Follow-up (years) (median, 25-75p)	8.9	5.9-10.9
Age (years) (median, 25-75p)	62.9	60.1-66.2
Clinical disease stage (n, %):		
T1c	395	64
T2a	157	25
T2b	37	6
T2c	30	5
PSA (ng/ml) (median, 25-75p)	4.5	3.5-6.4
Prostate volume (cc) (median, 25-75p)	35.1	28.3-45.1
PSA-density (ng/ml/cc) (median, 25-75p)	0.13	0.09-0.18
Total number of cores (median, 25-75p)	6	6-6
Number of positive cores (median, 25-75p)	2	1-3
Total benign tissue (mm) (median, 25-75p)	67.6	56.0-78.5
Total PCa tissue (mm) (median, 25-75p)	4.0	2.1-8.1
Percentage cancer per positive core (median, 25-75p)	30.5	14.7-64.3
Gleason sum:		
≤ 6	619	100
Prediction indolent cancer (median, 25-75p) (N=455 suitable for nomogram)	60%	40-78%
At radical prostatectomy		
Tumour volume (n, %)		
≤ 0.5 cc	284	46
> 0.5 cc	335	54
≤ 1.3 cc	497	80
> 1.3 cc	122	20
Gleason sum (n, %)		
≤ 6 (no pattern 4)	468	76
≥ 7	140	24
Indolent cancer (tumour volume ≤0.5 cc, T2, Gleason ≤ 3+3 disease)		
Yes (n, %)	229	37
No (n, %)	390	63
Indolent cancer (tumour volume ≤1.3 cc, T2, Gleason ≤ 3+3 disease)		
Yes (n, %)	356	58
No (n, %)	263	42
Indolent cancer (T2, Gleason ≤ 3+3 disease, no tumour volume cut-off)		
Yes (n, %)	410	66
No (n, %)	209	34

* 25-75p = 25-75 percentile

indolent definition, the AUC for PRIAS was 0.630, for Klotz 0.550, for Johns Hopkins 0.615, and for the refitted nomogram 0.646. For the NoTV indolent definition, the AUC for PRIAS was 0.603, for Klotz 0.530, for Johns Hopkins 0.589, and for the refitted nomogram 0.608.

Table 2 furthermore presents the number of men who experienced BCR after RP according to the three definitions of indolent disease in the different sets of rule-based criteria and the nomogram suitable cohort. A log-rank test showed that the number of men experiencing BCR do not differ statistically between the groups. However, the distribution of BCR over the indolent and significant group changes, with a rising percentage of BCR in the indolent group (TV0.5 = 3.4%, TV1.3 = 4.9%, NoTV = 6.3%). We found that in ROC analysis (appendix fig. 1), the nomogram (TV0.5) had a slightly better sensitivity-to-specificity ratio than the PRIAS rules. The AUC for the nomogram (TV0.5) was 0.610, for PRIAS 0.584, for Klotz 0.524, for Johns Hopkins 0.615, for the refitted TV1.3 nomogram 0.595, and for the refitted NoTV nomogram 0.570.

In terms of clinical usefulness, we found that in DCA analysis (appendix Fig. 2a-c), no large differences in NB were seen for threshold probabilities 50-70%, which are clinically most relevant.

Discussion

In our cohort of Dutch and Swedish screen-detected PCa patients who all underwent initial RP, 37% fulfilled the TV0.5 indolent PCa criteria at RP increasing to 58% for the TV1.3 indolent PCa criteria and 66% for the NoTV indolent PCa definition. More stringent rule-based AS inclusion criteria as well as stricter nomogram probability thresholds decrease the rate of misclassified tumors in a rather similar fashion, but both at the cost of a substantial number of patients no longer considered suitable for AS. The nomogram based on TV0.5 had slightly better sensitivity and specificity with respect to BCR outcome than the PRIAS and Klotz criteria. If we juxtapose the TV0.5 nomogram to the Johns Hopkins criteria, the latter performed better but at the cost of including less patients and thereby curatively treating patients that might also would have been suitable for AS.

On the basis of a Kaplan-Meier analysis (curves not shown), we cannot conclude that the use of the TV0.5 nomogram is preferred over the use of rule-based selection or vice versa. However, for BCR the TV0.5 nomogram outperformed the PRIAS and Klotz criteria. The TV0.5 nomogram, however, performed slightly worse than the Johns Hop-

Table 2: Sensitivity, specificity and BCR for several sets of rule-based and nomogram-based AS inclusion criteria for selecting indolent PCa at RP (N=619)

TV0.5	*Total low-risk PCa included*	*Total low-risk PCa missed*	*% included*	*Indolent PCa (TV≤0.5) at RP included*	*Indolent PCa at RP missed*	*Sens*	*Significant PCa at RP included*	*Significant PCa at RP missed*	*Spec*	*PPV*	*NPV*	*Total BCR (%)*	*BCR – Indolent PCa (TV≤0.5) (%)*	*BCR – Significant PCa (TV>0.5) (%)*
Total cohort	619	-	100%	229	-		390	-	-	-	-	82 (13.3)	21 (3.4)	61 (9.9)
PRIAS	354	265	57%	180	49	79%	174	216	55%	51%	82%	34 (9.6)	18 (5.1)	16 (4.5)
Klotz	537	82	87%	207	22	90%	330	60	15%	39%	73%	66 (12.3)	18 (3.4)	48 (8.9)
Johns Hopkins	171	448	28%	104	125	45%	67	323	82%	61%	72%	9 (5.3)	8 (4.7)	1 (0.6)
Nomogram														
Suitable	455	164	74%	193	36	84%	262	128	33%	42%	78%	51 (11.2)	16 (3.5)	35 (7.7)
PInd > 50%	283	336	46%	149	80	65%	134	256	66%	53%	76%	24 (8.4)	12 (4.2)	12 (4.2)
PInd > 60%	227	392	37%	123	106	54%	104	286	73%	54%	73%	18 (7.9)	9 (4.0)	9 (4.0)
Pind > 70%	161	458	26%	94	135	41%	67	323	83%	58%	71%	14 (8.7)	8 (5.0)	6 (3.7)

Table 2: Sensitivity, specificity and BCR for several sets of rule-based and nomogram-based AS inclusion criteria for selecting indolent PCa at RP (N=619) (continued)

TV1.3	*Total low-risk Pca included*	Total low-risk Pca missed	% included	Indolent Pca (TV≤1.3) at RP included	Indolent Pca at RP missed	Sens	Significant Pca (TV>1.3) at RP included	Significant Pca at RP missed	Spec	PPV	NPV	Total BCR (%)	BCR – Indolent Pca (TV≤1.3) (%)	BCR – Significant Pca (TV>1.3) (%)
Total cohort	619	-	100%	356	-	-	263	-	-	-	-	82 (13.3)	30 (4.9)	52 (8.4)
PRIAS	354	265	57%	243	113	68%	111	152	58%	69%	57%	34 (9.6)	21 (5.9)	13 (3.7)
Klotz	537	82	87%	324	32	91%	213	50	19%	60%	61%	66 (12.3)	26 (4.8)	40 (7.5)
Johns Hopkins	171	448	28%	133	223	37%	38	225	86%	78%	50%	9 (5.3)	8 (4.7)	1 (0.6)
Nomogram (refitted for indolent Pca with TV1.3)														
Suitable	455	164	74%	281	75	79%	174	89	34%	62%	54%	51 (11.2)	22 (4.8)	29 (6.4)
Pind > 50%	312	307	50%	218	138	61%	94	169	64%	70%	55%	29 (9.3)	16 (5.1)	13 (4.2)
PInd > 60%	246	373	40%	173	183	49%	73	190	72%	70%	51%	17 (6.9)	10 (4.1)	7 (2.8)
Pind > 70%	179	440	29%	129	227	36%	50	213	81%	72%	48%	15 (8.4)	10 (5.6)	5 (2.8)

Table 2: Sensitivity, specificity and BCR for several sets of rule-based and nomogram-based AS inclusion criteria for selecting indolent PCa at RP (N=619) (continued)

NoTV	Total low-risk Pca included	Total low-risk Pca missed	% included	Indolent Pca (pT2, Gl 3+3) at RP included	Indolent Pca at RP missed	Sens	Significant Pca (pT3-4, Gl > 3+3) at RP included	Significant Pca at RP missed	Spec	PPV	NPV	Total BCR (%)	BCR – Indolent Pca (pT2, Gl 3+3) (%)	BCR – Significant Pca (pT3-4, Gl >3+3) (%)
Total cohort	619	-	100%	410	-		209	-	-	-	-	82 (13.3)	39 (6.3)	43 (7.0)
PRIAS	354	265	57%	263	147	64%	91	118	56%	74%	75%	34 (9.6)	24 (6.8)	10 (2.9)
Klotz	537	82	87%	364	46	89%	173	36	17%	68%	44%	66 (12.3)	32 (6.0)	34 (6.3)
Johns Hopkins	171	448	28%	138	272	34%	33	176	84%	81%	40%	9 (5.3)	8 (4.7)	1 (0.6)
Nomogram (refitted for indolent Pca without TV)														
Suitable	455	164	74%	314	96	77%	141	68	33%	69%	41%	51 (11.2)	27 (5.9)	24 (5.3)
PInd > 50%	378	241	61%	273	137	67%	105	104	50%	72%	43%	40 (10.6)	25 (6.6)	15 (4.0)
PInd > 60%	299	320	48%	226	184	55%	73	136	65%	76%	43%	30 (10.0)	20 (6.7)	10 (3.3)
PInd >70%	202	417	33%	149	261	36%	53	156	75%	74%	37%	18 (8.9)	12 (5.9)	6 (3.0)

kins criteria. If we chose a slightly lower Pind and therewith allowing more men to be included on AS, sensitivity and specificity of the TV0.5 are still acceptable. This flexibility in application is a property of using a nomogram for selection rather than a strict set of rules and desirable in the light of individualized medicine and shared decision-making.

Because the classic definition of a pathologically indolent PCa may be too restrictive [14], we also used two more updated definitions of an indolent PCa. When juxtaposing the models, the TV0.5 nomogram (AUC 0.685) was slightly better in discriminating indolent from significant PCa than the PRIAS (AUC 0.658), Johns Hopkins (AUC 0.642), and Klotz (AUC 0.523) criteria. This trend of the nomogram predicting slightly better is also seen for the refitted TV1.3 and NoTV nomograms.

Perfect patient selection for AS using either rule-based selection criteria or by applying a nomogram seems difficult at present. The AUCs illustrate that both approaches are currently suboptimal in differentiating indolent from non-indolent disease at RP in a group of men with already low-risk features at diagnosis. This is confirmed by the study of Wang et al. [20] whom in a group of 273 AS patients who underwent multiple biopsies and/or delayed RP found that nomograms designed to predict indolent tumors only have a modest ability to predict biopsy progression and any progression on either biopsy or surgery in men choosing an AS management strategy. Wang et al. furthermore concluded that in a subgroup of 58 men, none of the various nomograms were able to predict surgical progression at RP [20]. Since AS is incorporated into many guidelines (AUA, NCCN, EAU, etc.) as a viable management strategy for men with either very low-risk or low-risk PCa, it is expected that more men will elect AS as their primary therapy. The optimization of both rule-based selection and probability-based selection is therefore warranted.

Over the past few years, magnetic resonance imaging (MRI) is emerging as a tool which may be able to more accurately determine the risk of significant disease and progression of disease over time by improving sampling through target biopsies [21]. MRI may therefore also help better select AS candidates [22]. Several studies have shown the additional value of MRI in an AS protocol [21-23]. Stamatakis et al. [22] combined MRI-based factors into a nomogram which generates a probability for confirmed AS candidacy. They found that three MRI-based factors, i.e. number of lesions, lesion suspicion, and lesion density, were associated with confirmatory biopsy outcome and reclassification. A created nomogram which uses these factors has promising predictive accuracy, according to Stamatakis et al. [22]. It could be that adding such factors to the currently existing rule-based selection criteria or the nomogram could improve sensitivity and specificity and therewith AS patient selection.

A first limitation of our study lies in the fact that men in our cohort were diagnosed with sextant biopsies. Sextant biopsy does not reflect current clinical practice anymore; nowadays, current practice relies on 8-18 core biopsies. Studies that applied more extended biopsy schemes argue that with a sextant biopsy protocol, 10-30% of cancers are missed [24]. Several studies reported that when 8-12 cores were taken, the PCa detection rate in a clinical setting might increase [24,25]. We validated the previously developed nomogram in multiple other populations in which more extended biopsy schemes were used. Results of these validation studies showed that the nomogram predicted indolent PCa with good discrimination, indicating that it can be broadly applied in contemporary urological practice [26,27]. In addition, we extracted correction factors for the adjustment of the nomogram with which contemporary extended biopsy schemes can be addressed [28]. Another limitation is that follow-up time of our study cohort is too short to assess mortality outcomes and relate these to baseline selection criteria. The lack of mortality outcomes was also the reason to choose BCR as an endpoint instead. Many men with BCR, however, will never develop metastasized disease or die from PCa [29]. Thirdly, patients underwent RP in different centers in either Sweden of the Netherlands. They were operated by different surgeons using different techniques for RP, which might influence outcomes. Finally, 247 cases included in this analysis were also used in the validation and construction of the nomogram. This may lead to an overestimated performance of the nomogram and Pind. The strength of this study lies in the fact that all men were diagnosed with PCa within ERSPC (Sweden and the Netherlands), resulting in standardized pathological examination of biopsy specimens and structured data follow-up [30].

In conclusion, in our cohort of Dutch and Swedish screen-detected PCa patients who all underwent initial RP, 37% had TV0.5 indolent PCa at RP increasing to 58% for the TV1.3 indolent PCa criteria and 66% for the NoTV indolent PCa definition. Performance of an ERSPC-based TV0.5 nomogram and rule-based selection by the Johns Hopkins and PRIAS criteria is comparable. Because the nomogram allows individual trade-offs, it could be a good alternative to applying rigid rule-based criteria. Furthermore, a nomogram anticipates on the continuous improvement of risk assessment by newly emerging risk criteria, including imaging modalities.

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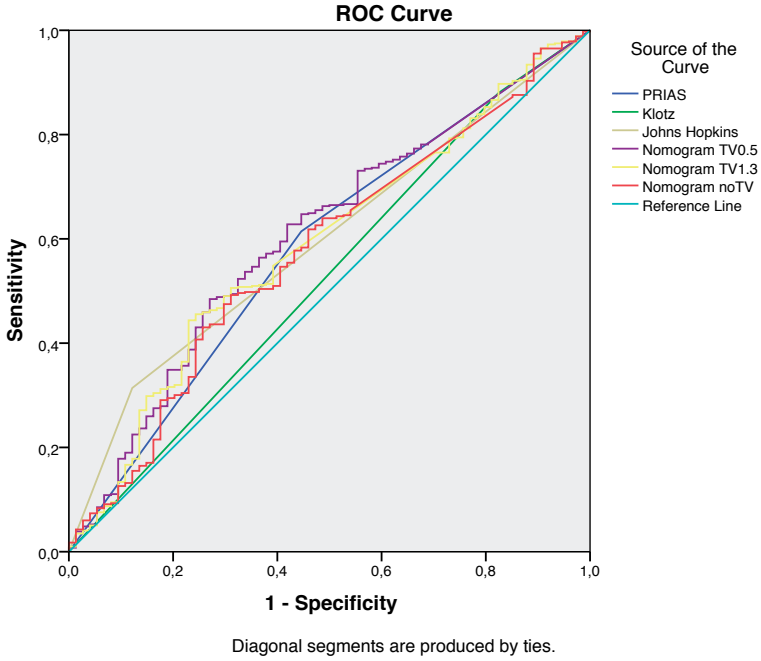
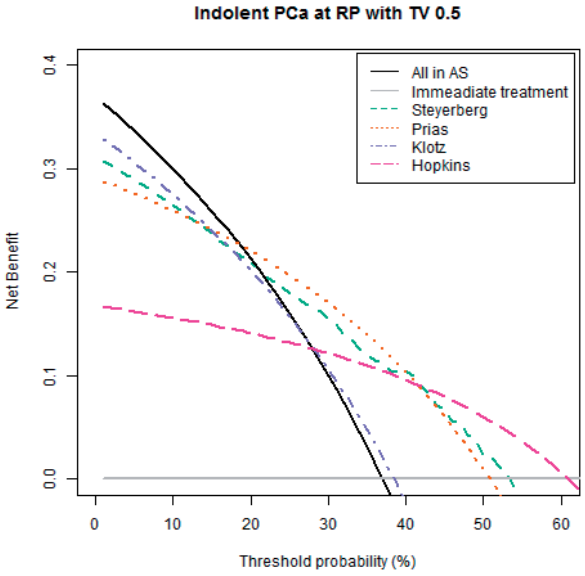
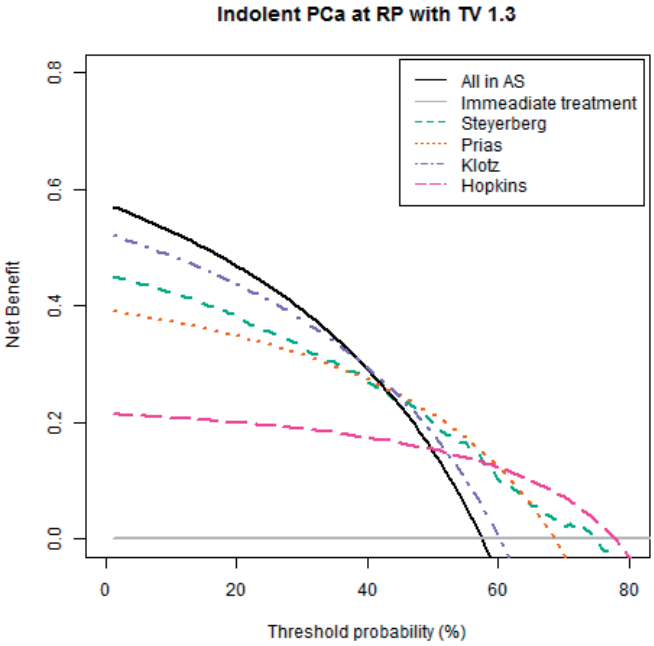
Appendix figure 1: Receiver Operating Characteristics (ROC) curve for men that experienced BCR after RP within PRIAS, Klotz, Johns Hopkins and the nomogram.



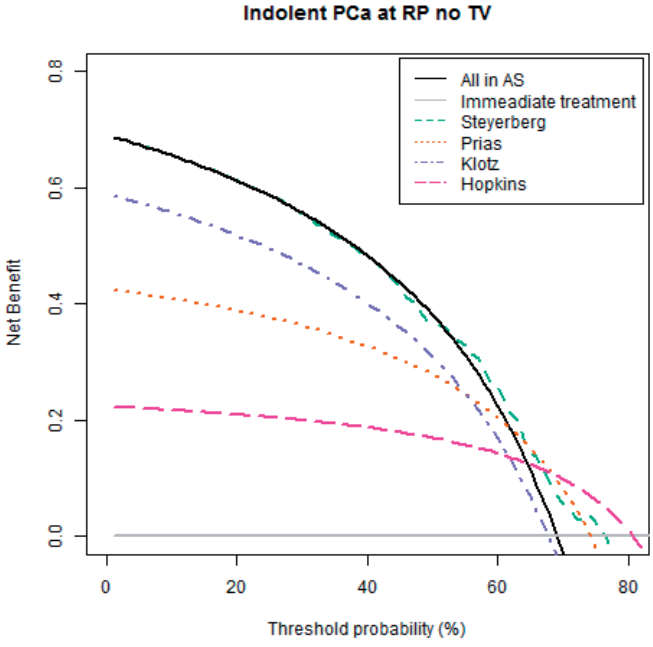
Appendix figure 2a-c: Decision Curve Analysis (DCA) showing the ability of the PRIAS, Klotz, Johns Hopkins and nomogram to discriminate between indolent and significant disease.



A. indolent PCa at RP with TV0.5



B. indolent PCa at RP with TV1.3



C. indolent PCa at RP with noTV

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Chapter 6

A longitudinal study on the impact of active surveillance for prostate cancer on anxiety and distress levels

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Abstract

Objective. Patients with potentially indolent prostate cancer (PCa) can be managed with active surveillance (AS). Our objective was to analyze how anxiety and distress develop in men with untreated PCa and whether highly anxious men quit AS.

Methods. One hundred and fifty Dutch patients who opted for AS in the Prostate cancer Research International: Active Surveillance study were invited to participate in an additional prospective, longitudinal quality of life (QoL) study within 6 months after diagnosis. Participants completed questionnaires with validated measures on anxiety and distress at inclusion (t=0), 9 (t=9) and 18 (t=18) months after diagnosis. We assessed changes in scores on depression (Center for Epidemiologic Studies Depression (CES-D) scale), generic anxiety (State-Trait Anxiety Inventory (STAI-6)), PCa-specific anxiety (Memorial Anxiety Scale for Prostate Cancer (MAX-PC)) and decisional conflict (Decisional Conflict Scale (DCS)) about patients' treatment choice between t=0, t=9 and t=18 using repeated measures analysis.

Results. Response rates for patients still on AS at t=0, t=9 and t=18 assessments were 86%, 90% and 96%, respectively. Nine patients (7%, 9/129) between t=0 and t=9 and 33 of 108 patients (31%) between t=9 and t=18 stopped AS, mostly (86%) because of protocol-based reasons. CES-D, total MAX-PC and DCS score did not change significantly ($p>0.05$) when comparing t=18 with t=9 and t=0 scores, but generic anxiety (STAI-6; $p=0.033$) and fear of disease progression (sub-score of the MAX-PC; $p=0.007$) decreased significantly. These differences, however, were clinically modest (0.089 SD and 0.281 SD). Overall, six of 129 men (5%) discontinued AS because of anxiety and distress.

Conclusions. When men with low-risk PCa are managed with AS, fear of disease progression and general anxiety decreased, and only few may discontinue AS because of anxiety and distress. This suggests that negative QoL effects are limited in men with favorable clinical characteristics who opted for AS. (Registered trial number, NTR1718)

Introduction

Screening and more intensive diagnostic work-ups lead to an increase in the detection of small, localized, well-differentiated prostate cancers (PCa). Therefore, the ratio between men dying with and from PCa is increasing. In many developed countries, detection and treatment are tightly linked; most patients with PCa receive radical treatment despite the favorable natural history of many tumors [1-3]. Treatment of small, localized, well-differentiated PCa tumors should ideally be selective, reflecting each patient's individual characteristics [4]. Active surveillance (AS), in that context, is considered a realistic initial alternative for curative therapy.

AS aims at selecting low-risk PCa with a likely favorable prognosis and strictly monitoring these tumors over time. If risk reclassification or disease progression occurs, men can opt for curative therapy. The aim of AS is to safely delay or even completely avoid side effects of active therapy [5].

From the moment low-risk PCa is diagnosed, anxiety, distress, beliefs and expectations may play a role in a patient's treatment decision-making [5], affecting the patient's quality of life (QoL). The choice between an AS management strategy or active therapy potentially affects various QoL aspects. Although active therapy may provide patients with a feeling of certainty and being in control of their disease, the trade-off might be the worsening of sexual, urinary and bowel functions. Choosing AS spares these functions because active therapy is delayed or, potentially, completely avoided, but comes at the trade-off of continued uncertainty, anxiousness and distress. For patients who choose AS, there is always the possibility of missing 'the window of curability' or waiting too long before starting active therapy, which might lead to worse outcomes when compared with those with immediate treatment. It is hypothesized that such possibilities might have an unfavorable effect on sexual, urinary and bowel function as well as on anxiety and distress levels [6,7]. It is therefore recommended that these potential negative effects are thoroughly considered before choosing AS.

QoL among men on AS has been studied before [2,8-10]. Results showed that short-term anxiety and distress levels were favorably low for men on AS compared with QoL of men choosing active therapy. Up to now, few studies reported longer-term QoL. With this longitudinal study, we report on the 18-month QoL of a cohort of men who agreed to participate in a well-defined, globally accepted AS protocol, the Prostate cancer Research International: Active Surveillance (PRIAS) study, and who accepted to follow the PRIAS protocol for an 18-month period. Of specific interest is how levels of anxiety and distress develop during follow-up. We hypothesize that anxiety and distress levels

remain favorable for men who continue AS for an 18-month period and that anxious men will discontinue AS early on.

Materials and methods

Patients included in this prospective QoL study were participants in the protocol-based, multicenter, prospective, observational PRIAS study [2,8,11]. PRIAS inclusion criteria are as follows: PCa diagnosis with a prostate-specific antigen (PSA) of ≤10.0 ng/ml; a PSA-density (PSA/prostate volume) of <0.2 ng/ml/ml; ≤T2; one or two positive prostate needle-biopsy cores, with a Gleason score of ≤3+3 = 6. The follow-up protocol included PSA measurements every 3 months for the first 2 years and every 6 months thereafter. Digital rectal examination was scheduled every 6 months for the first 2 years and once a year thereafter. Repeat biopsies were scheduled after 1, 4 and 7 years, and in the case of a PSA-doubling time between 3 and 10 years, yearly repeat biopsies were advised. Risk reclassification at repeat biopsy triggered a recommendation for active therapy and was defined as ≥3 positive biopsy cores and/or Gleason score of >6. A PSA-doubling time, which can only be reliably calculated after a minimum of one baseline and four follow-up measurements, of less than 3 years was also used as a trigger to initiate active therapy [11]. Men in our study thus have had several PSA measurements and underwent a repeat biopsy at 1 year post-diagnosis, that is, in between the t9 and t18 measurement. Participation in PRIAS requires informed consent.

The inclusion period May 2007-May 2008 determined the sample size [12]. All Dutch PRIAS participants who were diagnosed with PCa (at most 6 months earlier) in that year were invited to be included in an additional QoL study (n=150). Besides the above-mentioned PRIAS inclusion criteria, no additional inclusion or exclusion criteria were applied. Through regular mail, those who consented received a first QoL-questionnaire at their home address (t=0). If they had not returned their questionnaire within 1 month, they were reminded once by telephone. All patients who returned the first questionnaire received a second questionnaire 9 months after diagnosis (t=9). Patients who returned the second questionnaire received a third and final questionnaire 18 months after diagnosis (t=18).

The PRIAS study and its QoL study were approved by the Institutional Review Board of the Erasmus University Medical Center (MEC number 2004-339) and by the Institutional Review Boards of peripheral hospitals, taking local regulations into account. (Registered trial number, NTR1718).

Measures included in the questionnaire

With the use of validated questionnaires, we evaluated levels of anxiety and distress of men on AS for low-risk PCa. We defined distress as 'occurring when an individual cannot adapt to stress' [13]. Distress was measured through the Decisional Conflict Scale (DCS), Center for Epidemiologic Studies Depression (CES-D) scale and the self-estimated risk of progression scale.

We assessed potential decisional conflict regarding the choice for AS, using the DCS. The scale consists of 16 items with five response options each (score range per item is 0-4). Scale scores range from 0 (no decisional conflict) to 100 (extremely high decisional conflict). DCS scores ≤25 tend to be associated with implementing decisions, while scores ≥37.5 are associated with decision delay or feeling unsure about implementation of a decision [2,14,15]. Subscales of the DCS were not analyzed in this study.

Symptoms of depression were assessed with the CES-D. The scale consists of 20 items with four response options each (score range per item is 0-3). The total score ranges from 0 to 60; the higher the score, the more symptomatology of depression is present. An individual is considered to be at high risk of clinical depression with a score of ≥16 [2,16,17].

Furthermore, we assessed the self-estimated risk of disease progression with a self-designed, non-validated, two question measure (Question 1: 'Take in mind an average man with PCa who has also chosen an AS management strategy. What is his chance of progression of his PCa within the coming year?' – 'very unlikely, unlikely, average, likely, very likely'; Question 2: 'Now imagine your personal situation. Do you estimate your chance of deterioration of your PCa in the coming year to become larger or smaller as compared to an average male on AS for PCa?' – 'The chance of deterioration for me is "very unlikely-", "unlikely-", "average-", "likely-", "very likely" as compared to an average male'). The answering categories of both items are scored 1-5 (very unlikely = 1, very likely = 5). The total score of the self-estimated risk of progression scale ranges from -4 to 4 and is calculated by subtracting a man's own self-estimated risk of the self-estimated average risk that this man reported. This measure is based on earlier research by Essink-Bot et al. [18].

Anxiety was measured through the State-Trait Anxiety Inventory (STAI-6) and the Memorial Anxiety Scale for Prostate Cancer (MAX-PC).

Generic anxiety was assessed with the abridged STAI-6. This scale consists of six items with four response options each (score range per item is 1-4). The total score ranges

from 20 to 80, with 80 indicating maximum generic anxiety. A STAI-6 score of ≥44 defines an individual as highly anxious [2,19,20].

The MAX-PC was used to assess PCa specific anxiety. This scale consists of 18 items with four response options each (score range per item is 0-3). The total score ranges from 0 to 54, with 54 indicating maximum PCa specific anxiety. In earlier studies, a MAX-PC score of 27 has been applied to identify individuals with clinically significant PCa-specific anxiety [21]. The MAX-PC consists of three subscales that measure general anxiety related to PCa and treatment, anxiety related to PSA levels in particular and fear of recurrence (fear of disease progression) [2,21,22]. The MAX-PC subscale 'fear of recurrence' was not originally designed to measure fear of disease progression; it was designed to measure fear of recurrence after one was treated for PCa and the cancer was removed. With AS, it is not recurrence that men may be scared of, it is the progression of their cancer that they are worried about. Items of the subscale were structured in such a way that we consider them also applicable to fear of disease progression.

General physical health of participants was assessed at t=0 and t=18 with the short-form health-survey (SF-12). The total scale consists of 12 items with two to six response options each, with which two summary scores can be calculated: the mental component summary (MCS) and the physical component summary (PCS). All 12 items are necessary to calculate both the MCS and PCS. In calculating the MCS and PCS, the distributions of weights for each item differ. Because of the conceptual overlap of the MCS with the CES-D, STAI-6 and MAX-PC, in this study the MCS items were not included in the analyses. The total score of the PCS subscale can range from 0 to 100, with 100 indicating best overall health [23].

Validated Dutch translations of the DCS, CES-D, STAI-6, SF-12 and MAX-PC were used [24-28]. These measures had been validated in populations that are comparable to ours, that is, other cohorts of cancer patients, except for the CES-D, that had been validated in a cohort of older men from the general population. All measures were scored applying the official scoring system and regulations for missing values [14,19,21,23,29]. The Cronbach's alpha of the self-estimated risk of progression scale was 0.84, indicating that the two items in this scale measure the same construct. While validation was not the aim of our study, we will nevertheless look at some psychometric properties of the used validated Dutch measures.

Previously, we presented baseline QoL outcomes and outcomes after 9 months of follow-up [2,8]. In the current article, the differences between scores on DCS, MAX-PC, STAI-6 and CES-D between t=0, t=9 and t=18 were analysed using repeated measures

Table 1: Medical, demographic, and other characteristics at the moment of diagnosis of the total study population (N=129) [2]

Total number of patients	129	
Medical		
PSA* at diagnosis (median/25-75p**)	5.7	4.6-7.0 ng/ml
Last known PSA* before 2nd questionnaire (median/25-75p**)	5.6	3.8-7.0 ng/ml
Clinical stage at diagnosis		
Non palpable	91	71%
Localized	38	29%
Number of positive biopsies at diagnosis		
1	79	61%
2	50	39%
Demographics		
Age at diagnosis (median/25-75p**)	64.6	60.2-70.4 Years
Education		
Low (primary, secondary)	86	67%
High (college, university)	42	33%
Missing	1	
Employed		
Yes	76	60%
No	50	40%
Missing	3	
Hospital		
University/specialized	68	53%
Other	61	47%
Civil status		
Married/living together	119	92%
Other	10	8%
Other		
Major life event before diagnosis other than PC***		
Yes	15	12%
No	114	88%
Sexually active		
Yes	93	73%
No	35	27%

*PSA prostate specific antigen
**25-75p 25^{th} – 75^{th} percentile
***PC prostate cancer

analysis to assess changes over time. Differences in SF-12 (PCS) scores between t=18 and t=0 were analysed with paired samples t-test after log-transformation due to non-normal distribution. The clinical relevance of differences, that is, the smallest change in scores experienced as meaningful by patients, was determined using the minimal important difference, operationalized as half a standard deviation of the first measurement [30]. Differences ≥0.5 SD were considered as relevant. Men with STAI-6 scores >44

at baseline were considered as highly anxious [2,20]. We explored whether these men became less anxious during follow-up or whether these highly anxious men discontinued AS. Analyses were performed with SPSS, version 20 (IBM, Armonk, NY, USA) and SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The average age of participants at baseline was 64.6 years, and their average PSA level was 5.7 ng/ml (table 1).

The t=0, t=9 and t=18 questionnaires were completed by 86% (129/150), 90% (108/120) and 96% (72/75) of participants still on AS (figure 1). The questionnaires were completed at a median of 2.4 months (25-75p: 1.3-3.9), 9.2 months (25-75p:9.0-9.6) and 18.2 months (25-75p:17.6-18.6) after diagnosis. We compared the Cronbach's alphas we found for our measures to the Cronbach's alphas of Dutch validation studies: DCS 0.93 vs. 0.75-0.82 [24]; MAX-PC 0.77 vs. 0.77 [28]; STAI-6 0.77 vs. 0.83 [26]; CES-D 0.60 vs. 0.80-0.90 [25]; SF-12 0.72 vs. 0.81-0.91 [27]. Questionnaires contained low numbers of missing values, and respondents added no remarks about the questions.

Between the t=0 and t=18 questionnaire, 42 men switched to active therapy; six upon their own request (5%, 6/129) because of anxiety and distress and 36 (28%, 36/129) because of reclassification or progression of their PCa. Treatment for these 42 men consisted of radical prostatectomy in 17 patients (40%), brachytherapy in 15 (36%), external beam radiation therapy in six (14%), High-Intensity Focused Ultrasound in one (2%), and an unknown treatment modality in three (7%).

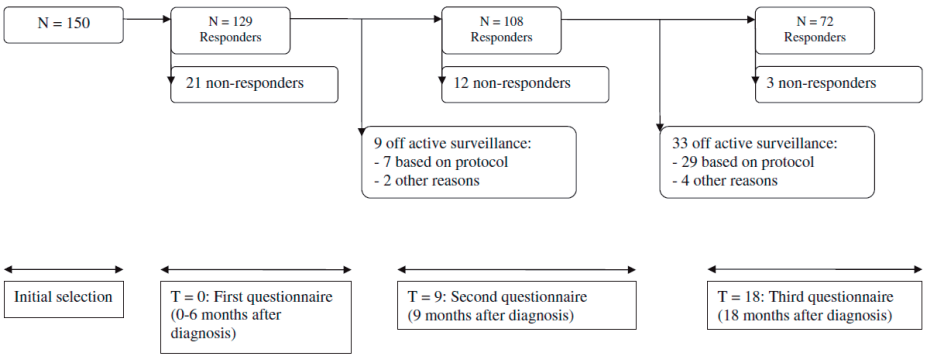

Figure 1: Patient cohort selection.

Table 2: Questionnaire scores at t0 (129 men), t9 (108 men) and t18 (72 men)

	Score Range	Clinical threshold	Mean/Median **t0** (IQR) (2)	Mean/Median **t9** (IQR) (8)	Mean/Median **t18** (IQR)	F-value	P-value*
DCS	0-100	37.5	27.0/28.1 (17.2-36.3)	27.9/28.1 (17.2-36.3)	27.0/26.6 (15.6-35.9)	1.10	0.336
CES-D	0-60	16	5.4/4.0 (0.0-9.0)	5.3/3.0 (0.0-8.8)	5.4/3.0 (0.0-6.0)	0.42	0.655
STAI-6	20-80	44	35.2/33.3 (30.0-40.0)	33.4/33.3 (30.0-36.7)	34.4/33.3 (30.0-36.7)	3.48	0.033
Total MAX-PC	0-54	27	13.7/13.5 (6.3-20.0)	13.4/14.0 (7.0-18.0)	12.6/11.5 (6.0-18.0)	1.11	0.331
- PC anxiety	0-33	-	9.1/8.0 (3.0-14.0)	9.5/9.0 (4.0-13.0)	8.7/8.0 (3.8-13.3)	0.83	0.438
- PSA anxiety	0-9	-	0.3/0.0 (0.0-0.0)	0.3/0.0 (0.0-0.0)	0.5/0.0 (0.0-0.0)	1.02	0.364
- Progression fear	0-12	-	4.2/4.0 (2.0-6.0)	3.5/4.0 (2.0-5.0)	3.5/4.0 (2.0-5.0)	5.15	0.007
Self-estimated progression risk	-4-4	-	0.2/0.0 (0.0-1.0)	0.5/0.0 (0.7)	0.6/0.0 (0.0)	-	- ^
SF-12 PCS	-	-	51.4/54.3 (48.9-55.9)	-	50.1/53.5 (47.9-54.3)	-	0.428**

IQR = Interquartile Range

* P-value t0/t9/t18 (Linear mixed model)

** P-value t0/t18 (paired T-test)

^ No statistical testing applied, Cronbach's alpha was 0.84

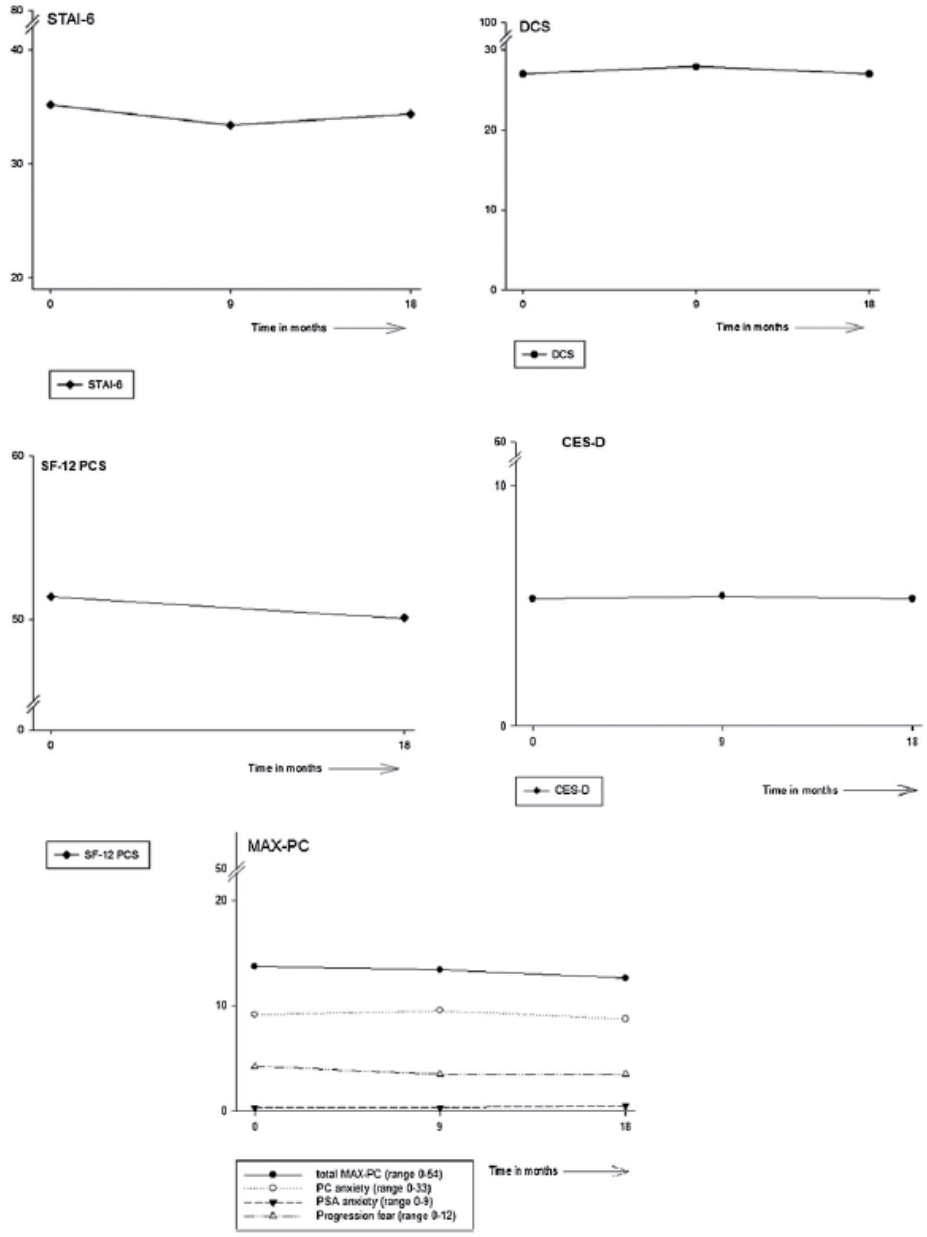

Figure 2: Mean questionnaire scores at t=0, t=9, and t=18 (in accordance with table 2).

Table 2 presents the mean, median and interquartile range of questionnaire scores at t=0, t=9 and t=18. Figure 2 shows a graphical overview of the mean questionnaire scores at t=0, t=9 and t=18. We noted non-significant decreases in the mean scores between t=0, t=9 and t=18 for the DCS (p=0.336), CES-D (p=0.655), total MAX-PC (p=0.331) and self-estimated risk of progression (p=0.457) scores. For the SF-12 (PCS), a non-significant (p=0.428) decrease was seen between t=0 and t=18. Generic anxiety (STAI-6) (p=0.033) and fear of disease progression (subscale of the MAX-PC) (p=0.007), however, decreased significantly when comparing t=0, t=9 and t=18. These differences, however, were clinically modest: 0.089 SD and 0.281 SD, respectively.

Twenty-six men presented with STAI-6 scores >44 at baseline. Eight of these 26 men (31%) became less anxious and remained on AS. Six (23%) men were highly anxious at t=0, t=9 and t=18 but remained on AS. Three men (12%) were highly anxious at baseline, their scores decreased to ≤44 at t=9 and at t=18 they quit AS because of tumor progression. Seven men (27%) were highly anxious at baseline and stopped AS because of reclassification of their PCa at t=9. Two men (8%) were highly anxious and therefore stopped AS; these latter two belong to the group of six men who stopped AS upon their own request.

Discussion

In men with low-risk PCa who were managed with AS for an 18-month period, average levels of anxiety and distress remained favorably low. Our findings suggested furthermore that generic anxiety and fear of disease progression tended to decrease in men remaining eligible for AS. Only six of 129 men (5%) discontinued AS because of anxiety or distress. Eight of 26 men who were highly anxious at baseline became less anxious while remaining on AS.

This study provides additional information on the effect of AS on longitudinal QoL scores. Anxiety and/or distress were uncommon reasons to stop AS and switch to active therapy. A significant trend towards lower scores of fear of disease progression was observed, which may be explained by the idea of stable disease providing confidence and tranquility of mind during follow-up [31] or by an upfront selection of those patients who expect that they can mentally deal with the potential progression of their disease. Our outcomes are supported by the results of a study among Finnish PRIAS participants that showed no deterioration of QoL after 1 [32] and 3 years [33] of follow-up. Instead, in this cohort of men, statistically significant QoL increases were seen, although clinically insignificant.

Not all men with low-risk PCa may be candidates for AS. It was found that men with more neurotic personalities tend to have a higher chance of anxiety or psychological distress, which may lead to not choosing AS at all or stopping AS early [2,34]. It has been hypothesized that such men could benefit from psychological support in making a treatment decision. Bellardita et al. found in multivariate logistic regression models that factors predicting poor QoL during AS were having no partner, impaired mental health, recent diagnosis, influence of clinicians and lower number of core samples taken at diagnostic biopsy [7]. They concluded that the assessment of such predictors at entrance in AS could be useful in identifying more vulnerable patients to prevent poor QoL by promoting educational support from physicians and emotional/social support. Such predictors can also help in designing and implementing educational psycho-social interventions to support patients and in promoting well-being and positive adjustment to cancer [7]. In the Finnish AS cohort, men newly diagnosed with PCa were thoroughly informed about their treatment options by a urologist as well as by a specialized PCa nurse [32,33]. Only patients who seemed to accept the idea of living with a possible clinically insignificant PCa for which no immediate treatment was needed were offered AS as a primary management option. The support that was provided in making a treatment decision led to none of the patients discontinuing AS because of anxiety in this cohort [32]. In our cohort, men were informed about all possible treatment options by their treating urologist. Potential additional methods of counselling were not standardized and decided upon by the individual centers. Applying predictors of poor QoL upfront inclusion on AS to prevent poor QoL by promoting educational support by physicians, as suggested by Bellardita et al. [7], or offering counselling, as suggested by Vasarainen et al. [32], to the two men who presented with STAI scores >44 could potentially have led to the continuation of AS.

The strengths of the present study are the prospective design and the availability of clinical parameters for all participants. The outcomes of our study provide support for AS as a management strategy for low-risk PCa. Furthermore, we consider the use of validated measures in our cohort as a strength. The measures show similar Cronbach's alphas compared with Dutch validation studies, except for the CES-D, which is potentially due to differences in the populations in which the Dutch translation of the measure was validated. The low number of missing values on the questionnaires indicates that patients considered the questions acceptable and that the questions were well understood.

Limitations of our study are the unavailability of a baseline measurement of anxiety and distress, the rather limited sample size, and that we cannot compare 18 months follow-up data of men on AS to QoL data of men who initially chose an AS strategy but later opted for curative therapy.

The fact that we were unable to obtain a baseline measurement of anxiety and distress levels before men made a treatment decision may have led to an underrepresentation in our cohort of men who expected to experience feelings of anxiety and distress about living with untreated PCa. It is therefore unknown how many men preferred active therapy over AS to avoid potential feelings of anxiety and distress of living with untreated PCa.

As men switching to active therapy during follow-up were not included in this study, we recommend focusing future research on QoL of men who switched from AS to active therapy. We found that of the six men who stopped AS because of anxiety and distress, two had reported high anxiety scores. It would be interesting to know how their QoL evolved after their decision to opt for curative therapy and the initiation of treatment. Also, four men discontinued AS because of distress, but this was not reflected in their anxiety scores.

Conclusion

When men with low-risk PCa are managed with AS, fear of disease progression and general anxiety decrease, and only few may discontinue AS because of anxiety and distress. This suggests that negative QoL effects are limited in men with favorable clinical characteristics who opted for AS. The sample size was small, however, and further research is needed to confirm our results.

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Chapter 7

Long-term follow-up after active surveillance or curative treatment: quality of life outcomes of men with prostate cancer

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Chapter 8

Urologists' opinion on active surveillance: USA versus the Netherlands

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And

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Abstract

Prostate cancer (PCa) treatment by active surveillance (AS) has emerged over the last 10 years. In the literature, AS is predominantly described from the point of view of patients and their potential benefit when they opt for AS. Throughout the years, several clinical studies were initiated and have reported their results, showing the feasibility of an AS program [1-4]. However, longer follow-up is needed to ensure the recognition of AS as an evidence-based treatment strategy. While much attention is paid to the validity and safety of AS, as well as the consequences for patients, also in terms of quality of life and psychological features, urologists' opinion about AS have been described less often. Therefore, this chapter will focus on urologists' acceptance of AS and their opinions about it within the USA and the Netherlands.

Background

In general, the concept of screening refers to identifying a disease at a stage in its natural history during which treatment can be applied to prevent death or suffering [5]. Potential benefits of screening should be an increased, however not excessive rate of early-stage detected cancers, a decrease in the occurrence of metastatic cancer and a reduction in disease-specific mortality. Screening for PCa is challenging as the natural history of the disease differs markedly between slow-growing indolent tumors and highly aggressive and potentially fatal forms [5]. Early detection of PCa was initiated around 1994, after the American Food and Drug Association approved prostate-specific antigen (PSA) as a screening test for PCa [6]. In that same period, several major screening studies, i.e. the European Randomized study of Screening for Prostate Cancer (ERSPC) [7], the Göteborg randomized population-based PCa screening trial [8], and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) [9], were started to assess whether PSA testing can reduce disease-specific mortality. In 2009 and 2010, the major screening studies provided evidence regarding the beneficiality of PSA screening for PCa-specific mortality. While the ERSPC and the Göteborg screening trial both reported a decrease in disease-specific mortality after a follow-up of 11 and 14 years, respectively, the PLCO trial did not show such an effect. On the contrary, according to the PLCO trial, screening for PCa does not lead to a decrease in disease-specific mortality. As the results are controversial, the efficacy of PCa screening using PSA remains debatable. What the studies have in common is that a large number of indolent cancers will be diagnosed when population-based screening would be applied. Although population-based programs have not been introduced, large numbers of men have had a PSA test at least once in their life.

Due to the introduction of PSA-based screening for PCa, increasing numbers of patients with low-risk tumors are being detected (low risk being defined as clinical stage T1c, biopsy Gleason score $\leq$6, the presence of disease in $\leq$3 biopsy cores, $\leq$50% PCa involvement in any of these cores, PSA density <0.15 ng/ml/g [10]). Data from the US Surveillance, Epidemiology and End Results (SEER) program confirm that between 1975-2005, the number of PCa cases increased substantially [11]. Later on, incidence declined again, though this did not retain to the level that was seen before the introduction of the PSA test. Currently, in the USA, nearly 200,000 PCa cases are diagnosed annually [12,13] versus nearly 9,900 PCa cases in the Netherlands [14].

The described increase in PCa incidence is not accompanied by an increase in disease-specific death rates. Apparently, the increased incidence does not reflect a true increase of the disease, and an explanation has to be found elsewhere. According to Challacombe

et al., the trend can be explained by the large stage shift from diagnosing palpable and locally advanced disease to diagnosing impalpable and localized disease [15]. Most of these screen-detected, low-risk tumors have favorable characteristics with high percentages of long-term survival [16-18]. Probably most of these malignancies would never have caused any symptoms if they had remained undiagnosed, because they resemble autopsy tumors [19,20]. Due to screening, these cancers are detected which leads to overdetection and therefore overdiagnosis [21], often resulting in overtreatment. Men diagnosed with these low-risk cancers are subjected to unnecessary costly and invasive treatment with the risk of the occurrence of side effects [22] and should therefore be protected against such overtreatment.

Active surveillance

Replacing initial active treatment by closely monitoring the disease and indicating curative treatment if risk reclassification occurs may contribute to achieve this aim. By avoiding or delaying active treatment - and its possible side effects - quality of life might also be preserved longer [22]. AS has been the subject of ongoing studies since the 1990s. Klotz et al. [2], Carter et al. [3], Kakehi et al. [4], van den Bergh et al. [1], Carroll at al. [23], Soloway et al. [24], Parker [25], Khatami et al. [26] and Stattin et al. [27] have all initiated studies regarding the value of AS. Klotz et al. [2] reported a median follow-up of 6.8 years in 2010; the other studies reported a shorter median follow-up [1-4, 23-27]. Up to now, reported results look promising; all studies show that a program of careful selection and monitoring of men who are likely to harbor clinically insignificant cancers is a rational alternative to active treatment. However, data still need to mature further for AS to be regarded evidence-based.

Comparison of the Official National Guidelines

Even though reported study results have not yet reached evidence-based status, guidelines in both the Netherlands and the USA already recommend AS as a treatment strategy for certain groups of men. In table 1, national guidelines from both countries are compared. Differences are seen with respect to last update, definition of AS, theoretical basis, groups to whom AS is recommended as well as the definition of low-risk PCa. The Dutch guideline was last updated in 2007, as compared to 2009, 2010 and 2011 for the American guidelines. Large differences are seen regarding the data on which the guidelines are based. The Dutch guideline is based on only two publications, whereas the American guidelines base their recommendations on 22, 7 and 7 publications, respectively. The guidelines of the NCCN and the American Cancer Society are based on more recent literature. A definition of AS is provided in three of the four guidelines. Where the Dutch guideline does not describe AS, the American guidelines do. The guidelines of both the NCCN and the American Cancer Society incorporate the defini-

Table 1: comparison of the official national guidelines

Guideline	URL	Most recent update	Definition AS	Basis of guideline	Groups AS is recommended to	Definition of low risk PC	Definition of very low risk PC
Guideline prostate carcinoma: diagnostics and treatment (Dutch)	www.oncoline.nl	2007	-	Albertsen et al. [16]; Vicini et al. [28]	Men > 75 years with low risk PC, men < 75 years with low risk PC AS will be discussed but curative treatment is preferred on the basis of currently available research results.	T1-T2a, Gleason < 7, PSA < 10	
NCCN Clinical Practice Guidelines in Oncology – Prostate Cancer	www.nccn.org	2011	Actively monitoring the course of disease with the expectation to intervene with curative intent if the cancer progresses.	Jemal et al. [29]; Schröder et al. [7]; Sakr et al. [30]; Thompson et al. [31]; Klotz [32]; Draisma et al. [33]; Epstein et al. [10]; Jeldres et al. [34]; Bastian et al. [35]; Chun et al. [36]; Bastian et al. [37]; Draisma et al. [21]; Lu-Yao et al. [38]; Sanda et al. [39]; Shappley et al. [40]; Bill-Axelson et al. [41]; Schröder et al. [42]; Schwartz [43]; Carter et al. [3]; Choo et al. [44]; Stephenson et al. [45]; van den Bergh et al. [46].	Men with very low risk PC and LE < 20 years, men with low risk PC and LE < 10 years.	T1-T2A, Gleason score 2-6, PSA < 10 ng/ml	T1c, Gleason ≤ 6, PSA < 10 ng/ml, < 3 biopsy cores positive, ≤ 50% cancer in each core, PSA density < 0.15 ng/mL/g
AUA: Prostate Cancer – Guideline for the management of clinically localized prostate cancer	www.auanet.org/guidelines	2007 (reviewed and validity confirmed 2009)	A monitoring program without initial treatment for the patient with localized cancer.	Albertsen et al. [16]; Klotz [47]; Johansson et al. [48]; Zietman et al. [49]; Adolfsson et al. [50]; Hardie et al. [51]; Warlick et al. [52].	Men with lower risk tumours and a shorter LE.	PSA ≤ 10 ng/mL, Gleason ≤ 6, T1c-T2a	
American Cancer Society Guideline for the early detection of prostate cancer	www.cancer.org	2010	The process of regularly monitoring disease activity through clinical parameters (PSA, DRE) and possibly periodic rebiopsy, with active treatment offered to men whose disease appears to be progressing.	Albertsen et al. [16]; Lu-Yao et al. [38]; Choo et al. [44]; Carter et al. [3]; Roemeling et al. [53]; van den Bergh et al. [46]; Burnet et al. [54].	Men whose cancers are Gleason ≤ 6.	-	

tion of AS as 'intervening with curative intent if the cancer progresses'. The decision to recommend AS or not is based on tumor characteristics, but also on life expectancy. The briefest description of the target population is presented by the American Cancer Society guideline; AS is offered to men who have a cancer with a Gleason score ≤ 6. The American Cancer Society guideline does not provide a description of a low-risk tumor. The Dutch guideline and the NCCN guideline use the same definition of a low-risk PCa, whereas the definition on the AUA guideline differs slightly (T1-T2a in the NCCN guideline, versus T1c-T2a in the AUA guideline). The NCCN guideline is the only one to distinguish a very low-risk PCa from a low-risk PCa. Overall, the authors feel that the NCCN guideline provides the most informative recommendation. The Dutch guideline requires updating, a definition on AS and a broader theoretical base.

Rate of men treated with AS

In the USA, currently approximately 200,000 new cases of PCa are diagnosed annually as compared to nearly 9,900 in the Netherlands. According to Snyder et al. [55] approximately 90% of the PCas are clinically localized at diagnosis. This is confirmed by Jemal et al. [56] who report that approximately 92% of the prostate cancers are diagnosed at either an early or regional stage. After having received the diagnosis of early or regional stage prostate cancer, the 5-year relative survival rate of these cancers approaches 100% [56]. Many of these men are eligible for AS; however, it is estimated that in the USA, currently only approximately 10% of all PCa eligible for AS is treated with AS [57]. Data from the SEER database show that the percentage of patients treated with AS has decreased in the last years [58].

Within the Netherlands, hospitals and insurers use a 'DBC pricing system'. A DBC is a code which describes a provided treatment, including the associated costs. It encompasses all activities and medical surgeries that a patient undergoes in hospital for the treatment of a certain disease during a certain time period. Currently, no DBC is available for AS, which makes it difficult to estimate how many men newly diagnosed with PCa are put on an AS regimen. Based on reports of Dutch urologists about the number of newly diagnosed patients with PCa they see every year and the number of patients opting for AS as a treatment strategy, we estimate that approximately 17.7% of the newly diagnosed PCa patients choose AS as their initial treatment strategy.

Viewpoint of the Dutch and American urologists

On the one hand, there is a rising demand for an evidence-based approach regarding AS; on the other hand, not all urologists have a positive attitude towards such a program of closely monitoring the disease and interfering when progression occurs. The way in which urologists describe PCa to newly diagnosed patients influences their

perceptions of the seriousness of their condition and sets the tone for the ensuing treatment consultations [57]. Other studies confirm that patients with PCa rely heavily on recommendations by urologists in their choice of treatment [69-61]. It is important that urologists are aware of this. The fact that not all urologists have a positive attitude towards AS is shown in a study by Gorin et al. [61]; of all respondents that were eligible for AS, 36% were actually offered AS by the urologist who had first diagnosed their PCa. Gorin et al. concluded that a significant proportion of the study population, i.e. 64%, were denied access to this option solely by their urologists' attitude about AS [61].

Observed opinion about AS of the urologists in the USA and the Netherlands

To analyze the opinion of the urologist on AS, a questionnaire was developed by the authors including questions on how many newly diagnosed patients with PCa the urologist sees every year, whether the urologist brings up AS as a treatment option, whether patients ever bring up AS as a treatment option, whether AS is offered to patients with a low-risk PCa, etc. (see table 2). Within the Netherlands, 328 urologists, all senior members of the Dutch Urology Society (NVU), were addressed of whom 180 responded (response rate 55%). Of the respondents 87% (156/180) were working in a peripheral hospital and 13% (24/180) in an academic hospital. All urologists report to bring up AS as a treatment option, especially for low-risk PCa (low-risk being defined as T1-T2a, Gleason score < 7, PSA $\leq$ 10 ng/ml). For intermediate PCa, 55 urologists (31%) bring up AS as a treatment strategy as opposed to 69% who do not offer AS. Urologists were also asked whether patients ever bring up AS during a consultation; 103 urologists (57.2%) confirmed this, while 77 urologists (42.8%) reported that their patients did not bring up AS. 128 urologists (71.1%) offer watchful waiting as an alternative for AS to patients eligible for AS. Overall, the Dutch urologists reported to have a positive attitude towards AS.

Table 2: Questions included in the urologists questionnaire

- How many newly diagnosed patients with PC do you see each year?
- Do you bring up AS as a treatment option?
- Do patients ever bring up AS as a treatment option?
- Do you offer AS to patients with low-risk PC? Low risk PC is defined as T1-T2a, Gleason score < 7, PSA < 10 ng/ml.
- Do you offer AS to patients with intermediate PC? Intermediate PC is defined as a T3 tumor.
- Do you offer watchful waiting (WW) as an alternative to AS?
- Are you familiar with the (Dutch) 'Guideline prostate carcinoma: diagnostics and treatment'.
- Opinion on the AS section in the Dutch guideline.
- Which factors influence your recommendation for AS; patient request, the guideline, own experiences, financial incentives, ongoing AS studies, or other factors. Please list in your order of importance.

Throughout the years, in the USA, awareness for PCa screening was raised by media stories and awareness campaigns sponsored by hospitals and by the US Postal Service who wanted to raise awareness for PCa by selling stamps (the PCa stamp was released in 1999) [62,63]. As a result, men visited the physician with the request for a PSA test. If the PSA test was negative, a patient would be grateful, but also when a suspicious PSA result was followed by a negative biopsy result. And a patient would also be grateful in the case of an early-detected PCa. For a professional, i.e. a physician or a urologist, the situation could be interpreted as a 'no-lose' situation. According to Ransohoff et al., time has to be spent in persuading a patient that screening for PCa is not necessary. At the same time, the health professionals risk an allegation of malpractice if screening is not performed and a cancer is found later, even when several discussions between the professional and the patient preceded the final decision not to screen [63]. Ransohoff et al. described that medical malpractice operates in a one-directional way; lawsuits only occur when a cancer is detected too late and not when a diagnosis is made too early so that an applied therapy is not beneficial. Because of the risk of malpractice allegation and the gratefulness of patients for being diagnosed early, a system without negative feedback regarding PCa screening has developed throughout the years [63].

AS can reduce the overtreatment that results from the overdiagnosis by screening for PCa. When on AS, the patient is closely monitored, and if risk reclassification occurs, curative treatment is started. In the in-between visiting periods, the chance of reclassification is at stake. Here again, the risk of malpractice allegation is present as reclassification of the tumor can arise too late in the sense that curative therapy is no longer possible; however, this is an exception rather than the rule. Klotz et al. performed a PSA test every 3 months in the first 2 years and then every 6 months in patients with a stable PSA [2]. They reported a 10-year cancer-specific survival rate of 97.2%. The cancer-related mortalities occurred in men who had been reclassified as higher risk and who had been offered radical treatment [2]. Krakowsky et al. report that some patients with favorable-risk disease at diagnosis harbor more aggressive disease and may be at risk for PCa mortality in spite of close monitoring [64].

To protect patients against inexpert and inaccurate performances of healthcare professionals and to maintain quality standards of care, cases of medical malpractice within the Netherlands can be reported at regional medical disciplinary tribunals [65]. In 2010, the regional medical disciplinary tribunals settled 11 urologic complaints (on approximately 600 professionals) which amount to 1.83 complaints per 100 professionals for that year [66]. In the USA, Stimson et al. report on 1,516 unsolicited patient complaints filed against 268 urologists from January 1, 2004 through December 31, 2007 [67], which amounts to 141 complaints per 100 professionals per year. Such patient complaints can

Table 3: Frequency of discussing active surveillance (AS) in various circumstances (n=180 Dutch urologists)

Question	Yes N (%)	No N (%)
Do you bring up AS as a treatment strategy for low risk PC	180 (100)	-
Do you bring up AS as a treatment strategy for intermediate risk PC	55 (30.6)	125 (69.4)
Do patients ever bring up AS during a consultation	103 (57.2)	77 (42.8)
Do you offer watchful waiting as an alternative for AS	128 (71.1)	52 (28.9)

result in malpractice claims. In the USA, Perrotti et al. report on urological malpractice claims that were filed with the Medical Liability Mutual Insurance Co. (MLMIC) of New York State that were consecutively closed between 1985 and 2004 with indemnity payment. MLMIC insured approximately 400 of the 1,100 urologists practicing in New York State. A claim was considered urological malpractice when the insured practitioner was a urologist. In most cases, the claim was directly related to the practice of urology, but it also included alleged negligent acts related to additional clinical data. A total of 469 urology malpractice claims were closed with indemnity payment [68], which averages to 6 claims per 100 professionals per year. For the Netherlands it is not clear how many complaints ended in indemnity payment. However, when comparing the 1.83 per 100 professionals rate with the 141 per 100 professionals, it is not likely that the rate of complaints ending in indemnity payment in the Netherlands will rise above the American rates.

In the USA, the option of expectant management is offered to a small percentage of patients, approximately 10% of healthy 65-year-old men who have a Gleason score > 4 or a PSA > 4.0 ng/ml [69,70]. Choosing AS is a complex decision a man has to make as he has to deal with the thought of living with untreated cancer. In it lies the concept of regret. According to Ransohoff et al., regret, just like medical malpractice, operates in a one-directional way; if cancer progresses during AS, a patient may regret not having acted sooner. On the contrary, regret may not occur when active therapy was chosen, because the patient knows that every possible measure to cure his cancer was taken [63]. Also here, radical therapy may lead to a no-lose situation for the professional; if radical therapy does not lead to cure, then still everything possible was done to cure the patient's cancer. If a patient remains asymptomatic without recurrence, he will ascribe his survival to both detection and therapy. Although many urologists in the USA refrain from offering AS to men with low-risk PCa and are cautious to recommend it, several urologists acknowledge that by opting for AS the management of early-diagnosed PCa can be individualized [3,11,25] and morbidity as a result of treating low-risk PCa can be avoided or delayed.

The Guidelines

Guidelines in the USA differ slightly in their definition of AS and recommendations about its target groups. However, the guidelines do provide a framework which is used in several American AS studies [2,3,24].

In the Netherlands, almost all urologists (96.7%) reported that they are familiar with the Dutch guideline. Most urologists agree with the current 2007 guideline on AS; however, some have the opinion that, instead of the current preference for curative treatment, AS could also be offered to men under the age of 75 years. Also, they would like to see a more specific description of AS in the guideline, as AS is now easily confused with watchful waiting, while the aim of the treatments differs. AS can be described as withholding initial radical treatment and instead closely monitoring the disease with the purpose of switching to invasive local therapy with a curative intent if risk reclassification occurs [1]. Watchful waiting is predominantly offered to older men who are physically unfit and have a limited life expectancy. It also consists of withholding initial treatment and monitoring the patient; however, when symptomatic progression occurs, often palliative therapy is offered to the patient instead of radical treatment. The aim of watchful waiting is to alleviate disease symptoms without attempting to cure the disease [25,71].

Factors that influence the opinion of urologists regarding AS

The opinion of urologists about AS influences patient treatment decisions. It is therefore worthwhile to take a closer look at the observed differences between the USA and the Netherlands and to identify factors that influence the choice of a urologist to recommend AS or not.

US urologists have been reported to be predominantly led by clinical characteristics of the patient such as PSA, PSA kinetics, PSA doubling time, digital rectal examination, transrectal ultrasound, results of repeat biopsies and patient comorbidity [25,72] in deciding whether or not to recommend AS. According to Klotz, who summarized the results of quality of life studies on AS [54,73-75], surveillance may be stressful for some men, but anxiety about PSA recurrence is common among both treated and untreated patients [11]. Klotz feels that such anxiety can be avoided by educating patients to appreciate the indolent natural history of most good-risk PCa [11].

We asked Dutch urologists which factors influenced their decision to offer AS most; the request of the patient, the guideline, own experiences, financial incentives and/or the current lack of mature follow-up data on AS. Urologists could list additional influential factors if desired. Dutch urologists reported to be predominantly led by the wish of the patient (55%, n=99 urologists); financial incentives played the least influential role

(<1%, n=1 urologist). More than half of the respondents reported that they also take into account patients' physical and psychological characteristics, as well as clinical characteristics when deciding which treatment would suit the patient best.

Financial incentives

Undoubtedly, there are different financial incentives that may play a role in the various medical care systems. Costs of treatments and their reimbursement are of continuous interest to health professionals. Also, when advising AS, urologists have to regard these aspects. The Dutch urologists - except one - reported that financial incentives did not play a dominant role, which does not have to mean that financial incentives never play a role at all. Also, within the USA, the potential role of financial incentives influencing medical malpractice is acknowledged by Barry et al. [76]. They report that when patients face medical decisions with multiple options, there are many stakeholders with different (financial) interests in promoting a particular choice, e.g. pharmaceutical agents, manufacturers of screening tests and medical devices, insurance companies and doctors [76]. According to Ransohoff, screening and therapy occur in an environment where financial incentives occur at several levels, which may give the impression that healthcare institutions and industry support screening for PCa [63]. We conclude that AS is possibly not offered to patients because of unfavorable clinical characteristics, the urologist not being convinced of AS as a treatment strategy or because more money can be earned by opting for other treatment options. Nguyen et al. described the latter and recognized that newer, more expensive technologies for treating prostate cancer have rapidly been adopted throughout the last years, without them being cost-effective [77]. Newer and more expensive alternative treatments will also be introduced in the future as technology keeps on striving forward. Interest from patients and providers in these new technologies as well as the belief by advocates that they could improve outcomes is sometimes sufficient to introduce these new technologies into clinical practice [77]. AS is said to be a novel strategy in treating PCa [25]; however, it does not enhance enormous earnings for healthcare providers and cannot be compared to, e.g. robotic surgery in which technology as such plays a crucial role. Perhaps we can say that although AS is a novel strategy, it is not a technology and as such the speed of its introduction is limited.

Discussion

Differences between the Netherlands and the USA regarding AS were described with respect to the guidelines, the rate of men treated with AS, the observed opinion towards AS and factors influencing the decision of the urologist in recommending AS including the possibility of financial incentives and the risk of malpractice allegations. The analysis

was performed on questionnaire data of Dutch urologists and on the available literature. We conclude that environmental circumstances are not likely to obstruct the adoption of AS as a treatment strategy; however, the circumstances do not encourage adoption either. It will depend to a large extent on the urologist and his working environment, whether or not AS is adopted as a treatment strategy.

The authors of this chapter feel that the Dutch guideline on AS should be updated and should take into account the available longer follow-up data on AS as well as including more literature on which to base the arguments for or against AS. With respect to the American guidelines, the authors feel that, in particular, the American Cancer Society guideline should be more explicit about to whom AS should be recommended as well as what should be considered a low-risk PCa.

The rate of men treated with AS is approximately twice as high in the Netherlands as in the USA. The difference can possibly be explained by the more reserved attitude of American urologists towards AS, as they encounter a higher risk of malpractice allegation. In both countries, however, the percentage of men treated with AS is considerably small. More mature follow-up data are necessary before AS can/will be recognized as an evidence-based treatment option. It should be taken into account, however, that the risk of malpractice allegation is not likely to change in the USA.

It is rather difficult to compare the opinions of the urologists from both countries. While results of the survey in the Netherlands show a very positive attitude towards AS so far, it cannot be judged whether the non-respondents share the same opinion as the respondents. Cultural differences between Dutch and American urologists may lead to different opinions. Also, within the USA, a segregation is seen between urologists who have a positive opinion about AS and the ones who do not. It is not likely that in the future all urologists will be positive towards AS.

In the light of possible malpractice allegation, it is likely that American urologists are predominantly led by clinical characteristics in recommending AS. Clinical characteristics are objective and therefore not subject of debate. When a patient opts for AS after having discussed it at length with a urologist, this discussion and weighing of pros and cons is of small use, with respect to malpractice allegation, when the cancer progresses unexpectedly and the patient dies as a result [63]. Such a situation does probably not reflect everyday reality; still, urologists may run into a claim which may translate into reluctance in recommending AS.

Conclusion

Differences between the Netherlands and the USA in recommending AS can possibly be explained by the judicial status of malpractice procedures. Within the Netherlands, such continuous risk of malpractice allegation is present, however, to a much lesser extent when compared to the USA. Next to that the possible lack of financial incentives for AS should be incorporated into the overall perspective on AS. Arguments like follow-up data of AS not being mature enough, professionals facing the risk of a malpractice allegation if not 'everything is done', new technologies being available for treating PCa patients with less side effects and patients feeling relieved when cured from PCa all influence the choice of a urologist to offer AS.

Epilogue

Longer follow-up data are awaited from ongoing AS studies. The availability of such data will, most probably, result in a slight increase in men put on AS. However, the discussed elements of malpractice allegation in combination with new technologies and the possible financial incentives resulting from immediate curative treatment will probably restrain an increase in the number of patients opting for AS as their preferred treatment option. The authors expect that the rate of men on AS in the Netherlands will increase gradually over the coming years as AS is seen as a realistic strategy in reducing overtreatment.

For the future, a more accurate differentiation between aggressive and potentially indolent PCa is important. Prediction models can support the provision of tailored risk predictions to the urologist and the patient. Van Vugt et al. provided insight into the implementation of the ERSPC risk calculator in five Dutch hospitals. Urologists in a clinical setting appeared to be prepared to use the prediction model and its treatment recommendations to support treatment decision-making in men with localized PCa [78].

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Chapter 9

Active surveillance for prostate cancer: a legal perspective

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Abstract

Active surveillance (AS) for prostate cancer (PCa) has become a viable management strategy for men with low-risk PCa. With AS being offered more often and more patients being included in AS studies, the aim of this paper is to describe AS from a legal perspective. What might be pitfalls in the management strategy that urologists should be aware of? In order to construct an answer to our research question, a patient from the Prostate cancer Research International: Active Surveillance (PRIAS) study will be used as an example. In the methods section, first some information on the PRIAS study is given. Then a PRIAS case will be described after which the Dutch legal framework will be set-out. Finally, the Dutch legal framework will be applied to the PRIAS case to find what would happen if that particular patient would file a complaint. On the basis of the analysis we can conclude that urologists that offer AS should be aware of the information they provide to the patient when entering AS but also during follow-up. It is furthermore important that urologists act in line with their medical professional standards. Therefore it is advised that urologists follow the progress that is made within the field of AS carefully, as the field is moving rapidly.

Background

One of the first publications describing prostate specific antigen (PSA) as a potential biomarker for prostate cancer (PCa) was published in the 1960's [1]. In 1986 the PSA-test was approved by the American Food and Drug Association (FDA) as a test to aid in the management of patients diagnosed with PCa, and in 1994 the FDA approved the PSA-test as a diagnostic tool [2]. Since then, much progress has been made in the field of PCa detection.

With increasing evidence that PSA could be used for the early detection of PCa [3], it was in the beginning of the 90's that researchers from Belgium and the Netherlands made plans to conduct a randomized study of screening for PCa [4,5]. Pilot studies were initiated of which the most important conclusion was that a randomized controlled trial of screening for PCa in Europe seemed feasible. However, it was necessary to seek international cooperation to meet the large sample size [6]. Finally, the European Randomized study of Screening for Prostate Cancer (ERSPC) was initiated in 1994. Around the same time in the US the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial was initiated [7].

After the introduction of the PSA-test and the initiation of screening trials, the incidence of PCa in Western countries increased remarkably. Data from the American Cancer Society as well as from the European Cancer Observatory confirm this [8,9]. Over time incidence declined; however, the incidence rates did not retain to the level that was seen before the introduction of the PSA-test as a diagnostic tool in the beginning of the 1990's. If this observation would reflect a true PCa increase, it should be accompanied by an increase in disease-specific mortality. This is, however, not the case, not even today [8]. The contrary seems to be true; PCa-specific mortality declined between 1975-2010 [8,10]. Now that the increase in incidence and mortality do not collide, another explanation for this phenomenon has to be found.

Screening for PCa has resulted in a marked stage shift; fewer men present with metastatic disease, while more men present with earlier and lower stage, lower grade and lower PSA at diagnosis [11,12]. Although screening has shown to be effective when done in a systematic way as compared to a situation with hardly no screening [13,14], it also causes overdiagnosis in the range of 27-56% [15,16]. Overdiagnosis occurs when a tumor is detected that, if left unattended, would not have become clinically apparent or caused death [11,15]. If such overdiagnosed tumors are actively treated, one speaks of overtreatment. Overdiagnosis and overtreatment are associated with harms from treatment, like incontinence and impotence, but also with a psychological burden. To date, a

lot of PCa research therefore focuses on how to reduce overdiagnosis. The discovery of a biomarker that would be able to distinct aggressive from indolent PCa (a PCa that is unlikely to become symptomatic during life, also known as a low-risk or minimal cancer) would solve a large part of the overdiagnosis dilemma; however, no such biomarker is currently available.

Because most PCa's found nowadays are low-risk PCa's which have favorable characteristics and a beneficial long-term survival, active treatment is not immediately necessary [17]. It is thought that the replacement of initial active treatment with active surveillance (AS) in patients with low-risk PCa is a realistic option [17]. The aim of AS is to avoid overtreatment. With AS the tumor is closely monitored with the purpose of switching to active treatment if progression occurs. Over the past decade several AS studies have been initiated worldwide, which so far show encouraging results [18].

That AS becomes a more viable option is also recognized by many national and international urological associations. Guidelines of the European Association of Urology (EAU), the American Association of Urology (AUA), the Societé International d'Urology (SIU), the German Urological Association (DGU) and the Dutch Urological Association (NVU) all have been updated in recent years, including AS as a management strategy for very low-risk or low-risk PCa [19-21].

Now that AS is more often offered to men with low-risk PCa and more patients are included in AS studies, the aim of this paper is to describe AS from a legal perspective. With AS the chance always exists that the 'window of curability' is missed and that switching to active treatment comes too late with worse outcomes on radical prostatectomy or radiotherapy as a consequence. What would happen if a patient who was in such a situation, would file a complaint? How will such a complaint be dealt with within the Dutch legal system? What might be pitfalls in the management strategy that urologists should be aware of?

Methods

Worldwide, several AS studies have been initiated. In this paper a patient from the Prostate cancer Research International: Active Surveillance (PRIAS) study will be used as an example. First some information is given on the PRIAS study. Then a PRIAS case, patient X, will be described after which the Dutch legal framework will be set-out. Finally, we will apply the Dutch legal framework to our PRIAS case to find out what would happen if that particular patient would file a complaint.

PRIAS

PRIAS is a protocol-based, multicenter, observational study which started in 2006. It was initiated by investigators of the Rotterdam section of the ERSPC and the Department of Urology, Erasmus University Medical Center, Rotterdam, the Netherlands. It was designed to validate a protocol designed on currently available knowledge and if necessary adapt the management of low-risk PCa with AS. The PRIAS study is entirely web-based [17]. Currently, PRIAS holds more than 4,300 patients.

PRIAS inclusion criteria are: PCa diagnosis with a PSA of $\leq$ 10.0 ng/ml; a PSA-density (PSA/prostate volume) of < 0.2 ng/ml/ml; T-stage $\leq$ T2; one or two positive prostate needle-biopsy cores, with a Gleason score of $\leq$ 3+3 = 6. The follow-up protocol includes PSA measurements every three months for the first two years and every six months thereafter. Digital rectal examination (DRE) is scheduled every six months for the first two years and once a year thereafter. Repeat biopsies are scheduled after 1, 4 and 7 years, and in case of a PSA-doubling time between 3 and 10 years, yearly repeat biopsies are advised. Risk reclassification at repeat biopsy triggers a recommendation for active therapy and is defined as $\geq$ 3 positive biopsy cores and/or Gleason score > 6. A PSA-doubling time (PSADT), which can only be reliably calculated after a minimum of one baseline and four follow-up measurements, of less than three years is also used as a trigger to initiate active therapy [22]. Men entering into PRIAS all sign an informed consent.

Study protocol versus guidelines

As said, many national and international guidelines have captured AS in their guidelines [19-21].

Although AS is recognized as a reliable management strategy, the inclusion criteria are not straightforward yet. Differences in the AS inclusion criteria are seen in different parts of the world and captured in the various guidelines. Furthermore, the guidelines on AS are not yet clear-cut and still leave room for interpretation and improvement. Currently, for instance, the feasibility of including multi parametric imaging (MRI) into the AS protocol is being researched. It is hypothesized that with the use of MRI the percentages of undergrading of systematic prostate biopsy and upstaging of the tumor may decline [23].

In 2013 the Movember – GAP3 project was initiated to integrate the various existing AS protocols into one straightforward, unambiguous protocol. The project started in 2014 and the results are expected within two years from now (www.movember.com).

AS in Dutch daily clinical practice

Earlier research shows that when offering AS to patients 84% of Dutch urologists follow the PRIAS protocol. Most urologists (97%) are also familiar with the NVU guideline on PCa [24]. In comparison; the PRIAS inclusion criteria are: PSA of ≤10.0 ng/ml; a PSA-density of < 0.2 ng/ml/ml; T-stage ≤ T2; one or two positive prostate needle-biopsy cores, with a Gleason score of ≤ 3+3 = 6. The NVU guideline AS inclusion criteria are: T1c-2a, Gleason score < 7, PSA < 10 ng/ml and one or two positive needle-biopsy cores.

Case description

PRIAS patient X, aged 63, is diagnosed with T2a, Gleason 6 PCa in 2 out of 12 cores in 2010. He is suitable for AS according to the PRIAS protocol and thus decides to undergo AS as an initial treatment option for his PCa. After 1 year he receives a repeat biopsy (according to protocol) which shows Gleason 6 PCa in 3 out of 12 cores. With more than 2 cores positive for PCa the protocol advised to switch to definitive treatment. In addition his PSA is rising (PSADT < 3 years) which would also be a trigger for active treatment. The patient and physician decide to ignore this advice and to continue with AS (most likely because the Gleason score is still 6, accepting the known undergrading rates of systematic prostate biopsies). One year thereafter, so two years after diagnosis, he receives another biopsy. This biopsy shows a Gleason 9 PCa in 2 out of the 12 cores. Patient discontinues AS and undergoes radical prostatectomy (RP).

One year post-surgery patient X experienced permanent erectile dysfunction, urinary incontinence and biochemical recurrence (defined as two subsequent PSA values of > 0.2 ng/ml after RP). The last PSA of patient X amounted to 21.6 ng/ml.

Dutch legal framework

In the Netherlands, the patient-doctor contract is regulated by the Medical Treatment Contract (Wet Geneeskundige Behandelingsovereenkomst, [WGBO]). The WGBO, which is part of the Dutch Civil Code, runs from article 7:446 to 7:468 Civil Code and contains the patient's core rights. According to art. 7:468 Civil Code the provisions of the WGBO are binding. Core values of the WGBO are the right of self-determination and human dignity [25].

Art. 7:446 Civil Code describes the patient-doctor contract that is realized once medical actions are performed. In the Netherlands such a patient-doctor contract is not explicitly signed, but is assumed to exist when medical actions are performed for the first time. Clauses 2 and 3 of art. 7:446 Civil Code define what medical actions are, i.e. all patient related actions that intend to cure the patient, to prevent sickness, to judge a person's

health condition or providing obstetrical assistance. Nursing and caring, in certain situations, can be defined as medical actions as well.

The patient-doctor contract holds rights and obligations for both the patient and the doctor. Doctors should provide their patients with information, they have to obtain consent from their patients before starting treatment, they have to act according to their professional standards, they have to file all patient information and give patients the right to inspect their files, they hold the oath of secrecy and only under very special circumstances can one-sidedly terminate the patient-doctor contract.

While the goal of the WGBO is patient protection, patients not only have rights. They also have obligations. On the basis of art. 7:452 Civil Code patients should provide all information that doctors need in their decision making process as well as cooperate and collaborate in effectuating the doctor-patient contract.

Art. 7:448 Civil Code mainly concerns the right of information that patients have. A doctor is obliged to provide information about the intended medical actions, treatment and the patient's current health status that is clear, relevant and adjusted to patients' educational level. It would be recommended if patients receive written information on these matters as well. Art. 7:448 Civil Code mentions the following aspects on which information should be provided: what the intended medical actions/treatment holds, risks, goal, nature and alternatives of the intended medical actions/treatment. Finally, the doctor informs the patient what all this means for their future health and the patient's perspectives. The right of information is intended to enable patients to make a well-informed decision on whether or not to provide consent on the proposed treatment. In providing the information, the doctor should be guided by what the patient should reasonably know regarding the nature and purpose of the treatment, the anticipated risks and effects, the possible alternatives and its prospects. Failing the fulfillment of this obligation raises the possibility that a patient cannot use, or only partly use, his right of self-determination which increases the risk of the patient making a choice he would not have made had he been well-informed. In case the discussed risks occur, the patient has to pose and proof that he, had he been well-informed, as a reasonably competent patient and/or due to personal circumstances would have made another choice [26-28].

Art. 7:450 Civil Code indicates that in line with the patient-doctor contract a patient's consent is needed before any medical actions are started. To overcome discussions on whether consent was provided by the patient, an option would be to have patients sign an informed consent (art. 7:451 Civil Code). Patients should only sign such an informed consent if they feel adequately informed and can take a well-considered

decision to consent. If this is not the case it would result in a violation of their right of self-determination.

Art. 7:453 Civil Code requests doctors to act according to their professional medical standards. Based on these professional medical standards, a doctor is required to work according to knowledge and competences deemed familiar in their area of expertise. Professional medical standards are based on knowledge and competences a doctor should learn during their specialist-training, knowledge gained from literature, attending medical conferences, sub-speciality consensus meetings, refresher courses, in-service trainings, protocols, guidelines and own experiences.

The WGBO holds the obligation that doctors should make an effort in treating their patients instead of contracting a result. Doctors are legally responsible if they have trespassed their obligation to make an effort, if they have not done their upmost best, i.e. a violation of art. 7:453 Civil Code. This is the case when a doctor has not acted in line with the professional medical standards of their specialty.

Furthermore, doctors are legally responsible if a patient foregoing medical treatment is not sufficiently informed about treatment, treatment related effects and possible alternatives. The patient has made a decision on the basis of poor information. A doctor is legally responsible for the adverse effects of that treatment in case the patient would have chosen another alternative had he received all relevant information.

On the basis of art. 7:463 Civil Code it is impossible for doctors to contractually limit or exclude their shortfalls.

A special feature of the patient-doctor contract lies in its central liability. Because patient-doctor contracts are often effectuated in hospitals where various healthcare workers are involved in the care process of a patient, it may be difficult for the patient to hold one of them responsible in case a fault is made. Art. 7:462 Civil Code determines that in such situations it would suffice if the patient holds the hospital responsible.

Art. 7:462 Civil Code therefore also protects patients. The article provides an additional point of contact for patients to turn to. This may be necessary in case a doctor cannot provide sufficient resources.

What happens when patient X from our case description holds its doctor legally responsible?

For a patient it is not easy to prove that due to the actions of his doctor damage occurred for which the doctor is liable. In principle it is up to the patient to prove this and he therefore should make use of the opinion of an independent medical expert. This expert will write a report in which he passes his judgment on the course of illness and/or about the effect of medical treatment on the course of the illness. The patient can take this report to court and try to convince the judge - who is not medically trained - the doctor is liable for the damages occurred. The medical expert thus plays an important role; the facts and the expert's opinion are in general decisive, unless valid and compelling reasons regarding the expert's report exist.

In court, parties can request a judge to appoint an independent expert. The judge will, in consultation with the parties, appoint an expert and formulate the questions the expert must provide his judgment on. Another possibility is that the parties themselves appoint an independent expert. When parties reach agreement on who is to fulfil the role of expert as well as the key question that he should answer, then, in practice, the report of the by parties appointed expert is valued the same as the report of the expert appointed by a judge.

For this article we have asked two urologists specialized in urologic oncology (one with over 30 years of experience and one who recently completed his residency) and both working in an academic setting to act as 'experts' and to provide an expert opinion on patients' X case. The authors have set-up a questionnaire (table 1) which was sent to the experts together with the patient file.

Table 1: A selection of questions included in the questionnaire sent to the experts

- How would you handle the conversation in which a patient has to choose his treatment?
- Which risks, complications and alternatives did a reasonable and reasonably competent urologist in 2010 should have discussed with patient X? Please refer to relevant literature, protocol and guidelines as much as possible.
- How often, in your experience, did patients choose AS after having provided all relevant information?
- Do you consider that the conduct of the urologist of patient X during the AS strategy between 2010-2012 at any time did not meet the standard of care that could be expected from a reasonable and reasonably competent professional? Please take into account the then prevailing medical standards.
- In case of a negligent act, please discuss the consequences for patient X?
- May the damage also have occurred when the urologist would have acted carefully? If so, please express through percentages.

After men are diagnosed with PCa a treatment strategy has to be chosen. Which treatment options are offered, depends on the physical conditions of the patient and his tumor characteristics. In case of low-risk PCa and a good physical condition of the patient the experts would offer either AS, RP, radiotherapy (RT) or brachytherapy (BT). The urologists' preference will influence the order in which the options are discussed.

Risks and complications of AS that, according to the experts, needed to be discussed were the risk of PCa progression and the subsequent possibility of being 'too late', meaning that a second treatment will no longer be curative. Furthermore, the risks of repeated biopsies should be discussed as well as the AS follow-up scheme. The patient information brochure of the Dutch Cancer Society (KWF) says that every three to six months the urologist will perform a DRE and a PSA-test. If the course of disease stays stable over a period of two years, the frequency of the follow-up visits decreases to once a year. If the PSA increases, a yearly echo of the prostate as well as yearly prostate biopsies will be taken. In case of signs of tumor progression, switching to curative treatment is advised.

The experts feel that for RP it is important to discuss the perioperative risks of the operation as well as the potential long term consequences. Perioperative risks of this abdominal/urological surgery are the possibility of haemorrhage, urine leakage, lymfocele, infections and thrombosis. Long term consequences that should be discussed are potential incontinence and impotence.

When discussing RT as a treatment option, it is important to discuss that besides the possibility of becoming incontinent or impotent, also radiation cystitis and proctitis can occur. This means that patients can experience radiation damage, which may cause urinary problems or fecal urgency. Side effects of BT are comparable to that of RT, although less intense.

The experts have experienced that once good information is provided, many patients (75-90%) comply with the initially advised AS protocol.

With respect to patient X, both experts feel that he was correctly included in the PRIAS protocol as he fulfilled the inclusion criteria of the study. According to the protocol patient X undergoes a repeat biopsy after 1 year. The outcomes of that biopsy showed a Gleason 6 PCa in three out of twelve cores taken. Protocol wise this was a reason to switch to curative treatment. Also his rising PSA which led to a PSADT < 3 years was a trigger to start curative treatment. It is at this moment in time that an important decision was made. The urologist and patient X decided to ignore this advice and to continue with AS. In the case of patient X it is unclear, due to the anonymity of PRIAS patients, which information was provided to the patient and how the decision was eventually made. One of the experts stated that when overlooking the case he feels that the urologist of patient X, taking into account the age of patient X, should have discouraged the decision to stay on AS. It is important to emphasize that it is the protocol's advice to switch to curative treatment and that continuation of AS comes with the risk of disease

progression which might lead to metastases. If, despite the before mentioned information, the patient decides to continue AS, the urologist should emphasize that that is the patient's decision. If the urologist has not discussed these matters, the expert feels that one might speak of a negligent act for which the urologist can be blamed. However, if the urologist provided the right information and the patient decided to continue AS anyway, the doctor lived up to his professional standards.

Due to the decision to continue AS the tumor had the chance to grow. Two years after patient X's PCa diagnosis he underwent a second biopsy (this second biopsy is in line with the PRIAS protocol). This time a Gleason 9 PCa is found in two out of twelve biopsies. Patient X underwent an RP. One year post-surgery he suffers from permanent erectile dysfunction, urinary incontinence and biochemical recurrence. His last PSA amounts to 21.6 ng/ml. The question that should be answered is not whether these outcomes would have been the same had patient X been treated a year earlier, although this does seem to be the obvious question from a medical point of view, but whether the decision to continue AS after the first repeat biopsy was justified. More specifically: does the decision to continue with AS after the first repeat biopsy meet the standards of art. 7:453 Civil Code?

The experts stated that regarding the question whether the urologist has acted as could be expected from a reasonable and reasonably competent doctor (art. 7:453 Civil Code) when continuing AS, it is likely that he has. Low-risk PCa is a complex disease and it is currently not possible to distinguish which low-risk cancers will become more aggressive and which will stay indolent and therefore not cause any symptoms or death of its carrier. The AS protocol has been designed to delay or avert curative treatment in men with true indolent PCa. It has been shown, however, that with the PRIAS AS protocol perhaps still too many men are advised to switch from AS to curative treatment, indicating that the protocol might still be too strict. Bul et al. [29], for example, showed that of the 446 PRIAS AS men that underwent deferred treatment after their initial biopsy, 189 underwent RP. For 167 men (88.4%) pathology results were available. 118 cases (71%) had favorable RP results (pT2 and Gleason $\leq$ 3+4), while 49 patients (29%) experienced unfavorable results (pT3-4 and/or Gleason $\geq$ 4+3). Of the 118 cases with favorable results, 88 (75%) had been given a protocol-based advice to switch. Assuming that the urologist of patient X is aware of the ongoing debate surrounding low-risk PCa and AS, the experts state that deviating from the protocol in itself is tolerable. The case described enters what the expert state as 'the grey zone' for which it is not entirely clear what is the best way to handle.

Discussion

In this article we have looked at AS for PCa from a juridical point of view. As AS is a viable management strategy that is incorporated into many national and international guidelines, the authors were interested in potential pitfalls - from a juridical point of view - for urologists.

With the help of two urologists, appointed as 'experts' - as would be done in practice - we found that there are two very important aspects that need to be taken into consideration when offering AS: (1) providing that type of information to the patient on which he can base his informed consent and (2) urologists acting according to their professional standards.

According to art. 7:448 Civil Code patients have a right of information, meaning that a doctor is obliged to provide information that concerns medical actions, treatment and patients' current health status. This information should be clear to the patient, relevant and adjusted to his educational level. When offering AS it is important that urologists provide information on the risk of PCa progression and the subsequent possibility of being too late and thereby missing the window of curability. The follow-up scheme should be explained, as well as the potential risks of repeated biopsies. Furthermore, it is important that the risks and benefits of the other treatment options are explained well so that the patient can make a well-informed decision on whether or not to provide consent on the proposed treatment.

We have seen that information plays an important role throughout the entire AS period. There are various points in time during which the decision to continue or discontinue AS has to be taken. It is important, and in line with art. 7:448 and art. 7:450 Civil Code, to constantly inform the patient well so that he can take the decision or agree on the decision to continue/discontinue AS. We would like to advise that the discussions between the doctor and the patient are surveyed into his medical record. Men entering the PRIAS study sign and informed consent. We would like to suggest that men who are offered AS outside study environment sign informed consent as well.

Furthermore, we found that in line with art. 7:453 Civil Code urologists should act in line with their medical professional standards. Patient X was assumed well-informed and therefore the question was whether continuation of AS was in line with art. 7:453 Civil Code. Due to the complex situation with respect to low-risk PCa, the experts stated that deviating from the protocol was tolerable. As the urologist of patient X engaged in including patients into the PRIAS study, it is likely that he is aware of the discussions

surrounding low-risk PCa and AS in particular. The national and international guidelines also leave room for interpretation with respect to offering and the (dis)continuation of AS. It is, however, of upmost importance that the progress within this area of expertise is followed carefully.

Conclusion

From a juridical point of view, urologists that offer AS to their patients should be aware of the information that they provide to patients, both when entering AS as well as during follow-up. Furthermore it is important that urologists act in line with their medical professional standards. To be able to do so, it is advised that urologists follow the progress that is made within this field carefully, as the field is moving rapidly.

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Chapter 10

General discussion

In the introduction of this thesis, several research questions were formulated. First, the main answers to each of these research questions will be summarized as key findings after which they will be discussed in more detail, both for population-based screening and for active surveillance. This chapter will conclude with recommendations for clinical practice and for future research initiatives.

10.1 Key findings

Part I – Screening for prostate cancer

Research question 1: How do tumor characteristics and treatment patterns change in the course of a screening trial for prostate cancer?

As described in chapter 2, the tumor characteristics of prostate cancers diagnosed in the screening arm of ERSPC showed a favorable shift over time. This development coincided with a change of treatment, namely an increasing choice for expectant management as initial treatment for indolent disease. Over time, the tumor characteristics of prostate cancers detected in the control arm became more comparable to those of prostate cancers in the initial screening round, pointing towards an increasing rate of opportunistic testing in men randomized to the control arm.

Research question 2: How to advice patients who consult their general practitioner or urologist with a screening request?

Men should be informed on the pros and cons of screening before having a PSA test, for which informed and shared decision making is the paradigm (chapter 3). Decision aids can help men weigh the pros and cons, making it possible for them to choose according to their own preferences and personal values. Shared decision making will give both professionals and men the option to express their thoughts on screening, to jointly participate in the decision making process and agree on a course of action that incorporates patients' preferences and is acceptable from a medical point of view. In case a PSA test is done, multivariable risk prediction models can help in deciding whether further diagnostic tests are needed.

Part II – Active surveillance for low-risk prostate cancer

Research question 3: As active surveillance cohorts mature, how do the related clinical outcomes develop?

So far, reported prostate cancer mortality under men on active surveillance is very low, which supports the suggestion that active surveillance is a safe management strategy for low-risk prostate cancer (chapter 4). Longer follow-up, is however, needed as present studies mostly have an average follow-up of less than 10 years. When considering intermediate outcomes such as PSA progression, local progression and metastases, it is difficult to draw conclusions, because less unequivocal definitions are used in the ongoing studies. It seems, however, that choosing an initial active surveillance strategy does not affect the clinical outcomes of men when compared to those who choose immediate active treatment. Active surveillance then has the advantage of delaying side-effects of treatment and preserving health related quality of life (chapters 6 and 7).

Research question 4: In the light of personalized medicine, what is the best way to select patients for active surveillance?

In chapter 5 we assessed whether patient selection can be improved by using risk stratification through a nomogram instead of the currently used rule-based inclusion criteria. The results showed that more stringent rule-based active surveillance inclusion criteria as well as stricter nomogram probability thresholds decrease the rate of misclassified tumors in a rather similar fashion, but both at the cost of a substantial number of patients no longer considered suitable for active surveillance. We concluded that the performance of a nomogram and rule-based criteria are similar. A nomogram could be a good alternative to the rule-based criteria as it explicitly allows for making individual trade-offs, taking into account, amongst others, the risk-averseness of urologists and patients.

Research question 5: How does quality of life develop in men who follow an active surveillance management strategy for a longer period of time? How does their quality of life compare to that of men who underwent direct curative therapy?

In chapter 6 we analyzed how anxiety and distress developed in men who were managed with active surveillance for an 18-month period and whether highly anxious men adhered to that protocol. We found that the average levels of anxiety and distress remained favorably low. Generic anxiety and the fear of disease progression tended to decrease in men who remained eligible for active surveillance. Six out of the 129 respondents (5%) discontinued active surveillance because of anxiety and distress. Among the 26 men who were highly anxious at baseline, eight became less anxious while remaining on active surveillance. Our results suggest that negative quality of life effects are limited in men with favorable clinical characteristics who chose active surveillance. Patient reported outcomes of longer follow-up (chapter 7) reveal that in terms of

general health men who underwent active surveillance have better physical and mental health than those on radical prostatectomy and radiotherapy and a reference group of men without cancer. All groups show low generic anxiety rates. Compared to the 18 month follow-up data, prostate cancer anxiety and the fear of disease progression (both subscales of the MAX-PC) decreased further for men on active surveillance. Men on active surveillance and the men without cancer reported very similar urination scores. Statistically significant differences are mainly seen between the radical prostatectomy and radiotherapy groups with respect to urinary function and urinary incontinence, with the radiotherapy group reporting better function. Regarding sexuality, the active surveillance group reported the best outcomes, while the radical prostatectomy group reported the worst. Overall, we can conclude that from a quality of life perspective, in the long run active surveillance is a good alternative to immediate active therapy.

Research question 6: With the increasing clinical acceptance of active surveillance as a feasible alternative to immediate active therapy, how do urologists value active surveillance and what should they be aware of in such a fast moving area of expertise? (Chapters 8 and 9)

Through questionnaire research we were able to get an insight into urologists' acceptance of active surveillance and their opinions about the newly emerged management strategy (chapter 8). All urologists reported to bring up active surveillance as a treatment option for low-risk prostate cancer and a third of the urologists did so for intermediate risk prostate cancer. Factors that influenced their decision to offer active surveillance mainly were the requests of patients, guidelines, own experiences, patients' physical and psychological well-being and their clinical characteristics. More than half of the patients that were seen by urologists tended to bring up active surveillance. Two-thirds of the urologists, furthermore, reported to offer watchful waiting as an alternative for active surveillance to patients eligible for active surveillance. Overall, we concluded that Dutch urologists tend to have a positive attitude towards active surveillance.

Because active surveillance has become a viable management strategy and is being offered more and more often, the aim of the study in chapter 9 was to describe active surveillance from a legal perspective. What might be pitfalls in the active surveillance management strategy that urologists should be aware of? From our analysis we can conclude that urologists who offer active surveillance to their patients should be aware of the information they provide on potential progression of the prostate cancer, the active surveillance follow-up scheme used and the potential risks of repeated biopsy, both before starting the management strategy as well as during follow-up, and that the information discussed and resulting discussions are surveyed shortly into patients'

medical records. Urologists should furthermore act in line with their medical professional standards. Urologists need to keep themselves updated on the evolving guidelines and the scientific literature published on active surveillance by, for instance, attending medical conferences, in-server training and participation in journal clubs.

10.2 Screening for prostate cancer

Having a median of 9 years of follow-up, the ERSPC reported for the first time a 20% mortality reduction in favor of the screening arm in an intention-to-screen analysis [1]. Such an analysis provides an estimate of the effectiveness of screening on a population level and is influenced by two types of noncompliance: (i) nonattendance in men who are randomized to the intervention arm, and (ii) contamination, i.e. the use of PSA testing in men randomized to the control arm [2]. In chapter 2 we looked for changes in tumor characteristics and treatment that could potentially indicate the occurrence of opportunistic testing in the screening and control arm of the ERSPC. It is important to assess such an effect as it can influence the primary endpoint of the trial due to the potential diminished differences between the screening and control arm, as was seen in the PLCO study [3]. In this thesis, data from the ERSPC study up until the end of 2006 were used. Study results showed that tumor characteristics became more favorable over time in both the screening and control arm of ERSPC, which was mainly reflected in increasing proportions of T1c tumors (29% in 1994-1998 vs. 50% in 2003-2006 for the control arm and 48% in the initial screening round vs. 75% at the third screening round). The stage and grade shift that was observed coincided with a change of treatment, namely an increasing occurrence of expectant management as the initial treatment strategy for organ-confined disease (15% in 1994-1998 vs. 23% in 2003-2006 for the control arm and 17% vs. 36% for the initial and third screening round, respectively). The observed tumor characteristics in the 2003-2006 control arm period were comparable to tumor characteristics in the first round of the screening arm. These findings point towards an increasing rate of opportunistic testing in men randomized to the control arm [4]. In our study we did not determine the order of magnitude of opportunistic PSA testing in the control arm (i.e. contamination). Roobol and colleagues assessed the rate of contamination in the control arm of ERSPC Rotterdam and extrapolated these data to the entire ERSPC study cohort [2]. They were thus able to estimate the efficacy of organized PSA testing in men actually screened, concluding that PSA screening reduces the risk of prostate cancer death by up to 31% in men who are actually screened [2]. Bokhorst et al. determined the prostate cancer mortality reduction from screening after adjustment for nonattendance and contamination a few years later in ERSPC Rotterdam. They concluded that prostate cancer screening as carried out in

ERSPC Rotterdam, could reduce the risk of dying from prostate cancer up to 51% for an individual man choosing to be screened repeatedly compared to a man who was not screened [5]. If, as a result of this increased individual risk reduction, more men choose to be screened, this will increase the rate of overdiagnosis and overtreatment.

How to advice a patient?

The advantages of screening should be weighed against its disadvantages. Because at this moment the harms of screening outweigh the benefits, population-based screening programs have not been introduced. Screening in its current form is not the way forward, nor is the recommendation by the U.S. Preventive Services Task Force not to screen at all [6-8]. In chapter 3 we highlighted the importance of informed and shared decision making. Informed decision making refers to a choice that is based on relevant knowledge and is consistent with the decision maker's value and is behaviorally implemented [9]. Men who are at the point of having their PSA measured should be aware of the consequences such a decision might have on their lives. This was well reflected in a qualitative study by Chapple et al. where most of the patients underwent a PSA test with minimal information given to them upfront [10]. Afterwards, some men felt relieved that they were treated for their prostate cancer and that it had been found at an early stage. Other men were more doubtful and sometimes regretted that a PSA test was done. They were thinking about what their lives would have looked like, had they not taken the test and not suffered the side-effects of treatment which affected their quality of life [10]. These men are cancer survivors and have to live with the consequences of treatment the remaining years of their lives [11]. In the first years after treatment the feeling of relief will prevail, but later on doubts may arise on whether it has all been worth it. Clinicians, general practitioners but also patients themselves need to be aware of the issues that can affect quality of life, both immediately after diagnosis and treatment, as well as in the many years that follow [11].

In practice it has been seen that the number of PSA tests requested in the Netherlands and the United States has decreased since the publications of the ERSPC and PLCO in 2009, indicating a slightly decreasing rate of opportunistic screening [1, 12-14]. Updated guidelines of the American Urological Association (AUA) [15], the American Cancer Society [16], the American College of Preventive Medicine [17], the European Association of Urology (EAU) [18], and the Dutch Urology Society (NVU) [19] in the meanwhile have all agreed on the importance of a combination of informed and shared decision making in deciding whether or not to screen for prostate cancer. It is expected that this will further decrease the rate of opportunistic testing.

10.2.1 Future research directions that can alter the balance between harms and benefits in individual and population-based screening

Risk prediction

PSA based screening for prostate cancer currently has substantial harms, such as over-diagnosis, overtreatment, and living an increased number of years with the adverse effects of treatment, which has resulted in the discouragement of population-based screening programs [20]. On an individual level early detection for prostate cancer can benefit some men specifically and therefore testing for prostate cancer should be made more selective. To find out who is likely to benefit and who is not, the use of individualized multivariable risk prediction modelling is encouraged in the literature as well as in guidelines [18,19]. Various nomograms have been developed with the aim of reducing the number of unnecessary biopsies and to selectively identify those men at elevated risk for a potentially life threatening prostate cancer [21-26]. Further validation of these models is needed as well as their extension with new risk markers. Most of the risk prediction tools currently available are targeted at urologists. It will be worthwhile to investigate whether such tools can be used by the general practitioner as well. In the Netherlands, the general practitioner serves as the gatekeeper; patients with questions concerning their health will first visit their general practitioner before being referred to a urologist. The application of risk prediction tools by the general practitioner in the prostate cancer diagnostic process can potentially reduce the number of referrals to the urologist and decrease the number of false-positive PSA tests.

The role of multi-parametric imaging (MRI)

Currently the role of MRI in screening for prostate cancer is being studied. Quentin et al. assessed the value of MRI in a clinical trial, concluding that MRI-guided in-bore and systematic TRUS-guided biopsies achieved equally high detection rates in biopsy naïve men with an increased PSA. MRI-guided in-bore biopsies required significantly fewer cores compared to TRUS-guided biopsy and revealed a significantly higher percentage of cancer involvement per biopsy core [27]. Grenabo and colleagues presented results of their pilot study in which they offered men with a PSA ≥1.8 ng/ml a pre-biopsy MRI in the final screening round of the Göteborg Cancer Screening Trial [28]. They compared three strategies including 1) PSA ≥3 + systematic biopsy, 2) PSA ≥3 + MRI + targeted biopsy and 3) PSA ≥1.8 + MRI + targeted biopsy. They found that the accuracy of prostate cancer detection significantly improved for the PSA ≥ 1.8 + MRI + targeted biopsy option compared to a strategy of PSA ≥ 3 and systematic biopsy alone (AUC 0.77, CI 0.6707-0.8621 vs. AUC 0.58, CI 0.48-0.69, p=0.035). The MRI missed 7 out of 28 prostate cancers of which 5 were Gleason 3+3 and 2 were Gleason 3+4. As a result of their findings, a randomized trial including 40,000 men will be initiated to

determine whether screening with PSA and MRI of the prostate cancer can improve the diagnostic accuracy of detection, potentially decreasing the amount of overdiagnosis and therewith attempting to balance the benefits and harms of screening [28].

In one of the first randomized controlled trials, Baco et al. compared the rate of detection of clinically significant prostate cancer in men who underwent prostate biopsy guided by computer-assisted fusion of MRI and TRUS to the rate in men who underwent 12-core random biopsy [29]. In this study 175 biopsy-naïve men with a suspicion of prostate cancer were randomized to the MRI (n=86) or the control group (n=89). The overall number of clinically significant prostate cancers found was similar between the two groups, indicating that the methods were comparable, rather than the MRI method being superior. More results from randomized controlled trials are needed with respect to the efficacy of MRI in the diagnostic process. In 2016 the results of an MRI-side study within ERSPC Rotterdam on the sensitivity and effectiveness of TRUS-guided systematic biopsy versus MRI-ultrasound fusion targeted biopsy in men previously screened are expected.

With respect to individualized medicine and the increasing use of nomograms in the detection, staging and follow-up of prostate cancer, MRI could play a role as well. Current nomograms such as the Prostate Cancer Risk Calculator (www.prostatecancer-riskcalculator.com) or the Prostate Cancer Prevention Trial risk calculator could be extended by adding MRI parameters. Salami et al. compared the performance of the PCPT high-grade risk calculator against multi-parametric MRI in predicting men at risk of prostate cancer [30]. The area under the receiver operating characteristic curve (AUC) of the PCPT high-grade risk indicator was 0.676 while the AUC of multi-parametric MRI for high-grade prostate cancer was 0.769 and 0.812 for clinically significant prostate cancer, indicating that adding MRI characteristics to a nomogram which already includes PSA, age, life-expectancy, etc., could potentially further enhance the predictive probability.

Markers

The perfect marker for prostate cancer screening is yet to be found. Recently published markers, for instance, prostate cancer gene 3 (PCA3) and the urine marker TMPRSS2:ERG have been shown to be of limited clinical value as a first line diagnostic tool [31,32]. Other PSA-related derivatives and subforms, such as the Prostate Health Index (PHI) and the 4-kallikrein panel, have shown an improved diagnostic accuracy as compared to PSA alone, but only a marginal improvement when incorporated into multivariable risk assessment [33-38]. The search for the "holy grail" marker is like searching for a needle in a haystack. Although further development of this area of research is urgently needed, on the short-term risk prediction combined with MRI is thought to be most promising.

10.3 Active surveillance for prostate cancer

As described above, screening coincides with overdiagnosis and subsequent overtreatment. Active surveillance has emerged as a management strategy for the by nature slow growing indolent prostate cancer from which a man is not likely to die, with the goal of delaying or completely avoiding active therapy to avert the potential side-effects of treatment, preserving quality of life [39,40]. Men are monitored instead and can switch to active therapy in case of reclassification or signs of disease progressions.

Feasibility of active surveillance
Most prospective active surveillance cohorts have only short- or intermediate-term data available. In chapter 4 of this thesis we reviewed mortality results from various active surveillance cohorts; low disease-specific mortality rates have been reported. After a median follow-up of 6.8 years, the five and ten-year disease-specific survival reported by Klotz [41] amounted to 99.7% and 97.2% respectively. The PRIAS and Johns Hopkins studies both reported a disease-specific survival rate of 100% after median follow-ups of 1.6 and 2.7 years respectively [42]. So far, these results seem promising. Longer follow-up is however needed because of the slow growing nature of this type of prostate cancer.

In our literature review we have furthermore evaluated intermediate outcomes from active surveillance cohorts, like PSA progression, local progression and metastases in men who initially opted for active surveillance and switched to either radical prostatectomy or radiotherapy. It is more difficult to interpret these outcomes, because studies report less unequivocal endpoints. Results after deferred radical treatment seem to indicate that proportion of men (8-31%) have less favorable outcomes. Whether these men should have been treated earlier is debatable. Compared to men who opted for immediate radical treatment we found results to be quite similar, suggesting that postponing treatment with one to two years did not affect intermediate outcomes. By initially opting for active surveillance the side-effects of treatment were delayed which positively affected patients' quality of life [43].

In the meanwhile, Klotz et al. [44], reported unique 15-year follow-up results from their prospective, single-arm cohort study carried out at an academic health sciences center in Canada; 2.8% (28/993) of patients developed metastatic disease and 1.5% (15/993) died of prostate cancer. Because this mortality rate is consistent with the expected mortality in favorable-risk patients who are managed with initial definitive treatment, Klotz et al. conclude that active surveillance seems safe within a 15-year time frame [44]. Xia et al. used a model to assess prostate cancer mortality among contemporary low-risk

cases on active surveillance who switched to radical prostatectomy due to disease progression. These projections were then compared to the rate of prostate cancer mortality had the cases received immediate radical prostatectomy. According to the model, 2.8% of men on active surveillance and 1.6% of men with immediate radical prostatectomy would die of their disease in 20 years' time. The model projected furthermore that on average men on active surveillance would remain free of treatment for an additional 6.4 years relative to men who were treated immediately [45]. Both studies, for now, confirm the safety of active surveillance as a management strategy. Longer-term results are required from other cohorts to confirm these results.

Patient selection for active surveillance

While the disease-specific mortality under active surveillance is low, research on how to improve the existing active surveillance inclusion criteria is needed as misclassification at diagnosis or reclassification after one-year repeat biopsy is common [42,46].

At this moment all active surveillance studies apply rather rigid patient inclusion criteria. In the light of individualized medicine and shared decision making (chapter 2), taking into account patient preferences like whether or not they are risk-averse, it might be preferable to apply more refined risk stratification. In this thesis we have assessed whether the use of a nomogram in selecting patients for active surveillance is preferable over the currently used rule-based criteria (chapter 5). We found that the performance of the PRIAS, Johns Hopkins and ERSPC-nomogram were comparable. Because patient selection with all three options is currently sub-optimal, reflected in areas under the curve when discriminating between indolent and significant disease of 0.59-0.69, risk stratification needs to be improved. MRI can play a potential role in selecting men for active surveillance [47]. Stamatakis et al. found that the number of lesions, lesion suspicion and lesion density were associated with confirmatory biopsy outcome and reclassification [48]. A nomogram that incorporates these three factors showed to have promising predictive accuracy through which active surveillance patient selection can be improved [48].

Quality of life

With the emergence of active surveillance as a new management strategy, the collection of quality of life data started as well. It was hypothesized that choosing active surveillance could lead to anxiety and distress due to living with 'untreated' prostate cancer. If so, better selection upfront, or targeted psychological interventions might be considered. Furthermore, it was unknown how men would appreciate the periodical control visits. In this thesis (chapters 6 and 7) quality of life outcomes of men who were

managed with active surveillance for a shorter period, up to 18 months of follow-up, and a longer period of follow-up (i.e. 5- to 10-years), are presented.

Men who followed an active surveillance strategy for an 18 month period on average reported favorably low levels of anxiety and distress (chapter 6). These results were in line with patient reported outcomes measured in the first six months of follow-up [49,50]. The fear of disease progression and general anxiety decreased, but that decrease was not clinically significant. Only a small percentage of men in our cohort stopped active surveillance for anxiety reasons. We furthermore analyzed whether highly anxious men quit active surveillance. Of the 26 men who were highly anxious at baseline (STAI-6 score > 44), eight became less anxious during the course of the active surveillance program, suggesting that the control visits and the stability of the disease provided tranquility of mind. Six (23%) men reported high anxiety scores during the entire 18 month follow-up period but remained on active surveillance. Three men (12%) were highly anxious at baseline, their scores decreased to ≤44 after 9 months of follow-up and after 18 months of follow-up they quit AS because of tumor progression. Seven men (27%) were highly anxious at baseline and stopped AS because of reclassification of their prostate cancer at 9 months of follow-up. Two men (8%) were highly anxious and therefore stopped active surveillance. Our results are in line with, for instance, the results of a study among Finnish PRIAS participants, who reported no deterioration of their quality of life after 1 and 3 years of follow-up [51,52] or a study amongst Australian men which suggested that no clinically significant anxiety was present amongst their cohort [53]. Published data so far all address relatively short follow-up periods. Longer-term quality of life data are currently lacking. Because of the maturing of the PRIAS active surveillance cohort we had the opportunity of obtaining unique 5-year patient reported outcome data (chapter 7). Furthermore, we were able to collect 5-year follow-up patient reported outcome data of men who underwent radical prostatectomy or radiotherapy, and compare our results to a reference group of men without prostate cancer. This is one of the rare publications in which such a direct comparison in terms of quality of life is made between the various treatment options for low risk prostate cancer. We found general health of men to be comparable between the four groups, with the active surveillance group reporting the best general health. With respect to urinary, bowel and sexual function, men on active surveillance report the best function as well. Our results seem to indicate that with longer follow-up active surveillance is not just a safe option from a clinical perspective, but also a good alternative from a quality of life perspective.

Because most patient reported outcome assessment instruments tend to capture the negatives of active surveillance, we developed questions that focused on the positives of active surveillance and included them at the 5-year measurement point (chapter 7).

These showed that the control visits provided tranquility of mind to most men (85%) and that they trusted the follow-up scheme (82%). 81% of men were glad that their cancer was diagnosed at an early stage and 77% said that they could cope with the thought of having prostate cancer. These results are somewhat biased, because men that truly cannot cope with active surveillance switch to deferred treatment in a much earlier stage, mostly within the first year [54]. It does, however, give a first overview of how men who opt for active surveillance perceive the periodical control visits.

Since qualitative research has shown that the use of generic quality of life instruments in a group of prostate cancer patients will not detect side-effects of treatment as they are domain specific [55,56], we combined in our research (chapters 6 and 7) generic and disease-specific measures, which is a strength of our study. A limitation is the lack of a baseline quality of life measurement.

Acceptance of active surveillance

From a clinical and quality of life perspective, evidence is pointing towards the widespread acceptance of active surveillance which is reflected in the fact that active surveillance is included in many urological guidelines (EAU, AUA, etc.). There is a group of urologists whose interest in active surveillance is reflected by their efforts to include patients in active surveillance studies or involvement in contributing to the literature. In chapter 8 we were interested in assessing the opinion of a larger group of urologists, including urologists that are not directly involved in studies like PRIAS. We therefore invited all senior members of the Dutch Urology Society to fill out a self-designed questionnaire and share their practice patterns and opinions on active surveillance. Most urologists reported a positive attitude towards active surveillance and applied the PRIAS inclusion and follow-up criteria (without including patients into the study). Urologists were predominantly led by the wish of the patient, the guideline, their own experiences, patients' physical and psychological well-being and their clinical characteristics when recommending active surveillance. Gorin et al. and Azmi et al. assessed the knowledge, acceptance and practice of active surveillance in American-based and European-based urologists [57,58]. They found that of the participants that replied (response rates amounted to only 9% and 8%, respectively), the majority were knowledgeable and accepting of active surveillance. The practice pattern for active surveillance, however, is heterogeneous, with urologists not adhering to a protocol or involved in an active surveillance study applying less rigorous criteria for both eligibility and monitoring of active surveillance [57,58]. While having urologists to participate in a survey on their attitude towards and experiences with active surveillance was challengeable, the increasing percentage of men choosing active surveillance instead of immediate active therapy may be seen as a proxy for the acceptance of active surveillance as a management strategy.

Up to a few years ago, only a small percentage of eligible men started an active surveillance management strategy [59]. Over the years, although solid worldwide statistics are scarce, it seems like regionally the percentage of men with low-risk prostate cancer that chooses active surveillance is rising [60-62]. Smaller initiatives, like the Michigan Urological Surgery Improvement Collaborative (MUSIC) reported that approximately half of their patient cohort underwent initial active surveillance [61]. The growing number of PRIAS participants - from approximately 2,100 patients included in July 2011 to almost 5,000 in May 2015 - is also an indicator that more men are nowadays included on active surveillance.

In chapter 9 of this thesis active surveillance was described from a legal perspective. Active surveillance is a realistic treatment strategy that is included in many guidelines. Still the chance exists that the 'window of curability' is missed. What should urologists be aware of, from a legal perspective, when offering active surveillance to patients? Urologists should be aware of the information they provide to patients, highlighting the importance of informed decision making (chapter 3), when entering active surveillance but also during follow-up. Deviating from, for instance, the PRIAS active surveillance protocol, is allowed as long as such a deviation can be substantiated and has been discussed and agreed upon by the patient (chapter 3).

10.3.1 Future perspectives – how is the field of active surveillance expected to move forward in the coming years?

Besides the PRIAS study, which includes over 5,000 participants in 17 countries, most other active surveillance studies are single-center, relatively small cohorts. It will be important to join databases to increase the number of patients, and therewith events. A first attempt is made with the Movember, GAP3 project in which at least 19 top institutions and candidate centers from all over the world will join their data and expertise, comprising a database of over 10,000 active surveillance patients. It will be of upmost importance to continue the GAP3 collaboration after the retrospective part of the study has ended and turn the then unique database into a prospective study, comprising the world largest active surveillance database. In 5-10 years that will give us the opportunity to report with much more certainty on the disease-specific mortality rate, number of metastases and other important end-points amongst active surveillance patients. This will influence the guidelines on active surveillance, by echoing a worldwide consensus statement on inclusion and follow-up criteria for active surveillance.

Patient selection and follow-up for active surveillance should, furthermore, be improved by means of risk stratification methods and the incorporation of MRI into the diagnostic pathway. The currently used nomogram in chapter 5 for the prediction of indolent dis-

ease is based on data from the ERSPC and should be updated. Currently it still includes Gleason 2+3 as a parameter, which does not reflect clinical practice any longer. It also includes length of cancerous tissue and length of benign tissue as parameters, which are not always clinically available. Alternatives have to be sought and the addition of MRI parameters should be considered. Inclusion of such parameters might reduce the need for invasive prostate biopsies that are not without risk, making the protocol more patient-friendly, while not losing performance.

With respect to measuring quality of life of men on active surveillance, a core set of measures is needed. At the moment it is not clear which quality of life measure can best be used to measure a certain domain, e.g. anxiety, urinary incontinence, erectile dysfunction, depression, regret, which has led to splintered quality of life reporting, making it difficult to compare published patient reported outcomes. A guideline which supports clinicians in deciding what tool to use for measuring a specific physical or psychological domain should be developed and will be helpful to the professional as well as for the patient. The professional is provided with a clear overview of tools that can help him pinpoint the area of unmet needs, while the patient is no longer burdened with filling out numerous questions that might be less relevant for him, saving them both time and improving quality of care.

Furthermore, quality of life research should focus on the inclusion of the pre-treatment decision moment. In this thesis it was shown that men who follow an active surveillance strategy for a longer period of time have good quality of life and do not seem to experience problems due to living with 'untreated cancer'. It is relevant to assess the motives of men that were diagnosed with low-risk prostate cancer and did not choose active surveillance. Would it be possible, for instance, to offer them active surveillance combined with a psychosocial intervention that helps them to cope with living with untreated cancer, while delaying or potentially avoiding treatment and its side-effects?

In recent years, patients' self-management of disease has gained very much attention. From the ProtecT trial we have learned that many men after having received their cancer diagnosis, have engaged in doing something themselves to be in control of their disease [63,64]. This ranges from changes in diet, increasing the amount of physical activity or to stop smoking. It will be worthwhile to assess whether men on active surveillance for prostate cancer in the PRIAS study are interested in self-management or perhaps already have adopted lifestyle changes and see how this affects their quality of life and perception of care.

Epilogue

Current research on prostate cancer focuses mainly on how screening for prostate cancer can be improved and how the associated overdiagnosis and overtreatment can be reduced. This quest will continue in the years to come. For active surveillance the research focus will mainly be how to improve patient selection and follow-up criteria, while not missing the disease's window of curability. Modelling studies, retrospective and prospective data contribute to the literature acknowledging active surveillance for low-risk prostate cancer being a safe approach, as the mortality rates are in the same range as those of favorable-risk patients that were managed with initial curative therapy. It has furthermore been found that active surveillance could be feasible for patients with intermediate-risk prostate cancer, based on short- and medium-term results [44,45,65,66]. It is not likely that active surveillance will become obsolete in the coming years, as the rate of overdiagnosis will not diminish to zero and the strategy itself will go through a 'response shift', extending its area of research to intermediate-risk prostate cancer. Expanding active surveillance to a selected group of intermediate-risk prostate cancer patients will most likely result in delaying rather than avoiding treatment in these patients. Research should focus on how to balance the number of men who can safely delay immediate active therapy, without compromising on the number of aggressive tumors missed. Furthermore, we will have to investigate whether such a period of delay adds to patients' quality of life as is seen for low-risk patients, or whether it diminishes it because of the higher likelihood of receiving treatment after all.

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Part III

Appendices

Summary

Chapter 1 holds an introduction to prostate cancer, prostate cancer screening and active surveillance. The European Randomized study of Screening for Prostate Cancer (ERSPC) and the Göteborg Randomized Population-based prostate cancer screening trial have shown that screening for prostate cancer resulted in a relative reduction of the disease-specific mortality by 21-44%. Once corrected for non-compliance and contamination, the effect increases further to 51-56%. Besides the positive effect of screening, it is also associated with overdiagnosis and subsequent overtreatment of low-risk prostate cancers that are likely never to cause any symptoms or lead to death. While methods are being researched to decrease the rate of overdiagnosis, active surveillance for prostate cancer has been introduced to lower the rate of overtreated prostate cancers. With active surveillance immediate curative treatment is delayed or completely avoided and replaced by a monitoring strategy. Herewith side-effects of treatment can be averted and quality of life preserved. If risk classification towards a higher risk or disease progression is suspected, a switch to curative treatment can be made.

The *first part* of this thesis focuses on screening for prostate cancer. In **chapter 2** it was studied how tumor characteristics and treatment patterns for prostate cancer change during the course of a screening trial. In the initial screening round T1c tumors were found in 48% of the cases versus 75% in the third screening round. The percentage of Gleason 6 tumors remained around 70% throughout all three screening rounds. In the control arm of ERSPC increasing proportions of T1c were seen as well; 29% in the 1994-1998 period versus 50% in the 2003-2006 period. The percentage of Gleason 6 tumors slightly decreased over time from 58% to 51%, Gleason grade 7 tumors increased over time from 21-32%, and a decreasing trend was seen for the Gleason 8-10 tumors (21% in the 1994-1998 period to 17% in the 2003-2006 period). The stage and grade shift that was observed coincided with a changing treatment pattern in both the screening and control arm. Active surveillance was more often the initial treatment strategy for organ-confined disease: 17% vs. 36% for the initial and third screening round; 15% in 1994-1998 vs. 23% in 2003-2006 for the control arm. Tumor characteristics in the 2003-2006 control arm period were similar to the tumor characteristics observed in the first round of screening, pointing towards an increasing rate of opportunistic testing (screening) in men who were randomized to the control arm.

Because of the conflicting messages regarding screening for prostate cancer, i.e. the ERSPC and Göteborg trial showing an effect of screening versus the PLCO trial not showing an effect, and the fact that screening is associated with overdiagnosis and overtreatment, in **chapter 3** we highlighted that men wishing to be screened for pros-

tate cancer should be informed about the pros and cons of screening before having a PSA test. Using decision aids to inform men can help them weigh the pros and cons in such a way that their choice balances their own preferences and personal values. Through shared decision making both the professional and the man requesting a PSA test can express their thoughts on screening and agree on a course of action that balances the man's preferences and is acceptable from a medical point of view.

The *second part* of this thesis focuses on active surveillance for low-risk prostate cancer. In **chapter 4** we reviewed the literature and how outcomes of active surveillance cohorts developed over time. Up to this point in time, the PRIAS and Johns Hopkins active surveillance cohorts, amongst others, reported a 100% disease-specific survival rate after a median follow-up of 1.6-2.7 years. Because active surveillance is still a relatively new management strategy, the follow-up of most studies is too short to effectively compare disease-specific mortality. We therefore evaluated some intermediate endpoints such as the percentage of PSA progression, local progression and metastases. We used cohorts of men who were radically treated after an initial active surveillance strategy (deferred treatment) and compared them to men who received immediate radical treatment to see whether men with deferred treatment had worse outcomes. We found that 8-31% of patients in the studies we reviewed seemed to have less favorable outcomes after deferred radical treatment. It could be hypothesized that these men would have had better outcomes if treated earlier. If compared to outcomes of men who were treated radically immediately, results seemed to be quite similar. This suggests that postponing treatment did not affect the outcomes of men who choose an initial active surveillance strategy within the follow-up time available.

In **chapter 5** we analyzed whether patient selection for active surveillance could be improved by using risk stratification through a nomogram instead of applying the current fixed active surveillance inclusion criteria. We assessed this in a group of men diagnosed with prostate cancer and treated with radical prostatectomy who would also have been eligible for active surveillance. The performance of the PRIAS, Klotz and Johns Hopkins fixed active surveillance inclusion criteria was compared to the performance of a nomogram that predicts indolent disease. It was found that the performance of the nomogram, the Johns Hopkins and the PRIAS active surveillance criteria was similar, indicating that the use of a nomogram is a good alternative to the fixed criteria, especially because the nomograms allows the urologist and the patient to make individual trade-offs.

Living with an untreated cancer can be regarded as counterintuitive and therefore cause anxiety and distress. The purpose of the study described in **chapter 6** was to analyze how anxiety and distress developed in men who were managed with active surveillance

for an 18-month period of time and whether highly anxious men switched to curative treatment. We found that the average levels of anxiety and distress were favorably low for men that choose to stay on active surveillance. Fear of disease progression and generic anxiety furthermore tended to decrease for men that remained eligible for active surveillance. Of the 26 men who were highly anxious at baseline, eight (31%) became less anxious over time. Overall, 5% (6/129) of men discontinued active surveillance and switched to curative treatment because of anxiety and distress. In **chapter 7** we evaluated quality of life of men who have been following an active surveillance strategy for more than four years (median follow-up 6.5 years) and compared the results to quality of life of men who underwent curative treatment (radical prostatectomy or radiotherapy) and a group of men without prostate cancer. Significant and clinically relevant differences regarding physical functioning, urinary function, urinary incontinence and sexual function were found for men on active surveillance as compared to men who underwent radical prostatectomy. When comparing men on active surveillance to men who underwent radiotherapy we found significant and a clinically relevant difference in sexual functioning. Furthermore we found that the quality of life of men on active surveillance was very similar to that of men without prostate cancer.

With the increasing clinical acceptance of active surveillance as an alternative to immediate radical treatment, in **chapter 8** we aimed to assess how urologists value active surveillance. We invited all 328 senior members of the Dutch Urology Society (NVU) to complete a questionnaire including questions on how many newly diagnosed prostate cancer patients the urologist sees on a yearly basis, whether the urologist mentions active surveillance as one of the treatment options, whether patients ever bring up active surveillance as a treatment option, etc. 55% (180/328) of the invited urologists responded. All urologists reported that they discuss active surveillance as a treatment option for low-risk prostate cancer. A third of the urologists also did so for men with intermediate risk prostate cancer. The requests of patients, guidelines, own experiences, patients' physical and psychological well-being and their clinical characteristics were factors that urologists were most influenced by in deciding whether or not to offer active surveillance. Urologists furthermore reported that approximately half of their patients tended to bring up active surveillance themselves. We concluded that overall, Dutch urologists have a positive attitude towards active surveillance.

Not actively treating a cancer can be a potential threat for both the patient and the physician. Therefore, in **chapter 9** active surveillance was described from a legal perspective. What potential pitfalls should urologists be aware of when offering active surveillance? In this paper a PRIAS case was used to see what would have happened had that patient filed a complaint. Just like in practice, two 'experts' were appointed who provided their

opinions regarding the patients' case. We found that there are two aspects that need to be taken into consideration when offering active surveillance: (1) providing the right type of information in a for the patient understandable manner on which he can base his informed consent and (2) urologists acting according to their professional standard. When offering active surveillance the experts pointed out that the following risks and complications of active surveillance should be discussed: the risk of prostate cancer progression and the subsequent possibility of being 'too late', the risks associated with repeat biopsies and the active surveillance follow-up scheme.

Finally, key findings of the studies described in chapters 2-9 were summarized and discussed in **chapter 10**. Regarding screening for prostate cancer, research will continue to focus on how to reduce the rate of overdiagnosis. In that context MRI and stratification will most likely play an important role. For active surveillance research will focus on, amongst others, patient selection; will it be possible to safely expand the inclusion criteria so that a selected group of intermediate-risk prostate cancers will become eligible for active surveillance as well? It will have to be studied how that affects the number of aggressive cancers missed and whether these intermediate-risk patients will experience similar good quality of life as was seen for low-risk prostate cancer patients on active surveillance. It is furthermore to be hoped that the Movember GAP3 initiative in which 19 top institutes and candidate centers from around the world have joined forces, will continue a prospective, unique database with over 10,000 patients, providing us with the opportunity to further add to the evidence on active surveillance as a safe management strategy.

Samenvatting

In het eerste hoofdstuk van dit proefschrift worden de onderwerpen prostaatkanker, prostaatkankerscreening en het actief afwachtend beleid (active surveillance) geïntroduceerd. De Europese gerandomiseerde studie naar de waarde van vroege opsporing van prostaatkanker (ERSPC) en de Göteborg prostaatkankerscreening studie toonden een relatieve risicoreductie aan van screenen op de ziekte-specifieke mortaliteit van 21-44%. Indien er wordt gecorrigeerd voor non-compliance en contaminatie, dan zien we dat het effect van screening toeneemt en in de orde van grootte van 51-56% ligt. Naast positieve effecten van prostaatkankerscreening, zijn er ook nadelen, te weten: overdiagnose en overbehandeling van laag-risico prostaatkankers. Deze laag-risico prostaatkankers zullen naar alle waarschijnlijkheid nooit tot klachten leiden en mannen met een dergelijke vorm van prostaatkanker zullen daar ook niet aan overlijden. Momenteel wordt er hard gewerkt aan het vinden van een methode om het aantal overgediagnosticeerde laag-risico kankers terug te dringen. In de tussentijd is er een strategie ontwikkeld waarmee de overbehandeling van laag-risico kankers kan worden tegengegaan. Met active surveillance wordt actieve behandeling uitgesteld danwel vermeden. Mannen worden in plaats daarvan volgens een vast follow-up schema in de gaten gehouden. (Op vaste tijdstippen (follow-up schema) wordt beoordeeld of er sprake is van een stabiele situatie). Zodra zich tekenen van reclassificatie of progressie van de kanker voordoen, zal een overstap naar actieve therapie worden gemaakt.

In deel één van dit proefschrift hebben we bekeken hoe het patroon van tumorkarakteristieken en behandeling in een screening- en controlegroep zich gedurende een prostaatkankerscreening studie ontwikkelt (**hoofdstuk 2**). In de eerste screeningsronde werd 48% van de mannen gediagnosticeerd met een T1c prostaatkanker. In de derde screeningsronde liep dit percentage op tot 75%. Het aantal Gleason 6 tumoren lag in alle drie de screeningsronden rond de 70%. Vergelijken we deze percentages met de controlegroep, dan zien we dat ook in deze groep het aantal T1c tumoren toenam naarmate de tijd vorderde: 29% in de periode 1994-1998 versus 50% in de periode 2003-2006. In tegenstelling tot de screening arm, nam in de controlegroep het percentage Gleason 6 tumoren af van 58% naar 51%. Het percentage Gleason 7 tumoren nam toe van 21% naar 32%, terwijl het percentage Gleason 8-10 tumoren daalde van 21% in de periode 1994-1998 tot 17% in de periode 2003-2006. De verschuiving in stadering (stagering – stadium) en gradering van de tumoren viel samen met een verandering in behandelingspatroon in zowel de screening als de controle arm van ERSPC. Het percentage deelnemers met een laag-risico kanker dat een initieel active surveillance beleid volgde nam toe van 17% in de eerste screeningsronde tot 36% in de derde screeningsronde en voor de controlegroep van 15% in de periode 1994-1998

tot 23% in de periode 2003-2006. Controlegroep tumorkarakteristieken in de periode 2003-2006 waren vergelijkbaar met de eerste screeningsronde tumorkarakteristieken. Dit wijst er op dat er een groter percentage controlegroep mannen is die zich opportunistisch laat testen.

Terwijl de ERSPC en de Göteborg prostaatkankerscreening studies aantoonden dat screening leidt tot een vermindering van de ziekte-specifieke mortaliteit, toonde de Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO studie) datzelfde effect niet. Met deze conflicterende uitkomst in het achterhoofd en het feit dat screening is geassocieerd met overdiagnose en overbehandeling, wordt in **hoofdstuk 3** aan mannen die bij hun huisarts om een PSA-test vragen geadviseerd zich eerst goed te informeren over de voor- en nadelen van prostaatkankerscreening met behulp van PSA. De huisarts en de Prostaatwijzer® kunnen mannen helpen de voor- en nadelen van prostaatkankerscreening met behulp van PSA af te wegen. Gezamenlijke besluitvorming tussen de huisarts en de man met het PSA-test verzoek zal - naar alle waarschijnlijkheid - leiden tot een beslissing waarin zowel de arts als de man zich in kunnen vinden.

Het tweede deel van dit proefschrift richt zich op active surveillance voor laag-risico prostaatkanker. In een review van de literatuur is bekeken hoe uitkomsten van verschillende active surveillance cohorten zich door de tijd ontwikkelden (**hoofdstuk 4**). Na een mediane follow-up van 1.6-2.7 jaar waren er in de PRIAS en Johns Hopkins active surveillance cohorten geen deelnemers overleden aan prostaatkanker. Omdat active surveillance nog een relatief nieuwe behandelstrategie is en de follow-up van de meeste studies te kort is, zijn er ook enkele intermediaire eindpunten bekeken, zoals de percentages PSA progressie, lokale progressie en metastasen.

In **hoofdstuk 5** onderzochten we of de selectie van patiënten voor active surveillance kan worden verbeterd door gebruik te maken van risicostratificatie met behulp van een nomogram, in plaats van de huidige vastgestelde inclusiecriteria. De uitkomsten laten zien dat de PRIAS en Johns Hopkins inclusiecriteria in vergelijking met het nomogram vergelijkbare resultaten vertoonden. Het gebruik van een nomogram voor het includeren van patiënten met laag-risico prostaatkanker in active surveillance kan dan ook als een alternatief worden gezien voor het gebruik van de huidige vastgestelde inclusiecriteria.

Omdat mannen op active surveillance angst en stress kunnen ervaren vanwege het leven met een niet-behandelde kanker, bekeken we in **hoofdstuk 6** hoe angst en stress zich ontwikkelden in mannen die 18 maanden een active surveillance beleid volgden. Daarnaast bekeken we of mannen met hoge angstscores kozen voor een switch naar curatieve behandeling. Uit onze resultaten blijkt dat mannen die 18 maanden een active

surveillance beleid volgden, lage angst en stress scores rapporteerden. Ten opzichte van een meting net na de start van het active surveillance beleid bleek, dat de angst voor progressie van de kanker en generieke angstscores significant waren gedaald na 18 maanden follow-up. In ons cohort koos 5% (6/129) van de patiënten vanwege angst ervoor het active surveillance beleid te stoppen en over te stappen naar curatieve behandeling. In **hoofdstuk 7** analyseerden we lange-termijn-kwaliteit-van-leven-uitkomsten voor mannen op active surveillance en vergeleken deze met de uitkomsten van mannen die curatieve therapie (chirurgische verwijdering van de prostaat of radiotherapie) ondergingen en met de uitkomsten van mannen die geen prostaatkanker hebben. Significante en klinisch relevante verschillen zagen we op het gebied van fysieke gesteldheid, urinefunctie, urine-incontinentie en seksueel functioneren van mannen die een active surveillance beleid volgden ten opzichte van mannen bij wie de prostaat chirurgisch werd verwijderd. Vergelijken we active surveillance met radiotherapie dan zien we significante en klinisch relevante verschillen in seksueel functioneren. In beide gevallen zijn de scores van mannen op active surveillance beter. Daarnaast bleek uit onze resultaten dat de kwaliteit van leven van mannen op active surveillance vergelijkbaar is met de kwaliteit van leven van mannen zonder prostaatkanker.

Omdat active surveillance vanuit klinisch perspectief meer en meer als een alternatief wordt gezien voor direct invasief ingrijpen, onderzochten we in **hoofdstuk 8** hoe urologen tegenover active surveillance staan. Alle 328 urologen, aangesloten bij de Nederlandse Vereniging voor Urologie, ontvingen een vragenlijst met vragen als: 'Brengt u active surveillance weleens ter sprake?', 'Brengen patiënten zelf active surveillance weleens ter sprake?', Biedt u weleens active surveillance aan, aan patiënten met een laag-risico prostaatkanker?', 'Volgt u bij active surveillance patiënten een protocol?'. De responsie bedroeg 55% (180/328). Alle urologen gaven aan active surveillance als een behandeloptie voor laag-risico prostaatkanker te bespreken. Een derde van de urologen doet dit ook als mannen een intermediair-risico prostaatkanker hebben. Factoren waardoor urologen zich het meest laten beïnvloeden in de keuze voor active surveillance blijken het verzoek van de patiënt, richtlijnen, eigen ervaringen, de fysieke en mentale gesteldheid van de patiënt en de patiënt zijn klinische karakteristieken. Urologen gaven aan dat ongeveer de helft van de patiënten die zij op het spreekuur zagen zelf active surveillance ter sprake brachten.

In **hoofdstuk 9** werd active surveillance vanuit een juridisch perspectief beschreven. Op welke potentiële valkuilen moeten urologen bedacht zijn wanneer zij active surveillance als behandelstrategie aanbieden? Een PRIAS casus werd gebruikt om te illustreren wat er zou kunnen gebeuren als een active surveillance patiënt een klacht zou indienen. Net als in de praktijk, werden er twee experts aangesteld die het dossier van de patiënt

bekeken en hun oordeel gaven over de situatie. Op basis van de analyse concluderen wij dat er twee belangrijke punten zijn waarvan urologen zich bewust moeten zijn bij het aanbieden van active surveillance: (1) de patiënt moet goed en volledig geïnformeerd worden om de juiste keuze te kunnen maken ten aanzien van de behandeling. Bij het verstrekken van de informatie dient de uroloog zich te laten leiden door hetgeen de patiënt redelijkerwijs dient te weten ten aanzien van de aard en het doel van de behandeling, de te verwachten gevolgen en de risico's daarvan, over eventuele alternatieven en vooruitzichten; (2) het is van belang dat de uroloog handelt volgens de professionele standaarden.

In **hoofdstuk 10** worden de belangrijkste studieresultaten van de hoofdstukken 2-9 bediscussieerd en in perspectief geplaatst. Onderzoek naar prostaatkankerscreening zal zich de komende jaren met name richten op het reduceren van overdiagnose. Hierbij spelen de toepassing van MRI en risicostratificatie naar grote waarschijnlijkheid een belangrijke rol. Ten aanzien van active surveillance zal onderzoek zich onder meer richten op patiëntenselectie; is het bijvoorbeeld mogelijk om een geselecteerde groep intermediair-risico prostaatkankers te includeren op active surveillance? Er zal moeten worden bekeken of de inclusie van dergelijke tumoren op active surveillance niet leidt tot het missen van potentieel agressieve kankers. Daarnaast is het interessant om te onderzoeken of de groep patiënten met een intermediair-risico prostaatkanker een vergelijkbaar goede kwaliteit van leven ervaart als werd gezien bij de mannen met laag-risico prostaatkanker op active surveillance. Verder is het wenselijk dat het Movember GAP3 initiatief, waarin 19 topinstituten hun krachten hebben gebundeld, wordt voortgezet als een prospectieve database-studie waarin de gegevens van meer dan 10.000 active surveillance patiënten zijn verzameld. Een dergelijke database biedt vele onderzoeksmogelijkheden evenals de mogelijkheid om over enkele jaren met veel meer zekerheid uitspraken te kunnen doen over veiligheid van active surveillance op de lange termijn.

About the author

Lionne Dysette Francella Venderbos was born in Woudrichem on June 11, 1988. She obtained her VWO diploma at the Altena College in Sleeuwijk in 2006. After secondary school, she started studying Health Sciences at the Erasmus University of Rotterdam and obtained her Bachelor of Science degree in 2009. In 2011 she obtained her Masters of Science degree in Health Economics, Policy and Law (HEPL) at the Erasmus University. In 2010, she started as a PhD candidate at the Department of Urology and Public Health of Erasmus MC, the Netherlands. She was involved in an international study on screening for prostate cancer. At the same time she started a part-time study of law at the Erasmus University of Rotterdam which she completed with a Bachelor of Laws degree in 2015. Currently, she is working as a postdoctoral researcher at the Department of Urology of Erasmus MC where she is involved in research on quality of life of low-risk prostate cancer patients.

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PhD Portfolio

Name	Lionne Venderbos
PhD period	September 2010-November 2014
Erasmus MC department	Urology/Public Health
Promotors	Prof.dr. C.H. Bangma, Prof.dr. E.W. Steyerberg
Supervisors	Dr. M.J. Roobol, Dr. I.J. Korfage

PhD training	**Year**	**Workload (ECTS)**
General courses		
Biomedical English Writing	2011	4
Classical Methods for Data Analysis	2011	5.7
Biostatistical methods II: Popular Regression Models	2011	4.3
Literature search course	2013	0.5
Specific courses		
Quality of Life Measurement	2011	0.9
Seminars and workshops		
CPO symposium EMC – Ethics relating to research	2011	0.3
Research meetings, department of Public Health	2010-2011	1
PhD meetings, department of Urology	2010-2014	1
CPO symposium EMC – How to write a grant application	2013	0.3
Workshop leader ESO – Active Surveillance Congress	2014	0.5
Presentations		
ERSPC meeting, Peschiera	2011	0.5
International Shared Decision Making Congress, Maastricht	2011	0.5
SIU, Berlin	2011	0.5
Kwaliteitsmarkt Stichting Kwaliteitsgelden Medisch Specialisten (SKMS), Utrecht	2011	0.5
SWOP donateurvergadering, Den Haag	2011	0.5
ESO, Active Surveillance Congress, Rotterdam	2012	0.5
ERSPC meeting, Yllasjarvi	2012	0.5
NVU Voorjaarsvergadering, Den Bosch	2012	0.5
Annual Meeting AUA, Atlanta	2012	1.0
ERSPC meeting, Göteborg	2013	0.5

Science meeting, department of Urology, EMC	2013	0.5
ISOQOL-NL, Tilburg	2013	0.5
IPOS Psycho-Oncology, Rotterdam	2013	0.5
ESO, Active Surveillance Congress, Amsterdam	2014	0.5
SIU, Glasgow	2014	0.5
ISOQOL, Berlin	2014	0.5
ERSPC meeting, Madrid	2015	0.5
Annual Meeting EAU, Madrid	2015	1.0
ISOQOL, Vancouver	2015	0.5
Conferences		
Annual ERSPC meetings	2011-2015	1
International Shared Decision Making Congress, Maastricht	2011	0.5
SIU	2011, 2014	1
ESO, Active Surveillance Congresses	2012, 2014	1
Annual meeting AUA	2012	1
Annual meeting EAU	2013-2015	1
ISOQOL	2014-2015	1
Teaching		
Bijscholingsavond huisartsen	2014	0.5
Total ECTS	**36**