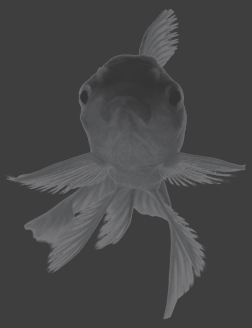

Low Risk Prostate Cancer and Active Surveillance

The studies reported in this thesis were performed at the department of Urology of the Erasmus Medical Center, Rotterdam, the Netherlands.

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Low Risk Prostate Cancer and Active Surveillance

Laag risico prostaatkanker en het actief afwachtend beleid

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam

op gezag van de rector magnificus
Prof. Dr. H.G. Schmidt
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
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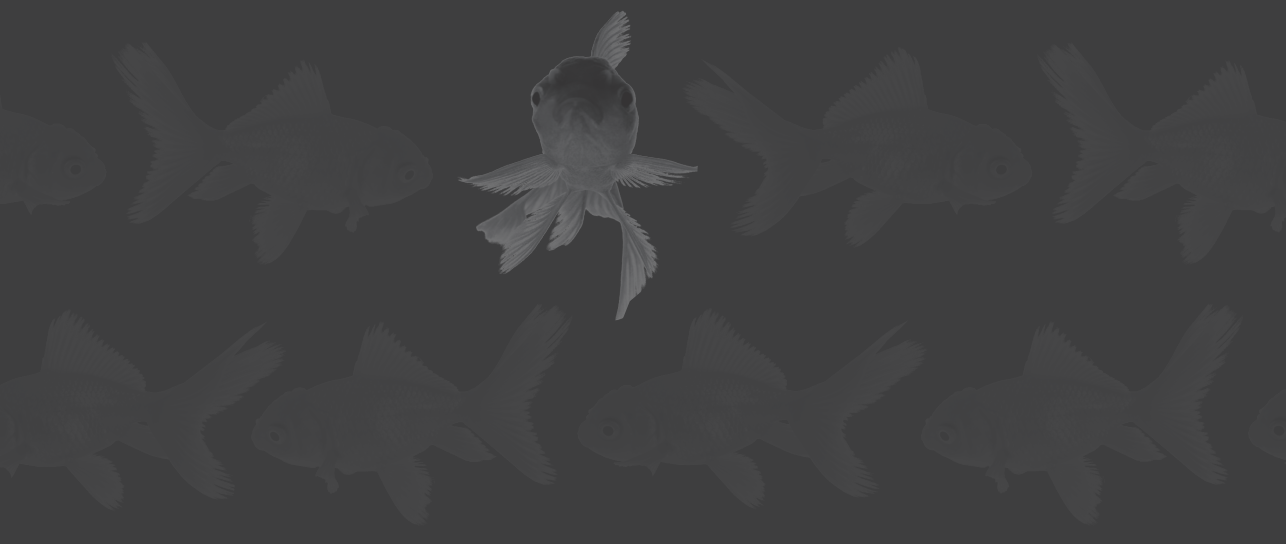
Co-promotor:	Dr. M.J. Roobol

If we knew what it was we were doing,
it would not be called research,
would it?

Albert Einstein

Voor mijn ouders

Table of contents



I | General introduction

1 Prostate cancer and screening

THE PROSTATE

The prostate is an exocrine gland that is part of the male reproductive system. It has the shape of a chestnut and is located just below the bladder, enveloping the proximal urethra and situated right in front of the rectum (figure 1). Its main function is the production of a fluid that forms part of the semen and the smooth muscles in the prostate help expel semen during ejaculation. Disorders of the prostate include benign conditions such as prostatitis, or prostate inflammation, and benign prostatic hyperplasia, which usually occurs in older men and may lead to urinary complaints. Prostate cancer (PCa) is a disease in which malignant cells form in the tissues of the prostate.

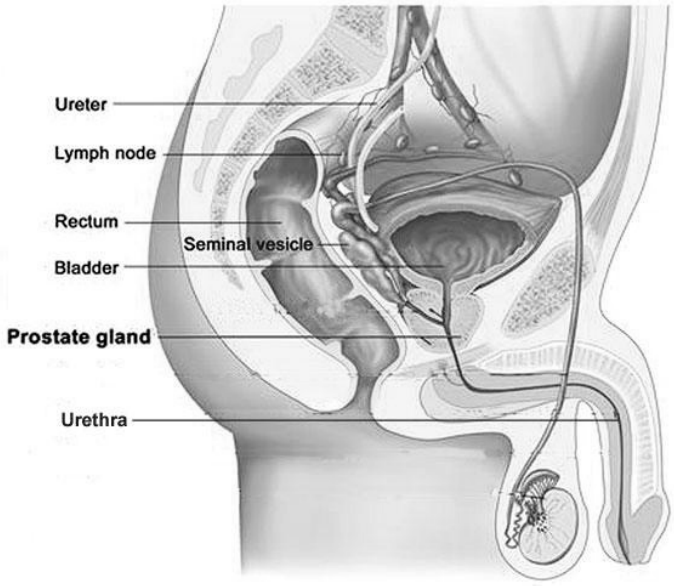


Figure 1 | Anatomy of the male reproductive and urinary systems [1].

PROSTATE CANCER

PCa is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males worldwide with more than 900.000 new diagnoses and 258.000 deaths in 2008 [2]. These numbers account for 14% of the total new cancer cases and 6% of the total cancer deaths in males [2]. This shows that PCa can be considered a major health problem.

The incidence of PCa in the Netherlands has been rising since the early 1990's (figure 2), which can be attributed to increased PCa awareness, diagnostic improvements, and early detection through prostate-specific antigen (PSA) testing [3]. The mortality rate,

however, has only shown a modest decline from 1996 onwards, that can most likely be explained by improvements in PCa treatment and possibly in part by screening for PCa. The substantial difference in incidence and mortality rates explains why many more men die *with* PCa than *from* PCa.

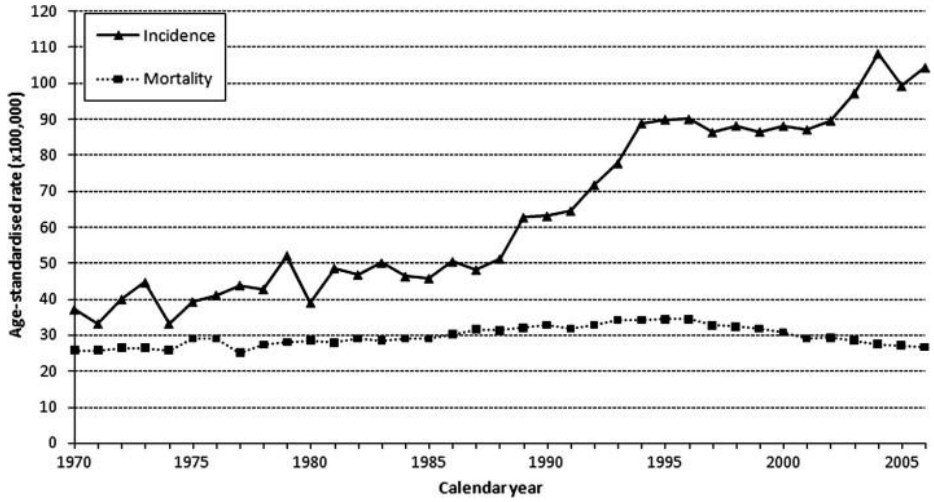


Figure 2 | Age-standardised rates for incidence and mortality of prostate cancer in the Netherlands 1970–2006 [3].

DIAGNOSIS OF PROSTATE CANCER

The most commonly used modalities to diagnose PCa include the serum PSA test, digital rectal examination (DRE), transrectal ultrasonography (TRUS) and prostate biopsy. In the early stages, PCa usually causes no clinical symptoms.

PSA is a protein that is secreted by the prostatic epithelium and has a role in the liquefaction of semen [4]. It was first described in 1979 [5] after which it became available as a biomarker [6] and potential screening tool [7] for the early detection of PCa. An increased PSA level indicates an increased risk for PCa [8], but an increase can also be caused by other conditions, such as an enlargement of the prostate in benign prostatic hyperplasia or inflammation of the prostate (prostatitis). So, elevated PSA levels are not specific for PCa, and in addition, PCa can even be found in the lowest PSA ranges [9]. Despite these shortcomings of PSA, it currently is the most important tumor marker for PCa and besides its use for screening purposes it is used for evaluation of treatment and follow-up in PCa patients.

Prior to the PSA era, DRE was the main method to diagnose PCa. The prostate can be examined by palpation through the rectal wall. Potential nodules that may raise the

suspicion of the presence of PCa can be evaluated as well as the volume of the prostate. Although the risk of PCa is higher in case of a suspicious DRE, the findings are only moderately reproducible between medical examiners [10].

TRUS provides images of the prostate, which allows the physician to examine for abnormalities. Furthermore, TRUS is normally used to guide prostate biopsies used to diagnose PCa in patients in whom there is a suspicion. Although these modalities (PSA, DRE and TRUS) do give an indication of the risk of PCa, histological assessment of prostate biopsies is still the golden standard to come to a definitive PCa diagnosis. A pathologist evaluates the extent of tumor in the biopsies, as well as the aggressiveness of the disease.

Other markers and imaging modalities for the diagnosis of PCa are being studied, and some even show promising results. However, these tests are not yet routinely used in clinical care.

PREDICTION MODELS

Prediction models, or nomograms, can be used to optimize the predictive accuracy in predicting disease status or prognosis and can be of help in informed decision-making [11]. The PCa risk calculator (www.prostatecancer-riskcalculator.com) is such a prediction model that incorporates the available pre-biopsy information in addition to PSA to calculate the possibility of a positive biopsy. This individualized approach was shown to lead to a considerable reduction in prostate biopsy due to improved predictive capability when compared to applying solely a PSA cut-off for screening, while very few significant PCa would be missed [12]. The risk calculator can also be used to calculate the probability of indolent disease, using the PSA level, prostate volume and biopsy results [13]. The final probability can be used to guide physicians and patients in the decision-making process to elect the most appropriate management strategy in an individual.

PROSTATE CANCER STAGING AND GRADING

The extent of the disease is commonly classified by the Tumor/Node/Metastasis (TNM) classification. The 2002 TNM classification is shown in table 1. This classification is used to predict prognosis of patients and to select appropriate treatment, based on the extent of the disease. Pre-operative evaluation and imaging of the prostate determine the clinical stage of the disease, while a definitive pathological stage can only be determined after radical prostatectomy.

Table 1 | TNM classification for prostate cancer (version 2009)

Primary tumor (T)		
Tx	primary tumor cannot be assessed	
T0	no evidence of primary tumor	
T1	clinically inapparent tumor not palpable or visible by imaging	
	T1a	tumor incidental histologic finding in ≤5% of tissue resected
	T1b	tumor incidental histologic finding in >5% of tissue resected
	T1c	tumor identified by needle biopsy (e.g. because of elevated PSA)
T2	tumor confined within prostate	
	T2a	tumor involves one-half of 1 lobe or less
	T2b	tumor involves more than one-half of 1 lobe but not both lobes
	T2c	tumor involves both lobes
T3	tumor extends through the prostatic capsule	
	T3a	extracapsular extension (unilateral or bilateral)
	T3b	tumor invading seminal vesicle(s)
T4	tumor fixed or invades adjacent structures other than seminal vesicles (e.g., bladder, levator muscles, and/or pelvic wall)	
Regional lymph nodes (N)		
NX	regional lymph nodes were not assessed	
N0	no regional lymph node metastasis	
N1	metastases in regional nodes(s)	
Distant metastasis (M)		
MX	distant metastasis was not assessed	
M0	no distant metastasis	
M1	distant metastasis	
	M1a	nonregional lymph nodes(s)
	M1b	bone(s)
	M1c	other site(s) with or without bone disease

Grading of PCa is used to indicate the aggressiveness of the tumor. PCa is graded according to the Gleason grading system, which was last updated in 2005 [14]. The Gleason score ranges from 2 to 10 and consists of 2 summed grade patterns that can vary from 1 (well differentiated) to 5 (poorly differentiated; figure 3). When the grading system was last updated, for prostate biopsies it was agreed that not the two most common patterns, but both the primary pattern (most common) and the highest grade should be recorded. Also, certain patterns originally considered pattern 3 are now considered pattern 4. These changes have resulted in relative upgrading of disease, leading to an artificial change in prognosis, often referred to as the Will Rogers phenomenon [15].

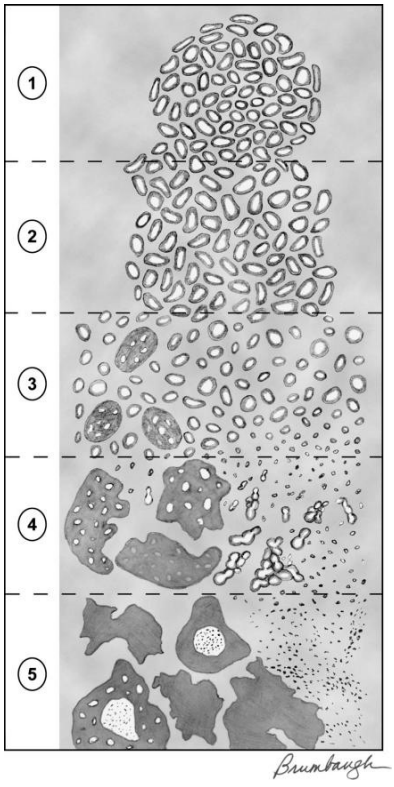


Figure 3 | Gleason grading system for prostate cancer [14].

SCREENING FOR PROSTATE CANCER

Cancer is very often associated with an unfavourable natural course and poor prognosis due to its metastatic potential that will eventually have fatal consequences.

In an earlier era, this idea used to be a good description of the often poor prognosis of the disease. However, in a new era of advances in medical care and technology, implementation of diagnostic tests has changed the stage in which cancers are diagnosed. Screening programs for cancer aim to diagnose aggressive cancer in an early stage, long before they lead to clinical symptoms, which subsequently facilitates curative treatment.

Several research programs were initiated to evaluate the feasibility of population-based screening for PCa in terms of mortality reduction, but also in terms of costs and quality of life. In 2009, the two largest study studies on screening for PCa reported their interim data [16,17]. The European Randomized study of Screening for Prostate Cancer (ERSPC) was initiated in the early 1990's as a randomized, multicenter trial of screening for PCa, with the main endpoint being PCa mortality [16].

Men were randomized between either a screening group or control group in eight different countries. The core age group consisted of 162.387 men aged 55-69 years. Screening was performed with a 2 to 4 year interval by means of a PSA test with a cut-off of 3.0 ng/ml as an indication for lateralized sextant biopsy. After a median follow-up of 9 years, a significant PCa mortality reduction of 20% was found in the screening group. When adjusted for non-compliance (i.e. men in the screening arm who did not undergo screening) and contamination (i.e. men in the control arm who sought opportunistic screening), a further enhancement of the mortality reduction up to 31% was shown [18]. In the meantime, analyses after 2 additional years have become available [19], which showed a consolidation of the relative risk reduction of 21% in favor of PCa screening. Moreover, it was found that at 11 years of follow-up a total of 1055 men would need to be invited for screening and 37 men would have to be diagnosed with PCa in order to prevent one death from the disease.

Another large screening trial, the Prostate Lung, Colorectal and Ovarian cancer screening (PLCO) trial [17,20], was not able to show a mortality benefit in screened men.

However, due to important differences in design and execution compared to the ERSPC trial, it is questionable whether a difference in PCa mortality can ever be shown in the PLCO trial [21].

OVERDIAGNOSIS AND OVERTREATMENT

Unfortunately, the mortality reduction shown in the ERSPC trial comes with a price. A major downside of screening for PCa was found to be the vast amount of cancers detected that would otherwise not go on to cause symptoms or death. This phenomenon is described by the term overdiagnosis. The rate of overdiagnosis in the ERSPC trial was estimated to be no less than 50% in the screening group [22]. If such cancers are treated, patients are unnecessarily exposed to the risk of side-effects of the treatment, while the prognosis of their so-called disease and their life expectancy are not improved. This is called overtreatment. Thus, many more cancers are detected than the number of men in whom the disease actually leads to clinical symptoms during lifetime, and radical treatment will not lead to improved prognosis over expectant management in these patients. Of course, overdiagnosis would matter less if treatment had no adverse effects. Furthermore, quality of life might be decreased by side-effects of unnecessary treatment and substantial costs are involved with the various therapies.

SIDE-EFFECTS OF RADICAL TREATMENT

Localized PCa may be treated radically with surgery (radical prostatectomy) or radiation therapy (brachytherapy or external beam radiation therapy). It would be more acceptable to treat all PCa cases if radical treatment would not go hand in hand with side-effects. Adverse effects of radical treatment include erectile dysfunction, impotence, urinary irritation and problems with the bowel or rectal function.

Rates for erectile dysfunction 5 years after radical prostatectomy for localized PCa were reported to be around 71-88%, while urinary incontinence was reported in 14-31% [23,24]. Erectile dysfunction after radiation therapy was reported in 64%, while problems with bowel function were seen in 11% [24]. Applying adjuvant hormone therapy was shown to exacerbate the adverse effects of radiation therapy [25]. Compared with surgery, brachytherapy may be associated with lower rates of incontinence but greater transient problems with urinary obstruction and irritation while having similar long-term effects on sexual and bowel function [26]. Reduction of adverse effects of radical treatment can be achieved by nerve-sparing in surgical procedures [25], as well as improvements in surgical techniques and more selectively delivered radiation therapy.

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2 | Active surveillance

Active surveillance: the European experience.
Active surveillance for localized prostate cancer
– A new paradigm for clinical management. Page 81-94.
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Meelan Bul, Monique J. Roobol, Chris H. Bangma

ABSTRACT

Prostate cancer (PCa) is the most frequently diagnosed malignancy in men across Europe. After prostate-specific antigen (PSA) became available as a potential screening tool for the early detection of PCa, the incidence of the disease has been increasing, as well as the relative amount of low-risk and potentially overdiagnosed disease. Active surveillance has emerged over the last few years as an alternative treatment strategy for the management of potentially overdiagnosed prostate cancer.

In this chapter, the European studies and initiatives with respect to screening for prostate cancer, and feasibility and effectiveness of active surveillance are described. There are two ongoing prospective active surveillance studies in Europe; the study at the Royal Marsden hospital in the United Kingdom was initiated in 2002 and the PRIAS study was initiated in the Netherlands in 2006 and is now an international web-based program with the highest number of participants worldwide.

Current results regarding active surveillance look promising, but longer follow-up is warranted to improve inclusion and follow-up criteria, and evaluate the safety of this approach. Furthermore, future research will focus on the improvement of the individualized management of patients with low-risk prostate cancer by means of predictive tools, and the incorporation of new biomarkers and imaging techniques for the differentiation between potentially aggressive and indolent disease.

INTRODUCTION

Incidence and mortality

Prostate cancer (PCa) is a major public health problem worldwide being the most frequent (non-cutaneous) cancer among men. In 2008, an estimated 382.000 cases of PCa were detected in Europe and 89.000 men were estimated to have died of the disease in the same year, ranking it the third most common cause of cancer death among men, after lung and colorectal cancer [1]. After prostate specific antigen (PSA) became available as a biomarker [2] and potential screening tool for the early detection of PCa[3], the incidence of PCa increased rapidly over the last 2 decades. A consistent increase in PCa incidence rates by 3% or more per year was observed throughout Europe from 1990, with declining rates only in the high incidence countries Sweden, Finland and the Netherlands from 2004 on. Mortality declines were more heterogeneous and were observed subsequently in some European countries, which can be attributed to improvements in treatment and as an effect of PSA testing and early detection of PCa. However, the correlation between incidence and mortality has weakened, most likely because of the amount of opportunistic PSA testing in contemporary practice causing overdiagnosis of indolent disease, thereby increasing incidence more and more, while the observed effect of early detection and treatment on mortality reduction was relatively modest [4].

Overdiagnosis and overtreatment

Autopsy studies have shown that indolent disease is quite common, with 30-80% of men aged 40-80 years harbouring histological evidence of PCa [5]. Detecting disease that would otherwise not lead to symptoms or death, or *overdiagnosis*, is one of the major side-effects of PSA-based screening for the detection of early PCa. Such cancers will either not progress at all or progress slowly enough that patients die of something else before the disease becomes symptomatic [6]. These patients will not benefit from treatment in terms of increasing life expectancy, but they can be harmed by the serious side-effects of radical treatments [7-9]. Minimizing overdiagnosis by accurately predicting tumor behavior is a very important objective for future studies evaluating new biomarkers and genetic factors. However, the ideal screening tool for PCa, which could identify potentially aggressive cancers in an early, curative stage, but could also avoid detection of cancers that would never cause any symptoms, let alone deaths, unfortunately does not yet exist. An important development in an attempt to avoid unnecessary biopsies while still detecting most clinically important PCa cases is a clinical strategy that uses algorithms for individualized risk-stratification to assist in the decision to perform a biopsy. It was shown that the predictive value of a screening test can be increased by incorporating clinically available risk modifiers such as ultrasound volume, digital rectal exam, transrectal ultrasound [10], percentage free PSA [11] and PCA3 [12]

together with the PSA value in a model, thereby reducing the number of unnecessary biopsies and decreasing overdiagnosis and, once potentially indolent cancers are diagnosed, unnecessary treatment.

Rationale for active surveillance

Active surveillance (AS) has emerged over the last years as an alternative strategy for the management of potentially overdiagnosed PCa. This strategy aims to delay or even avoid unnecessary treatment of indolent tumors and its subsequent adverse side-effects [13-15], with the advantage of preserving quality of life and potential benefit of advances in available therapy.

AS consists of initially withholding radical treatment and intensively monitor the patients instead with PSA measurements, rectal examination and repeat prostate biopsies. If there is reason to suspect disease progression or risk reclassification towards higher risk, a switch to radical treatment with curative intent and within the window of curability is advised.

The difficulty in selecting patients for AS, is to identify those patients who have indolent disease, i.e. tumors that will not surface clinically during lifetime when left untreated. Because there is not yet a marker available that differs between indolent and aggressive PCa, identification of patients is based on favorable clinical parameters at diagnosis. Frequent follow-up should warrant early detection of potential misclassification of low-risk disease or true progression in order to preserve the same prognosis as immediate radical treatment would have had.

In this chapter we will review studies for screening of PCa that form the initial setting for observations on AS and next, studies evaluating feasibility and effectiveness of AS in Europe.

SCREENING FOR PROSTATE CANCER IN EUROPE

The increasing use of PSA as a screening tool for the early detection of PCa has led to the diagnosis of disease in men who would not have experienced clinical symptoms or death from the disease during their lifetime. In response to increasing overdiagnosis, AS evolved as a treatment modality, aiming to avoid invasive treatment in many men.

Next to results on PCa mortality, screening studies for PCa have provided insight into the amount of PCa cases that can be expected to be over detected when identified by PSA-based screening. Over detection is one of the major drawbacks of screening for PCa, with an over detection rate that has been estimated to be as high as 50% within the European Randomized Study of Screening for Prostate Cancer (ERSPC) [16]. Since the origin of AS is so closely linked to screening for PCa, the European studies concerning this topic will be reviewed below.

European Randomized Study of Screening for Prostate Cancer

The ERSPC is a randomized, multicenter trial of screening for PCa that was initiated in 1991 [17]. The main endpoint of this study is whether screening for PCa can actually lower disease-specific mortality. Men in 8 different European countries, aged 50-74 years, were identified from population registries and randomized to either a screening or a control arm. The core age group in this study was 55-69 years and consisted of 162.243 men, who were screened with a 4-year (87%) or 2-year (13%) interval. Screening was performed with PSA measurements, followed by (mainly) lateralized sextant biopsy cores in case a PSA value of $\geq$4.0 ng/ml, or later $\geq$3.0 ng/ml was found. The different centres have used slightly differing values for PSA cut-off (2.5-4.0 ng/ml) and ancillary tests, such as digital rectal examination and transrectal ultrasound, throughout the study period. After randomization, a total of 72.890 men were assigned to the screening group and 89.353 to the control group, with a mean age of 60.8 years. After a median follow-up of 9 years, PCa was detected in 5990 (8.2%) men in the screening group and in 4307 (4.8%) men in the control group. PCa deaths occurred in 214 and 326 men, respectively, corresponding to a significant reduction of 20% fewer men dying of PCa in the screening group (p=0.04). This intention-to-screen (ITS) analysis showed a number of 1410 men who need to be screened (NNS) and another 48 men who need to be treated (NNT) in order to prevent one PCa death. This result could not be contributed to a treatment effect [18]. A secondary analysis [19] was carried out to assess the impact of adjustment for men assigned to the screening arm who did no undergo screening (noncompliance,) and for men assigned to the control arm who sought opportunistic PSA-based screening (contamination). This analysis showed a further enhancement of the PCa-specific mortality reduction for those men who are actually screened, after adjustment for both noncompliance and contamination by up to 31%.

In the meantime the results of the Göteborg screening trial have been published [20]. This trial was initiated as an independent study in 1994 but joined the ERSPC trial shortly thereafter. With a follow-up of 14 years, results show a rate ratio for PCa death of 0.56 (95%CI 0.39-0.82, p=0.002) in the ITS analysis and of 0.44 (95%CI 0.28-0.68, p=0.002) after adjustment for non-compliance. This resulted in a NNS of 293 and a NNT of 12, and for attendees after adjustment for non-compliance a NNS of 234 and NNT of 15. The main differences with the ERSPC as a whole are the type of randomization, younger age, a shorter screen interval, and, most importantly, a longer follow-up due to the simultaneous randomization of all participants in 1994 in Sweden.

Prostate testing for cancer and Treatment (ProtecT) and Comparison Arm for ProtecT (CAP) studies

These studies were initiated about 10 years after the commencement of the ERSPC and have a different design that, besides enabling evaluation of the effectiveness of PCa screening in the population (CAP trial), enables evaluation of various treatment strategies for localised PCa in a randomised setting (ProtecT trial) [21]. Both trials are carried out in the United Kingdom (UK) and have disease-specific survival as a primary outcome, with secondary outcomes of overall survival, costs and quality of life.

For the CAP trial, primary care centres in and around 8 UK cities were randomised to either a comparison group where standard care was applied or an intervention group where men received a single round of PSA testing. All men without PCa diagnosis at randomisation, aged 50-69 years, were tracked for PCa diagnosis or death. An independent, blinded adjudication committee reviewed all cases of possible PCa (related) deaths. Over 550 primary care centres included over 450.000 men, comprising 8% of the England and Wales male population in that age category [21].

In the ProtecT trial, men aged 50-69 years and registered in the CAP intervention group were invited for PSA testing. A PSA level between 3.0-19.9 ng/ml resulted in a recommendation for ultrasound-guided 10-core prostate biopsies, a repeated PSA test and digital rectal examination. If clinically localised PCa was detected, participants were offered randomisation to external beam radiotherapy, radical prostatectomy or active monitoring. From 111.000 ProtecT attendees, 10.000 men were detected with a raised PSA, of which 3000 were diagnosed with PCa and over 1500 participants with localised PCa agreed to randomisation to one of three treatment strategies [21, 22].

Results from CAP en ProtecT so far have contributed to knowledge of metabolic and nutritional factors in affecting PCa risk, genetic variations linked to PCa risk within the genome-wide association studies, psychological impact of cancer screening and detection, and cancer detection and individual risk assessment [21], which can contribute to improving the detection process. The ProtecT trial will provide information on the effectiveness of three treatment strategies for localized PCa, while the CAP trial will provide insight in the effect of population-based screening, which will complement ERSPC findings and will shed more light on the screening policy and management of screen-detected disease. The main trial publication with 10-year follow-up results is expected to be published in 2016.

Tyrol Prostate Cancer Demonstration Project

Another study evaluating the effectiveness of an early detection program for PCa was carried out in Tyrol, Austria from 1993 to 2005 [23]. From 1993, PSA testing was offered for free to all men, aged 45 to 75 years, living in the Tyrol area. Men were advised and encouraged to undergo PSA-testing and eventually 86.6% of the eligible men have been

tested at least once during the study period. Age-referenced PSA levels in combination with percentage free-PSA levels were used for recommending biopsy and (radical) treatment was advised in case PCa was diagnosed. Morality rates for Tyrol were compared to the rates for the rest of Austria, where there was no such early detection program for PCa. The authors report a significant reduction in PCa deaths between the Tyrol region where PSA testing and treatment are freely available to all men and the rest of Austria. They also found a significant stage migration to lower stage disease in Tyrol, with pathologically organ-confined disease detected in 23.7% of the cases in 1993 to 78.7% in 2005. The authors state that the results of this study are most likely due to the early detection of PCa with subsequent down staging, and effective treatment of the disease. However, it should be kept in mind that a nonrandomized design was used in this study, which leaves some important questions unanswered on aspects of the implementation of population-based screening for PCa that can only be elucidated by large, randomized clinical trials such as the ERSPC.

EUROPEAN ACTIVE SURVEILLANCE STUDIES

Feasibility of active surveillance

Several European studies have contributed to the understanding of the natural course of PCa and the feasibility of AS as a treatment strategy. Because long-term results for AS are lacking, these retrospective studies contribute greatly to the knowledge of outcomes of patients who were managed expectantly.

Khatami et al [24] reported on the outcome of an AS cohort, derived from screen-detected cases from the Swedish arm of the ERSPC. A total of 270 patients were managed with surveillance, of whom 39% received active treatment after a mean follow-up of 63 months. The men who received treatment were found to be significantly younger and had shorter PSA-DT. PSA relapse was observed in 9 of 70 patients who received RP after mean follow-up 37 months. PSA-DT was a significant ($p = .031$) predictor for PSA relapse; 7 out of 9 patients had a PSA-DT <2 years before RP, while none of the 37 operated patients with a PSA-DT >4 years experienced a PSA relapse. They classified men with low-risk tumor characteristics and a PSA-DT >4 years as the most optimal candidate for AS.

The Scandinavian Prostate Cancer Group-4 (SPCG-4) study [25] compared PCa survival in a group of patients that received radical prostatectomy (RP) to a group receiving watchful waiting (WW). A total of 695 men with a mean age of 65 were randomly assigned to either RP (N = 347) or WW (N = 348). After a median follow-up of 10.8 years a total of 137 (39%) and 157 (45%) men died in the RP and WW groups, respectively (RR = 0.82; $p = .09$).

The cumulative incidence of deaths due to PCa in the RP group at 12 years was 12.5% compared to 17.9% in the WW group (RR = 0.65; $p = .03$). Distant metastases were more common in the WW group (26%) than in the RP group (19.3%) at 12 years follow-up (RR = 0.65; $p = .006$). These relative risks for overall mortality, disease-specific mortality, and distant metastases correspond to absolute risk reductions at 12 years of 7.1%, 5.4% and 6.7% respectively. They found that the benefit of RP in disease-specific death was primarily achieved during the first 5 years of follow-up without further increase thereafter. A critical question raised by the authors is whether the results are generalizable to contemporary settings in which most PCa are detected by screening. In this study, only a very small minority of the men was screen detected. Moreover, the results show a benefit of RP that is limited to younger men under the age of 65, with intermediate or high-grade disease (Gleason score $\geq$7). Critics point out that, besides the favorable outcome of RP in younger men, these results suggest that many such treatments for men over 65 years could be avoided entirely and that men with low-risk disease might be best served by AS [26, 27]. It should however also be noted when interpreting these results, that WW was used in the control arm of this study instead of AS, which is a different strategy, regarding the lack of a follow-up protocol and the intent for curative treatment if necessary. Moreover, most patients in this study had more unfavorable baseline characteristics than we would find in (mostly) screen-detected men in AS study cohorts nowadays.

A population-based retrospective cohort study in Sweden by Stattin et al [28] evaluated PCa mortality and the risk of death from other causes in patients with low- or intermediate risk PCa (clinical stage T1, Gleason score $\leq$6, PSA <10 ng/ml and stage $\leq$T2, Gleason score $\leq$7, PSA <20 ng/ml, respectively), receiving either AS or WW, radical prostatectomy (RP) or radiotherapy. Of 6849 men, 2021 were offered WW or AS. Results after 8.2 years follow-up showed a 10-year PCa-specific mortality of 3.6% in the 'surveillance' group and 2.7% in the curative intent group; for those with low-risk disease these values were 2.4% and 0.7%, respectively. The authors argue that overall mortality was much higher in the conservatively managed group than in the treatment group (19.2% vs 10.2%), which indicates that men with a short life expectancy were selected for AS or WW more often. Another strong selection bias was caused by a higher proportion of healthy patients with PCa with adverse factors being assigned to RP than to AS or WW. They conclude that the low disease-specific death rate in men with low-risk PCa justifies this strategy for many.

Another Swedish study [29] describes a case-control analysis of 26 men on AS receiving RP at the moment of progression, which did not prove to comprise curability.

A collaboration between four ERSPC centres led to a retrospective study validating eligibility criteria for AS [30]. Data from 616 men were used, who had a screen detected diagnosis of PCa between 1994 and 2007 in one of four ERSPC centres. All patients had

favorable characteristics to suit AS criteria (PSA ≤10 ng/ml, PSA density (PSA-D) 0.2 ng/ml/ml, clinical stage T1c or T2, Gleason score ≤6 and ≤2 positive biopsy cores) and all were initially managed expectantly. Results after a median follow-up of 3.91 years showed a 10-year disease-specific survival of 100%, while the 10-year overall survival was 77%. During follow-up, 34% of the patients switched to active therapy after a mean of 2.6 years, resulting in a 10-year deferred treatment free survival rate of 43%. The authors concluded that a considerable number of men harbouring low-risk PCa die of other causes before their disease surfaces, justifying their expectant management. During follow-up, just over half of their patients switched to deferred treatment. In the greater part of cases this took place in the absence of any signs of progression, indicating that therapy could have been avoided in more patients. This might partly be explained by the fact that no follow-up protocol as currently used in prospective AS programs was applied. However a great part of men achieved complete avoidance of active therapy while treatment was often deferred for many years in the remainder, which can be precious in deferring potential side-effects of radical treatment in healthy men.

Another study was carried out by van den Bergh et al to evaluate potential impaired chances of curability in men in whom radical treatment was delayed [31]. They retrospectively compared patients who would have suited the AS criteria as mentioned above and who received immediate (N = 158) versus delayed RP (N = 69) after a mean duration of 0.5 and 2.6 years after diagnosis, respectively. Histopathological and biochemical outcomes after a mean follow-up of 5.7 years showed no significant differences between the groups regarding Gleason score >6, extracapsular extension, tumor volume or biochemical progression rate. Time interval to RP was not predictive for any adverse outcomes within these 2 groups. All data did seem to be in favor of the immediate RP group, however it is imaginable that the delayed RP group was biased due to changing characteristic during follow-up, provoking the decision for active treatment. If similar low-risk patients with stable favorable characteristics over time would be taken into account in the delayed RP group, then the effect of unfavorable findings in delayed RP would very likely be diluted due to more favorable outcomes that are expected in this group. A randomized study design with low-risk patients receiving either immediate or delayed RP would help to clarify this issue, but is hard to realize. The findings from this study, together with the knowledge of the natural course of PCa with an estimated lead-time of >10 years in low-risk disease [16] support the assumption that a potential harmful effect of AS protocols is small.

Because the use of PSA as a screening tool for the early detection of PCa has been expanding over the last two decades, more men are being classified as having Gleason score ≤6 PCa. Whether or not these tumors should be treated is still a controversial issue.

More data from randomized trials such as ProtecT [21, 22] are needed to shed more light on the effects of various treatment strategies for localized disease, including AS for low-risk PCa.

These retrospective studies in Scandinavia and The Netherlands show favorable outcomes in men on AS with low-risk PCa after medium to long-term follow-up. However, results are sometimes difficult to interpret because of potential selection biases and therefore, prospective trials are necessary to evaluate the outcome in true AS cohorts in which men are intensively monitored following a strict schedule.

Prospective active surveillance studies

Over the past decade, AS studies have been initiated in Europe. These studies aim to evaluate the outcome of patients with low-risk PCa who are managed expectantly and follow a strict follow-up scheme, while treatment with radical intent within a curable stage can be provided if necessary. There are two prospective AS studies in Europe, which will be discussed in this chapter.

Active surveillance in the United Kingdom

The first study was initiated in the UK at the Royal Marsden Hospital in 2002 [32, 33] and is still ongoing. Eligible patients have PCa with a clinical stage T1 or T2a, a PSA value less than 15 ng/ml, a Gleason score equal to or less than 7 with a primary Gleason grade less than 4 and cancer present in 50% or less of the total number of biopsy cores. All patients are aged 50-80 years and are fit for radical treatment, but chose AS as their initial treatment strategy. Follow-up consists of monthly PSA measurements in the first year, every 3 months in the second year, and half-yearly thereafter. A digital rectal examination (DRE) is performed every 3 months in the first 2 years and half-yearly thereafter. Repeat biopsies are scheduled after 18-24 months and every 2 years thereafter. Indications for radical treatment comprise biochemical disease progression with a PSA velocity (PSA-V) greater than 1 ng/ml/yr, or histological disease progression on repeat biopsy with a primary Gleason grade of 4 or more, or presence of disease in more than 50% of the total number of biopsy cores (table 1).

Results of this study showed 73% of men (N = 326) remaining on surveillance after a median follow-up of nearly 2 years, while 20% had radical treatment, 5% switched to watchful waiting and 2% died of other causes. No patients developed metastases and no PCa deaths occurred. Of 18 patients who underwent RP, all had Gleason score less than 8 and 2 had seminal vesicle involvement. They found free/total PSA ratio and clinical stage to be predictors of time to radical treatment [33]. They also compared the accuracy of PSA-V and PSA doubling time (PSA-DT) for predicting the repeat biopsy results in 199 men on AS and found PSA-V to be more accurate in predicting adverse findings [34].

Table 1 | Inclusion criteria, follow-up schedule and indications for radical treatment for the European active surveillance studies

Inclusion criteria	**Royal Marsden hospital**	**PRIAS study**
Clinical T stage	T1 - T2a	T1c – T2
PSA value	≤15 ng/ml	≤10 ng/ml
PSA density	-	<0.2 ng/ml/ml
Biopsy Gleason score	Equal to or less than 3+4=7	Equal to or less than 3+3=6
Positive cores	Equal to or less than 50%	No more than 2
Follow-up		
Serum PSA	Year 1: monthly, year 2: 3-monthly, then every 6 months	Years 1-2: 3-monthly, then every 6 months
DRE	Years 1-2: 3-monthly, then every 6 months	Years 1-2: 6-monthly, then every year
Repeat biopsy	After 18-24 months, then every 2 years	After 1 year, then every 3 yrs
Indications for radical treatment		
Clinical T stage	-	T3 – T4
PSA velocity	>1 ng/ml/year	-
PSA doubling time	-	≤3 years
Biopsy Gleason score	Equal to or more than 4+3=7	Equal to or more than 3+4=7
Positive cores	More than 50%	3 or more

PRIAS, Prostate Cancer Research International: Active Surveillance; PSA, prostate-specific antigen; DRE, digital rectal examination

The PRIAS study

The Prostate Cancer Research International: Active Surveillance (PRIAS) study, which originated from the ERSPC, was initiated in the Erasmus MC in The Netherlands in December 2006 and is still ongoing. It is an international observational prospective study that provides a protocol for the inclusion and follow-up of men with low-risk disease to validate the management of PCa with AS. The number of participating countries and centres is still expanding (figure 1 and 2). A web-based instrument is used for inclusion and follow-up of patients (www.prias-project.org [35]). The website offers information for patients and, after login, can be used by physicians to enter follow-up details and include new patients. The site automatically generates a graph presenting the patient's PSA values over time and the current PSA-DT value. Furthermore, the site generates an automatic, individualized recommendation whether AS can be continued or active treatment is indicated, based on the follow-up criteria. This internet tool was developed to facilitate evidence-based decisions when considering AS [36].

The eligibility criteria for PRIAS comprise a clinical stage T1c or T2, a PSA level of 10.0 ng/ml or less, a PSA-D of less than 0.2 ng/ml/ml, a Gleason score 3+3=6 or more favorable, and 1 or 2 biopsy cores invaded with PCa. The follow-up schedule consists of 3-monthly PSA measurements and half-yearly DRE for the first two years and half-yearly

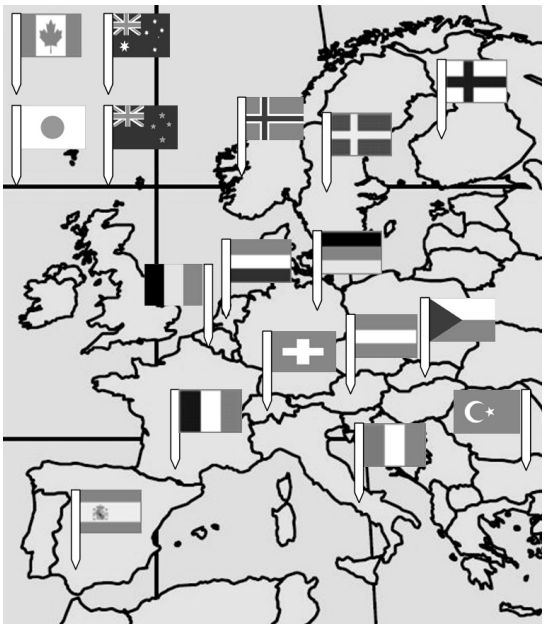

Figure 1 | Countries participating in the PRIAS study.

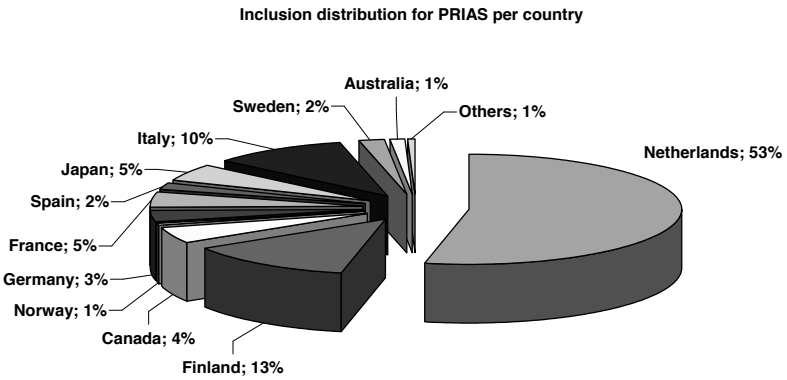

Figure 2 | Distribution of inclusions for PRIAS per participating country at January 1, 2011.

PSA measurements and yearly DRE thereafter. Repeat biopsies are scheduled after 1, 4 and 7 years. Prostate volume-dependent biopsies are advised: <40cc: 8, 40-60cc: 10, and >60cc: 12 biopsy cores. Whenever PSA-DT is between 3 and 10 years, yearly repeat biopsies are recommended. PSA-DT is advised to be used only after at least 1 year of follow-up when 5 measurements are available. Indications to switch to deferred active treatment during follow-up are a PSA-DT shorter than 3 years, a clinical stage exceeding T2, more than 2 positive biopsy cores on repeat biopsy, or a Gleason score higher than 6 (table 1). Whenever PSA exceeds 20 ng/ml, a bonescan is recommended [37].

In 2009, the first results were published for PRIAS [37]. The main outcome parameter in this study, describing the first 500 patients in the study, was active therapy-free survival. Patients had been followed between December 2006 and July 2008 for a median of 1.02 years after PCa diagnosis. The 2-year active therapy-free survival rate was 73%, with most men switching to active treatment based on protocol advice (83%). A total of 10% of the study participants chose for treatment due to anxiety. Repeat biopsies (N = 261) in this cohort showed no evidence of PCa in 34%, low-risk ("PRIAS suitable") PCa in 44% and more unfavorable PCa in 22%, for which univariate analysis showed the number of cores at initial biopsy (2 vs 1) to be the only predictor. During the available follow-up period, no man died due to PCa, lymph node metastases were detected in 1 man and 2 men died due to other causes, leading to a 100% disease-specific survival rate and a 99.6% overall survival rate in this cohort. Although the follow-up of in this study is limited, these data support AS as a feasible strategy to reduce overtreatment on short-term after diagnosis without comprising curability.

At the moment of printing this book more results from PRIAS are available, but yet unpublished. Up to October 2010, 757 men had a first repeat biopsy taken after a median of 1.03 years. The results of these repeat biopsies were favorable (no or low-risk PCa) in 594 patients (78.5%) and led to risk reclassification in 163 (21.5%). Multivariate logistic regression showed the number of initial positive biopsy cores (2 vs 1) and PSAD to significant predictors for risk reclassification to higher risk on repeat biopsy. A PSA-DT less

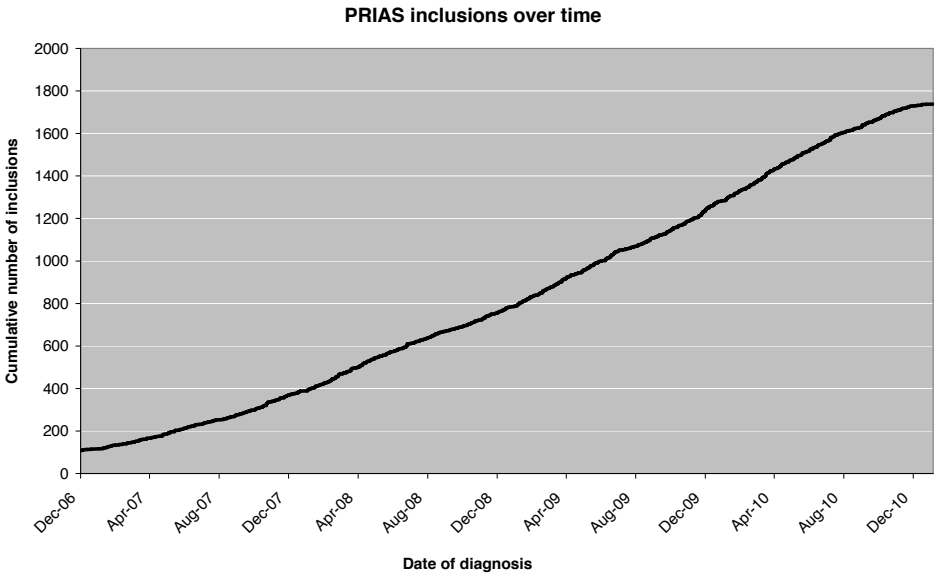

Figure 3 | Number of inclusions for PRIAS over time, from December 2006 to January 2011.

than 3 years at the time of repeat biopsy was also found to be predictive of unfavorable results. These data might contribute to the biopsy and follow-up strategy used in AS.

With a number of participants exceeding 1700 in the first half of 2011, PRIAS has included more patients than any other prospective study (figure 3). This high number of inclusion can be explained by the international character of PRIAS with 17 participating countries, and its easily accessible web-based inclusion and follow-up possibilities. This study will hopefully contribute greatly to the knowledge of the natural course of low-risk PCa and the applicability of AS as a treatment strategy for low-risk PCa with longer follow-up.

Quality of life issues

A number of studies were performed, evaluating quality of life issues in 150 men on AS in the PRIAS study [38-40]. One of the main findings in these questionnaire-based studies was that patients on AS had adequate knowledge of their disease and realistic perceptions of their treatment strategy and its possible advantages (most frequently reported as 'delay of side effects') and disadvantages (most frequently reported as 'risk of disease progression') [38]. Furthermore, favorable levels of anxiety and distress were reported among men on AS, showing comparable, or even more favorable results for depression and (disease-specific) anxiety than men who underwent other treatments for localized PCa. A neurotic personality however, was associated with more unfavorable scores [39]. Assessing the changes of the levels of anxiety and distress of men with low-risk PCa over time led to favorably low results up to 9 months after diagnosis. Men with low neurotic personality and good physical health seemed to perform best on the psychological level [40].

OTHER ONGOING RESEARCH IN EUROPE

Several other studies have been initiated across Europe, of which the results will contribute to the differentiation between aggressive and indolent PCa at diagnosis and to the knowledge of the effectiveness of AS as a treatment strategy for low-risk disease.

Predictive models

Prognostic models have been designed to predict indolent PCa in a screening setting [41, 42]. These nomograms predict the probability of clinically indolent PCa by incorporating multiple clinical variables besides PSA, such as prostate volume, biopsy Gleason score, and length of noncancerous and cancerous tissue in biopsy cores, in order to support patients and clinicians when considering different treatment options. The nomogram reported by Steyerberg et al [42] is an updated and validated version of the original nomogram reported by Kattan et al [41] and when applying the nomograms to a recent, clinical population, the resulting areas under the ROC-curve for predicting indolent

disease were 0.779 and 0.777 respectively, indicating good and comparable discrimination for both models [43]. These individualized screening algorithms can help to identify substantial groups of PCa cases that are likely indolent and can therefore be considered for AS. Further validation and improvement of these nomograms can be achieved with longer follow-up of AS programs and potential addition of novel biomarkers or imaging results, which will be discussed later on in this paragraph.

HAROW study

The Hormone therapy, Active Surveillance, Radiotherapy, Operation and Wachtful Waiting (HAROW) study is a German initiative to study the effectiveness of different treatment strategies on localised PCa. In this non-interventional study that was initiated in 2008, neither the physicians nor the patients participating are selected. The aim is to provide prospective data on invasive therapies and defensive strategies regarding cancer history, quality of life, patients' satisfaction and costs through questionnaires and medical records of 5000 patients. In patients opting for AS, HAROW uses the PRIAS criteria for enrolment and indication to switch to deferred treatment. Up till 2009, over 900 patients were included and approximately 9% chose AS as their preferred treatment option. The first results of this study are expected within the next years [44].

Imaging

Magnetic Resonance Imaging (MRI) is one of the imaging techniques being studied to evaluate its role in the selection and follow-up of PCa patients on AS. Although transrectal ultrasound (TRUS) is still the mainstay for imaging of the prostate, underestimation of the tumor volume on TRUS and under sampling of Gleason score are potential causes for inadequate identification of PCa aggressiveness. Functional MRI techniques and MRI-guided biopsies can be used for detection and localisation of PCa, as well as to optimize the staging accuracy, which might prove valuable for the future selection and follow-up of AS patients [45, 46]. Results of two studies on diffusion-weighted MRI in patients managed by AS showed significant differences in apparent diffusion coefficients in those who showed signs of progression compared to those who did not, supporting the potential of this technique to monitor patients with low-risk PCa and to help identify those who might be better of with radical treatment [47, 48]. Another study showed that MRI did not improve the prediction of unfavorable disease features in the RP specimen of AS suitable patients, when these patients were selected based on an extended 21-core biopsy scheme and the most stringent inclusion criteria for AS [49].

Another imaging technique that might support detection and characterisation of PCa is computer-aided ultrasonography (HistoScanning) [50]. First results showed accurate detection of PCa foci with a volume $\geq$0.50 ml [51], but further validation of this technique is needed to evaluate its use in PCa screening and AS.

Biomarkers

Research on new biomarkers will hopefully contribute to the improvement of the selection for AS in addition to the current AS criteria. So far, European initiatives have already contributed to better knowledge of this topic. Prostate cancer antigen 3 (PCA3) was found to show improvement in the identification of serious disease in a pre-screened population [52] and other results showed PCA3 to be strongly indicative for tumor volume and insignificant disease in men suitable for AS undergoing RP [53]. However, the real benefits and limitations of this screening test still have to be established. Another study evaluated the prognostic value of the molecular markers EZH2, MIB-2, p27(kip1) and BMI-1 on biopsy cores from men with low-risk PCa who were subsequently treated with RP. A high EZH2 and a low p27(kip1) expression showed to be predictive for significant disease [54], which could improve the pre-treatment risk assessment and the selection of men with indolent disease. Thomasson et al [55] found LRIG1 expression to be a predictor for disease-specific survival in Swedish patients that were left untreated, while the study by Jhavar et al [56] showed that Ki-67 LI predicted for progression to radical treatment in an AS cohort.

These preliminary results justify further study on these (and other) biomarkers that might prove to contribute to distinguish indolent and potentially aggressive disease and support the guidance of treatment decisions.

REFLECTION OF ACTIVE SURVEILLANCE IN EUROPE

Up till now, results of AS are encouraging, however longer follow-up is warranted to validate the safety of this approach in terms of PCa survival. Ongoing prospective trials in Europe, such as PRIAS and the Royal Marsden study, are needed to further optimise the inclusion and follow-up criteria for AS. Randomized studies, such as ProtecT, will hopefully provide information on the effectiveness of AS as a treatment strategy for localized PCa, compared to other treatments. Selection of men suitable for AS should be improved, thereby increasing the active therapy-free survival and preventing treatment delay of potentially aggressive tumors beyond the so-called window of opportunity for cure. The psychological aspect is another important scope for further research.

Future studies on the use of already existing algorithms that incorporate multiple clinical characteristics to predict the chance of harbouring indolent disease, will contribute to the individual management of patients. Furthermore, research on new molecular and genetic biomarkers is needed to improve the differentiation between potentially aggressive and indolent PCa. Ideally, only those men who will truly benefit from radical treatment should be subjected to active therapy with its subsequent side-effects. Investing in research to optimise AS programs should bring us closer to this goal.

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3 | Scope and outline of the thesis

SCOPE

The use of prostate-specific antigen (PSA) as a marker for the early detection of prostate cancer (PCa) has shown an effect in mortality reduction, but has also led to some controversial issues. PSA lacks specificity, which in a screening setting results in large numbers of unnecessary biopsies and, at the same time, missing diagnoses in men with PSA values in the lowest ranges. The controversies in screening, as well as the natural course of low-risk PCa are assessed in the second part of this thesis.

Major worries caused by the increasing use of PSA that need to be dealt with are the subsequent overdiagnosis and overtreatment. Prognostic models have been developed to improve predictive accuracy of screening tests and prognosis in order to contribute to solve these problems. The PCa risk calculator is such a prognostic model that was developed with data from the ERSPC trial, which might limit its applicability for contemporary practice. The third part of this thesis contributes to improvement of the PCa risk calculator.

Another way to decrease the amount of overtreatment is to reduce the amount of invasive treatment, especially in patients who are diagnosed with low-risk PCa. Active surveillance is a relatively new management strategy that aims to prevent, or at least delay, invasive therapy and its potential side-effects in selected men with seemingly low-risk PCa features. In part four of this thesis, short-term outcomes of the Prostate Cancer Research International: Active Surveillance (PRIAS) study are shown and current limitations of this strategy are discussed.

OUTLINE

Part two of this thesis focuses on screening for PCa and low-risk disease. In **chapter 4**, the controversial points of screening in the ERSPC trial will be put in perspective and priority issues for improvement of screening will be indicated. The outcome of men with initial PSA values <3.0 ng/ml in the Rotterdam screening arm of the ERSPC will be assessed in **chapter 5** to evaluate the risk of applying such a threshold and contribute to risk stratification. Because not many long-term results are available for active surveillance, in **chapter 6** the feasibility of this strategy will be assessed by evaluating the outcome of men who elected to withhold radical treatment for either low or intermediate-risk PCa.

In part three, **chapter 7**, correction factors will be extracted for extended biopsy schemes to adjust PCa risk calculator predictions based on 12 and18 core biopsy regimes.

Results of the PRIAS study will be shown in part four. **Chapter 8** will report on routinely obtained 1-year biopsies and factors predicting reclassification to higher risk on repeat biopsy, which can potentially be used for risk stratification. The outcomes of men who underwent radical prostatectomy after initial active surveillance will be discussed in **chapter 9**. An overall impression of the short-term outcomes in active surveillance will be presented in **chapter 10**. The challenges in active surveillance that have to be faced, as well other future perspectives will be discussed in **chapter 11**.

II | Low risk prostate cancer

4 Screening for prostate cancer – The controversy continues, but can it be resolved?

Acta oncol. 2011;50:4-11.

Meelan Bul and Fritz H. Schröder

ABSTRACT

Background

In 2009, the European Randomized Study of Screening for Prostate Cancer (ERSPC) was one of two studies to report interim data on the effect of screening for prostate cancer (PCa) on the disease specific mortality. Contradictory results caused considerable discussion and misunderstanding in secondary literature.

Methods

This document is based on a non systematic review of recent evidence for and against screening for PCa, specifically considering three recently published randomized screening trials [1-3].

Results

The ERSPC data are based on a core age group of 162.387 men, aged 55-69 years, who were identified through population registries in 7 European countries. Men were randomized between a screening group that received screening at an average of once every 4 years and a control group. After a median follow-up of 9 years, a reduction in the rate of death from PCa by 20% was shown which increased to 31% after adjusting for noncompliance and contamination. Overdetection and subsequent overtreatment (with a number needed to treat (NNT) of 48) are considered to be the major down sides of screening. The recently published 14-year results have shown that these down sides strongly depend on the duration of follow-up.

In response to the outcomes of the ERSPC, several points of discussion have been brought up by various authors concerning the usefulness of screening considering benefits, harms and costs, the methodology of the ERSPC and the interpretation of its outcomes. Important issues to address regarding PCa screening are addressed.

Conclusions

This paper sheds a light on the controversial points of the ERSPC as well as on the priority issues of PCa screening. On 2 July 2010 the Swedish section of ERSPC (Göteborg screening trial) published their results with a median follow-up of 14 years. With longer follow-up the data confirm the trend seen in improvement of PCa mortality and suggest much more favorable future outcomes also with respect to the NNT to prevent one PCa death.

INTRODUCTION

In 2009, two large, randomized, controlled trials [1, 2] reported their interim data on prostate cancer (PCa) specific mortality, addressing the matter of screening for prostate cancer. The two studies have apparently contradictory results, which created considerable discussion and misunderstanding in secondary literature. Recent literature profoundly outlined the differences between the two trials and the underlying causes explaining the contradictory outcomes [4]. However, as one editorial stated [5], the main point regarding present prostate cancer screening studies, is to avoid meaningless controversy over which study is right or wrong, thus hiding the real issues behind a smoke screen.

In this paper we would like to define the results of the ERSPC as well as its supposed controversial points as they were mentioned in various communications, in order to throw light on different sides of the study and to report the priority issues and the way they should be taken on. In addition, the recently published results of the Göteborg screening trial [3], which is part of the ERSPC, will be considered in the context of the ERSPC trial as a whole.

EVIDENCE FROM THE EUROPEAN RANDOMIZED STUDY OF SCREENING FOR PROSTATE CANCER

The European Randomized Study of Screening for Prostate Cancer (ERSPC) [1] was initiated in 1991 as a randomized, multicenter trial of screening for PCa, with PCa mortality being the main endpoint. In 8 different countries men, aged 50-74 years, were randomized between either a screening group or control group. The core age group consisted of men aged 55-69 years (N=162.387), who were screened with a 4-year (87%) or 2-year (13%) interval. Screening was performed by means of a prostate-specific antigen (PSA) test, with a cut-off value of 3.0 ng/ml as an indication for lateralized sextant biopsy. Nevertheless, slightly differing PSA cut-offs of 2.5-4.0 ng/ml with ancillary tests as digital rectal examination, free to total PSA ratio and transrectal ultrasound have been used by different centres during the study period as was all clearly reported earlier in the original paper (table 1).

After randomization, a total of 72.890 men were assigned to the screening group and 89.353 to the control group, with a mean age of 60.8 years. Of all PSA-tests performed, 20.437 (16.2%) were positive and led to biopsy recommendation, which 17.543 (85.5%) of men complied with. In 24.1% of men biopsied, results turned out positive (positive predictive value or PPV), amounting to 75.9% of false positive results. PCa was detected in 5990 (8.2%) men in the screening group and in 4307 (4.8%) men in the control group.

Table 1 | Methods used for the ERSPC

Recruitment	**Men identified from population registries**
Randomization	
- Before consent	Finland, Sweden, Italy
- After consent	Netherlands, Belgium, Switzerland, Spain
Core age group	55-69 years (range 50-74 years)
Biopsy indication	
- Netherlands	PSA ≥4 or positive DRE or TRUS at PSA ≥3; since 1997 PSA ≥3
- Finland	PSA ≥4 or positive DRE or TRUS at PSA ≥3
- Sweden	PSA ≥3
- Italy	PSA ≥4 or positive DRE or TRUS at PSA ≥2.5
- Spain	PSA ≥4
- Belgium	PSA ≥4 or positive DRE or TRUS
- Switzerland	PSA ≥3
Biopsy procedure	(lateralized) sextant biopsies
Screening interval	4-years (87%)
	2-years (13%)

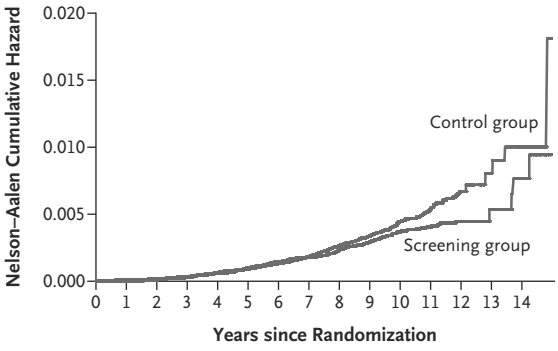
PSA, prostate specific antigen (ng/ml); DRE, digital rectal examination; TRUS, transrectal ultrasound

After a mean and median follow-up of 8.8 and 9.0 years respectively, 214 PCa deaths occurred in the screening group and 326 PCa deaths in the control group (table 2). This corresponded to a significant reduction of 20% fewer men dying of PCa in the screening group (p=0.04). The cumulative risk of death from PCa over time for both groups is shown in figure 1, with diverging rates of death from 7 to 8 years on and a trend suggesting larger effects with longer follow-up.

Table 2 | Results of the ERSPC

	Screening group	**Control group**
Number of participants	72.952	89.435
Mean age, years	60.9	60.7
Mean follow-up, years	8.8	9.0
PCa detected (%)	5990 (8.2)	4307 (4.8)
PCa deaths	214	326
	ITS analysis	**Secondary analysis**
Mortality reduction	20%	30%
Metastatic disease reduction	25%	32%

PSA, prostate specific antigen; PPV, positive predictive value; PCa, prostate cancer; ITS, intention to screen



No. at Risk			
Screening group	65,078	58,902	20,288
Control group	80,101	73,534	23,758

Figure 1 | Cumulative risk of death from prostate cancer.

The intention-to-screen (ITS) analysis showed an absolute risk reduction of 7 per 10.000 screened men, with a number of 1410 men who need to be screened (NNS) and another 48 men who need to be treated (NNT) in order to prevent one PCa death. When adjusted for noncompliance, a 27% reduction in PCa mortality was seen in men who were actually screened. After adjustment for the differences in stage distribution between the two arms, no difference was seen in treatment, which makes a mortality reduction solely caused by a treatment effect very improbable [6].

One of the major drawbacks of PCa screening in general is detecting PCa in men who would not have clinical symptoms during their lifetime if it was not for screening, with an over detection rate in the ERSPC screening group that has been estimated to be as high as 50% [7].

A secondary analysis [8] was carried out according to the method described by Cuzick et al. [9] to assess the impact of adjustment for men assigned to the screening arm, who did no undergo screening (*noncompliance*) and for men assigned to the control arm, who sought opportunistic PSA-based screening (*contamination*). This analysis showed a further enhancement of the PCa-specific mortality reduction after adjustment for both noncompliance and contamination by up to 31%.

The effect of this secondary analysis on the rate of metastatic PCa was analyzed by Kerkhof et al. [10]. The ITS analysis resulted in a significant reduction of 25% (RR 0.75, 95%CI 0.59-0.95, p=0.02) for developing metastatic PCa in the screening arm, with an even more distinct reduction of 32% (RR 0.68, 95%CI 0.49-0.94, p=0.02) in the adjusted analysis reckoning noncompliance and contamination. This hence leads to an improvement in the relative risk of 7% in the secondary analysis. While the ITS analysis is diluted by noncompliance and contamination it shows the effect on the study population as a

whole, where the secondary analysis has the ability to give a better adjusted estimate of the effect of screening at the individual level for those men who are actually screened.

In the meantime the results of the Göteborg screening trial have been published [3]. This trial was initiated as an independent study in 1994 but joined the ERSPC trial shortly thereafter by signing the 'agreement of participation', a research contract. The adjusted power calculation is based on the randomization of 20.000 men, aged 50-64 years, identified in the population registry in 1994. A power of 80% was predicted with a follow-up of 14 years and a participation rate of 76% to show a difference of 40% in prostate cancer mortality by screening. These conditions were met when the follow-up was complete up to the end of 2008. The results show a rate ratio for PCa death of 0.56 (95%CI 0.39-0.82, p=0.002) in the ITS analysis and of 0.44 (95%CI 0.28-0.68, p=0.0002) after adjustment for non-compliance. This resulted in a NNS of 293 and a NNT of 12, and for attendees after adjustment for non-compliance a NNS of 234 and NNT of 15. The main differences with the ERSPC as a whole are the type of randomization, younger age, a shorter screen interval, and, most importantly, a longer follow-up due to the simultaneous randomization of all participants in 1994.

WHAT IS TRUE AND WHAT IS NOT TRUE IN THE CONTROVERSY AROUND ERPSC?

So what are we to believe? This year, the 'inventor' of PSA, Richard Ablin, called PSA-based screening a "public health disaster" and pictured the idea of 1 man being saved by screening while 47 other men might experience loss of sexual function or urine leakage for no good reason [11]. The numbers in this example clearly relate back to the NNT outcome of the ERSPC. Are the future prospects really that bad and, if so, why should we try to decrease PCa mortality at all?

PCa is a major public health problem being the most numerous cancer among men and the second most important cause of cancer related deaths with 192.280 and 27.360 incident cases respectively in the US in 2009 [12]. Worldwide numbers of PCa, show an incidence of 679.023 and a mortality of 221.002 in 2002 [13]. With a seemingly achievable 35% mortality reduction, this could lead to the prevention of 77.350 men dying from PCa, provided that the price we have to pay to do this is acceptable. In the US, a mortality reduction of 35%, would lead to PCa going from a second to a fifth place in leading cancer related deaths [12].

Despite these large incidence numbers and a substantial disease-specific mortality reduction in the ERSPC, the effect on overall mortality will be minimal even if the

PCa mortality reduction would double, as seen in the Göteborg trial. Some critics [14] promote the view that overall mortality would be the appropriate end point. A trial addressing overall mortality as an end point would need several million participants to create enough statistical power to show an overall mortality reduction and this would thus be very unlikely to ever be accomplished. At present, the aim of health care systems worldwide is to gain improvements in mortality of different types of cancer that will in the end hopefully decrease the total burden of cancer mortality. The ERPSC study contributes to this process.

Some authors have suggested that ERSPC is not a coherent study and that pooled analysis is not justified, but should be replaced by a meta-analysis. These authors suggest that the ERSPC actually is a collection of 7 studies with differing screening protocols and consider this to be a weakness [15, 16]. Truth is, that agreement on a common data set with central data collection and agreements on mutually accepted small differences per country including the core age group (55-69 years), were already agreed upon in 1994 and 1995, at the time European cooperation was initiated. National regulations caused randomization protocols to differ among countries, which led to a population-based effectiveness trial in Finland, Sweden and Italy, where randomization took place before informed consent. In the Netherlands, Belgium, Switzerland, Spain and the 2005 late comer France, men were randomized after providing informed consent, also known as an efficacy trial. Irrespective of the way of randomization, population registries were used to identify trial subjects [1]. Validation of randomization to test for heterogeneity of outcomes between (groups of) centres was pre-planned as was defined in the published ERSPC monitoring plan [17] and was carried out with successful results [1]. Since in all centres a trend toward mortality reduction by screening can be observed, the agreed differences in national protocols apparently do not exert major effects on the outcome. The described heterogeneity must be considered as a strength rather than a weakness of ERPSC.

Critical remarks have been made in various communications [15, 18] about the effect on PCa mortality being due to treatment instead of being due to screening. In a screening study cases in both arms should be treated similarly to rule out treatment as a confounder in mortality reduction. If treatment is reported to be more aggressive in the screening arm then inequalities in treatment choices between the two groups could be causing the mortality reduction instead of screening. Within ERSPC however, after correcting for stage and grade, no difference favoring more aggressive treatment in the screening arm could be found. The observed mortality reduction is therefore very unlikely to be solely caused by treatment effect [6]. This study also shows that the only difference in treatment that was found, was the combination of radiotherapy and endocrine treatment which is superior in high-risk patients and was applied more often in the control

arm, so if any effect was expected it might be in favor of the control arm. Noteworthy is, that treatment decisions in PCa cases in both arms were left to regional care providers, as was recorded in the study protocol (www.erspc.org; publications). In practice, general practitioners were encouraged to refer patients to regional urologists and both were contacted in this respect beforehand. Also the Göteborg trial did not report treatment difference which could impact on screening as the determinant of outcomes.

Then, there is the issue of α-spending that could cause future analyses to lack power and become statistically invalid, because of the interim analyses that were performed previously. When sequential testing is performed in interim monitoring of clinical trials, the α-value should be adjusted accordingly at each look to preserve the overall type-I error (i.e. stating an event is significant when it is not). This was already anticipated in the monitoring plan [17] and described in the 2009 publication [1]; an α-spending curve (O'Brian-Fleming rule) of ≈ 1% each time was used, with a division of uneven weights and higher weight at the end. All 3 interim analyses of the ERSPC had their power adjusted for α-spending.

Others stated that the re-assurance of men with negative test results is not appropriate [16, 19]. This is indeed a statement that embodies a continuous worry. Studies show that there is no PSA cut-off below which a man can be reassured that he has no PCa. As was shown in the only empirical analysis of the performance characteristics of PSA, a cut-off value of 3.0 ng/ml misses 67.8% of biopsy detectable PCa and 42.4% of potentially aggressive ones [20]. Low PSA levels can therefore not even rule out the presence of high-grade PCa, although both risks of finding a PCa on biopsy are directly related to PSA levels, also in the lower range.

For the ERSPC it was calculated that, of 48.867 men in 6 of the participating countries with an initial PSA <3.0 ng/ml, 5% was diagnosed with PCa after a mean follow-up of 9 years, of which 4.6% was confirmed to be high-grade [21]. Substantial numbers of cancers must be therefore assumed to be missed. Only long term follow-up, as it is planned within the ERSPC, can shed light on their natural history and on the rate of their detection at subsequent screens. In addition to this, results of ERSPC Rotterdam [22] showed 9.4% of men who had initial negative biopsies to develop PCa over an 11-year follow-up period, with the number of potentially missed cancers with a poor outcome in terms of progression-free survival (9%) and deaths from PCa (2.4%) being very low. More aggressive screening may result in the detection of additional aggressive PCa, but this would be at the cost of detecting a lot of potentially indolent PCa, which will increase overdiagnosis, overtreatment and the NNT.

Does the benefit shown in the ERSPC match the damage? We expressed this as an important down side in our 2009 paper [1], when we addressed overdiagnosis and overtreatment as the most important adverse effects induced by screening. Overdiagnosis in the ERSPC was estimated to be no less than 50% in the screening group [7] and although this is a major concern, it is also one of the main achievements of the ERSPC to quantify and report on these events. Furthermore, the NNS and the NNT are time dependent and can be expected to become more favorable with longer follow-up, as the mortality reduction increases.

Unfortunately, PSA lacks the specificity to be a solid tool in determining a biopsy indication, resulting in large numbers of unnecessary biopsies and, at the same time, missing PCa diagnoses in men with PSA values <3.0 ng/ml. The ideal screening tool for PCa, which could identify potentially aggressive cancers in an early, curative stage, but could also avoid detection of cancers that would never cause any symptoms, let alone deaths, unfortunately does not yet exist. However, the unnecessary treatments can with some as yet unidentified risk for the patient, be delayed by offering "active surveillance". About 25% of men in ERSPC have made this choice.

Since PSA testing can not distinguish lethal PCa from indolent disease and a lowering of the PSA threshold to proceed to prostate biopsy would imply detecting more and more PCa that would be overdiagnosed and potentially overtreated. Addressing this issue, Roobol et al. [23] have applied the PCa Riskcalculator (www.prostatecancer-riskcalculator.com) to reduce the number of unnecessary biopsies, while still detecting most clinically important PCa cases. Including ultrasound volume, digital rectal exam and transrectal ultrasound together with the PSA value in a model, while applying an additional probability cut-off value of, for example, 12.5% to trigger a biopsy, resulted in a substantial increase of PPV in initial (from 29 to 38%), as well as repeat screening (from 19 to 25%). The predictive value for PSA alone showed an AUC of 0.64, which increased to 0.77 when the Riskcalculator was used. With this method, cancer diagnoses would be missed, but this would predominantly concern indolent PCa (70-81%) and only a very small proportion of potentially important PCa. Just increasing the PSA cut-off to $\geq$4.0 ng/ml for example, would also result in a considerable decrease in biopsies, but considerably higher numbers of missed PCa diagnoses (1.8-2.6 times higher). This individualized screening algorithm might contribute to counteract two of the most negative side-effects of screening, namely unnecessary invasive testing and overdiagnosis with the related overtreatment. The fact that some cancers will always be missed by increasing test specificity must however be considered. It is unknown at present what proportion of cancers will escape all efforts and which cancers can be safely detected during a subsequent round of screening. Besides this, hopefully in the future, new markers and improved nomograms will become available to lead to a more selective detection of aggressive PCa.

WHAT ARE THE "REAL ISSUES" AND HOW CAN THEY BE DEALT WITH?

As incidence rates are high and PCa is one of the most frequent causes of cancer related deaths, it is a relevant public health problem to decrease the PCa mortality provided that this can be done at an acceptable price. This 'price' should comprise of a number of considerations.

First, the quality-adjusted life years (QALY's) and other costs and benefits of screening should be matched against the achievable decrease of PCa mortality. A paper on this subject addressing the cost effectiveness and quality of life in the ERSPC is in preparation and will be updated with increasing follow-up.

Then, testing for PCa should become more selective, resulting in detecting less non-aggressive cancers and decreasing the amount of overdiagnosis and resulting over-treatment. As discussed earlier, PSA alone is not an optimal marker for PCa screening, but individualized screening by means of the ERSPC based Riskcalculator is a step in the right direction. These decision tools use risk modifying techniques to identify the cancers that will most likely be indolent and can be managed with active surveillance. An example of the application of the Riskcalculator (step 3) to three different men all presenting with a PSA value of 4.0 ng/ml is presented in figures 2-4. The ERSPC based Riskcalculator, among others, calculates the probability of having a positive biopsy (step 3) and of indolent cancer (step 6). The calculator was updated and validated [24] and used for the study by Roobol et al. [23] mentioned above. Nevertheless, better markers and more accurate, advanced nomograms should be developed in order to decrease overdiagnosis even more.

Next, continued follow-up of the ERSPC is needed, since until now about 22% of participants died, there are still many more events to be expected. In the Scandinavian SPCG-4 study of clinically diagnosed locally confined PCa [25], the difference in cumulative incidence of death due to PCa between groups assigned to radical prostatectomy or watchful waiting, remained stable only after about 10 years. In the Göteborg trial, even after 14 years of follow-up, the mortality curves still continue to diverge. This illustrates that the follow-up in the ERSPC study is still too short to draw definite conclusions and further follow-up has to be awaited. If longer follow-up shows a larger difference in PCa mortality -which can be expected from the 2009 mortality curves- , the NNS and NNT will decrease. With an assumed 35% relative risk reduction in the intention to screen analysis, the NNS would decrease to 806 and the NNT to 27. If a 40% reduction would be accomplished, this would lead to a NNS of 256 and NNT of 14. For those men with PSA values <3.0 ng/ml, longer follow-up will help quantify the predictive value of a negative result and to better be able to reassure men with certain characteristics.

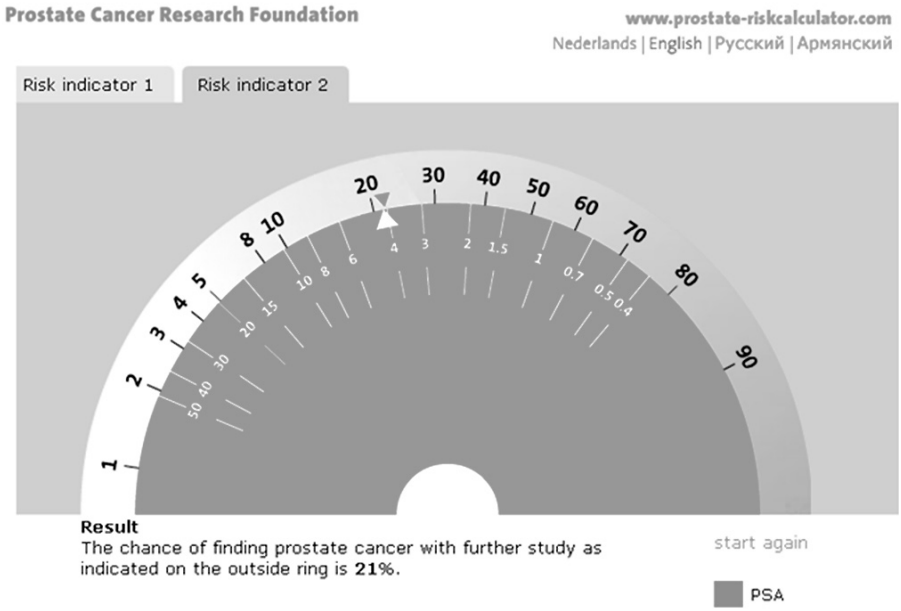


Figure 2 | Riskcalculator predicting the risk of positive biopsy based on solely PSA. This figure shows the predicted risk of having a positive biopsy, solely based on the PSA-value, irrespective of any other values of ancillary tests. In this example a man with a PSA-value of 4.0 ng/ml has a predicted risk of 21%. The estimation is based on data from the first 6288 participants in the Rotterdam arm of the ERSPC.

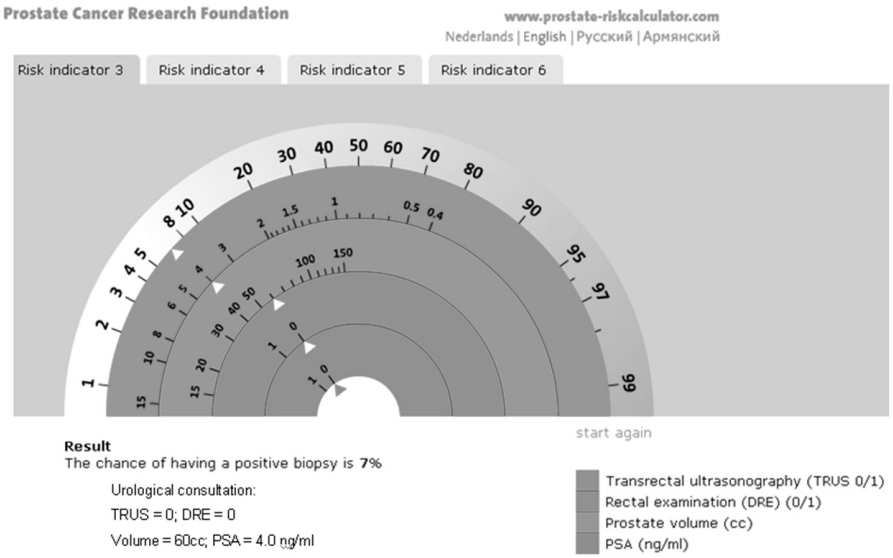


Figure 3 | Riskcalculator step 3. Prediction of the chance of a positive sextant biopsy in a man who was never screened before; PSA = 4.0 ng/ml, low risk. This figure shows the prediction of a positive biopsy, making use of the results of transrectal ultrasound (TRUS), digital rectal examination (DRE), prostate volume at ultrasonography and PSA-value. In this example a man with a PSA-value of 4.0 ng/ml, normal TRUS and DRE and prostate volume of 60cc were used, which results in a 7% chance.

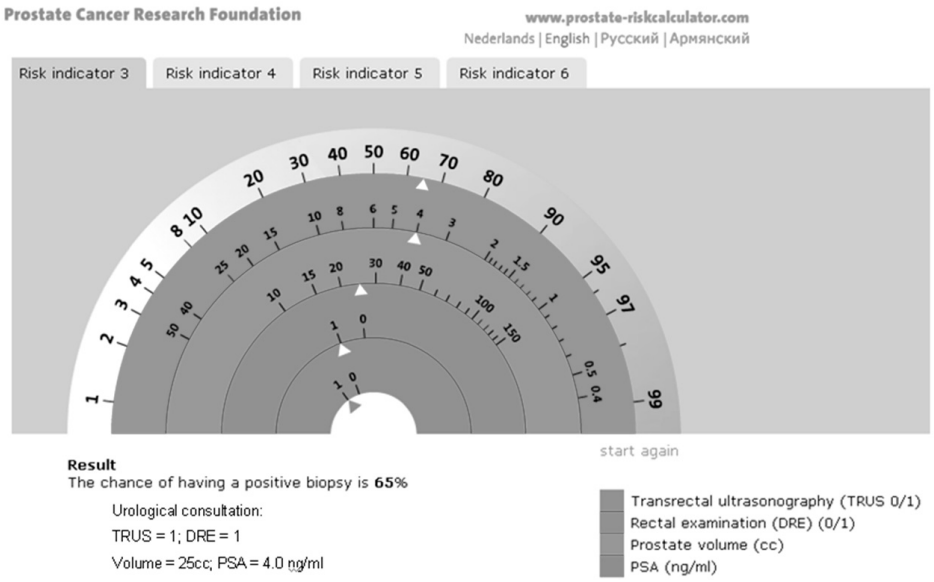


Figure 4 | Riskcalculator step 3. Prediction of the chance of a positive sextant biopsy in a man who was never screened before; PSA = 4.0 ng/ml, high risk. This figure shows the prediction of a positive biopsy, making use of the results of transrectal ultrasound (TRUS), digital rectal examination (DRE), prostate volume at ultrasonography and PSA-value. In this example a man with a PSA-value of 4.0 ng/ml, abnormal TRUS and DRE and prostate volume of 25cc were used, which results in a 65% chance.

These estimates are similar to the results of the Göteborg screening trial. If effects of similar size were shown in ERSPC as a whole, these findings are likely to be more relevant because of the size of the trial, the European multiple country setting, the fact that small protocol differences still produce identical trends, the possibility to study multiple aspect on how to screen best for PCa and the ongoing analysis of QALY's based on ERSPC findings.

Another important issue to study in this context, will be the screen-detected PCa that escape all efforts in spite of early detection and treatment. We are co-operating internationally to indentify the characteristics of such patients and the mechanism that causes these "escapes". Again, the resulting knowledge can be used to improve testing and screening. There will always be a group of unavoidable "escapes" which, when defined and quantified, will contribute to resolving many controversies.

Finally, validated mechanisms for shared decision taking should be established. Results of the ERSPC have been adopted in several guidelines, including those of the European Association of Urologists [26], but so far no commonly accepted information material exists about the proper interpretation of the trial results and for men who wish to be

informed about the possible risks and uncertainties. Effort should be taken at an international level to create validated decision aids.

So, what should we tell patients who wish to be screened, taking the contemporary evidence into account? This message has changed dramatically by the results of recent studies and should include the following statements. In the case of PCa detected with screening, the chances of dying of the disease are decreased by at least 31%. The downside remains though, as long as we have to deal with a high chance of being diagnosed and treated for disease which otherwise may not harm you within a period of nine years or longer. However, when non aggressive disease is suspected, treatment can be avoided at least for some time.

CONCLUSION

In conclusion, we can say that the ERSPC shows a reduction of PCa mortality for screened men of 20-31% at 9 years of follow-up. In the Göteborg screening trial these figures amount to 44-56% at 14 years. The resulting overdiagnosis and overtreatment are major worries, but can be decreased by screening less aggressively and more selectively using available risk modifying calculators. Establishing population based screening for PCa as a health policy, will depend on lowering the NNT, while focussing on methods for more selective screening and achieving an acceptable risk-benefit ratio.

We think screening will become an accepted health policy, but it will take time and work to be done. Key developments in the field of screening show, that PSA should be used as a marker within an algorithm instead of a single biopsy indicator, to achieve better predictions of positive biopsies. Nevertheless, we have to work hard to find new, better and more selective markers for screening purposes. It is important however to be aware of the fact that we will always miss cancers with screening and we have to learn to selectively miss the ones that would otherwise stay indolent and those that will always escape all efforts in spite of screening.

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5 Prostate cancer incidence and disease-specific survival of men with initial prostate-specific antigen less than 3.0ng/ml who are participating in ERSPC Rotterdam

Eur Urol. 2011;59:498-505.

Meelan Bul, Pim J. van Leeuwen, Xiaoye Zhu, Fritz H. Schröder, Monique J. Roobol

ABSTRACT

Background

The European Randomized Study of Screening for Prostate Cancer (ERSPC) applies a prostate-specific antigen (PSA) cut-off value of ≥3.0 ng/ml as an indication for lateralized sextant biopsy.

Objective

To analyze the incidence and disease-specific mortality for prostate cancer (PCa) in men with an initial PSA <3.0 ng/ml.

Design, setting and participants

From November 1993 to December 1999, a total of 42.376 men identified from population registries in the Rotterdam region (age 55-74 years) were randomized to an intervention or control arm. A total of 19.950 men were screened during the first screening round.

Interventions

A PSA <3.0 ng/ml was below the biopsy threshold. PCa cases were indentified at 4-yearly re-screens or as interval cancers.

Measurements

Distribution of incidence, aggressiveness and disease-specific mortality of PCa per PSA range was measured. Causes of death were evaluated by an independent committee and follow-up was complete until December 31, 2008.

Results and limitations

From 1993 – 2008, 915 PCa cases were diagnosed in 15.758 men (5.8%) with an initial PSA <3.0 ng/ml and a median age of 62.3 years. Median overall follow-up was 11 years. PCa incidence increased significantly with higher initial PSA levels. Aggressive PCa (clinical stage ≥T2c, Gleason score ≥8, PSA >20 ng/ml, positive lymph nodes or metastases at diagnosis) was detected in 66 out of 733 screen-detected PCa (9.0%) and 72 out of 182 interval-detected PCa (39.6%). There were 23 PCa deaths in the total population (0.15%), with an increasing risk of PCa mortality in men with higher initial PSA values.

Conclusions

The risk PCa, aggressive PCa and PCa mortality in a screening population with initial PSA <3.0 ng/ml increases significantly with higher initial PSA levels. These results contribute to the risk stratification and individual management of men in PSA-based screening programs.

INTRODUCTION

After first being described in 1979 [1], prostate-specific antigen (PSA) became available as a biomarker [2] and potential screening tool for the early detection of prostate cancer (PCa) [3].

With PCa being the most frequent cancer diagnosed in men and playing an important role in cancer related deaths worldwide [4, 5], randomized studies set up to determine whether PSA-based screening can reduce the PCa specific mortality [6, 7], address an important health issue. Results of the European Randomized Study of Screening for Prostate Cancer (ERSPC) have shown that PSA-based screening can decrease PCa mortality by up to 30% [6, 8].

However, despite the value of PSA in terms of lowering PCa mortality, its use for screening is limited as a result of its lack of specificity in lower PSA ranges [9]. Since 1997, the ERSPC used a PSA value ≥3.0 ng/ml as an indication for biopsy. To assess the risk of applying this cut-off value, we analyzed data of men with initial PSA <3.0 ng/ml in the Rotterdam section of the ERSPC and evaluated PCa incidence and disease-specific mortality stratified by PSA group.

METHODS

From November 1993 to December 1999, a total of 42.376 men aged 55-74 years, identified in the Rotterdam population registry, were randomized to an intervention or a control arm. During the first screening round, 19.950 men were screened (excluding men previously diagnosed with PCa), with lateralized sextant biopsies being initially recommended for an abnormal digital rectal examination (DRE) or PSA level ≥4.0 ng/ml. From May 1997 on, DRE was abandoned as a screening test and a PSA level ≥3.0 ng/ml was applied to recommend biopsies. Men diagnosed during the first screening round were excluded from this study to focus on the risk of being diagnosed with PCa during follow-up. During the second screening round (November 1997 - December 2003), two side studies were carried out. The first side study (November 1997 - April 2001) provided a biopsy indication for men who doubled their PSA at the second screen in the PSA range 1-3 ng/ml. The second side study (April 2001 - August 2002), investigated the positive predictive value (PPV) and detection rate in men with PSA values 2.0-3.9 ng/ml. The third round started in November 2001 and concluded in December 2007 and the fourth round started in November 2005 and is still ongoing. Another side study was carried out (September 2007 - February 2009), providing a biopsy indication for men with a PCa antigen 3 score ≥10. The cancers found in the side studies are considered as screen-detected in the context of this report. Total PSA was measured with the use of

Hybritech assay systems (Beckman Coulter, Fullerton, CA, USA) and a 4-year screening interval was used. Follow-up of PCa cases and causes of death was carried out as previously described [10, 11]. Data were complete for a total period of 15 years (December 1993 – December 2008).

Aggressive cancer was defined as clinical stage ≥T2c, PSA at diagnosis >20 ng/ml or Gleason score ≥8, according to the D'Amico criteria [12], next to positive lymph nodes or distant metastases at diagnosis. Co-morbidity at study entry was evaluated by assigning a Charlson score to each subject, based on an independently completed questionnaire on medical history. For the purpose of this study, cases were scored as no (Charlson score = 0), mild (Charlson score = 1) or severe (Charlson score ≥ 2) co-morbidity. Interval cancers were defined as all cancers detected clinically (either triggered by lower urinary tract symptoms, symptomatic disease or opportunistic screening) during a screening interval or after reaching the 75-year age limit.

The number of PCa cases, overall deaths and disease-specific deaths classified by PSA group (<1.0 ng/ml, 1.0-1.9 ng/ml or 2.0-2.9 ng/ml) and number per 1000 life years (LY) were recorded, as well as the tumor characteristics (Gleason score and TNM classification) at diagnosis.

Cox regression analysis was used to determine PCa incidence and overall survival (OS) and disease-specific survival (DSS) adjusted for age and co-morbidity and classified by PSA group. For incidence, the duration of follow-up from first screen to whatever came first of either diagnosis, death or censor date was calculated. For survival, time from first screen to either death or censor date was used. The proportional hazard assumption was tested and found to be applicable, using log-log survival curves. OS and DSS were assessed using the Kaplan-Meier method. Statistical analyses were performed using SPSS v.17.0 (SPSS, Chicago, IL, USA). All statistical tests were 2-sided, and a p value <0.05 was considered statistically significant.

RESULTS

A total of 21.210 men were randomized to the screening group of which 19.950 men were actually screened. An initial PSA value <3.0 ng/ml was measured in 15.837 men. The population used for this analysis consisted of 15.758 men (15.837 – 79 first round PCa). The number of detected cancers per screening round and interval is indicated in figure 1. From 1993 to 2008 a total of 915 PCa cases have been diagnosed in 15.758 men. Of these, 733 were screen-detected and 182 were interval-detected cases of which 63 men (34.6%) were diagnosed when they were 75 years of age or older. Median follow-up amounted to 11.1 and 11.5 years overall and for PCa cases, respectively. Median age of

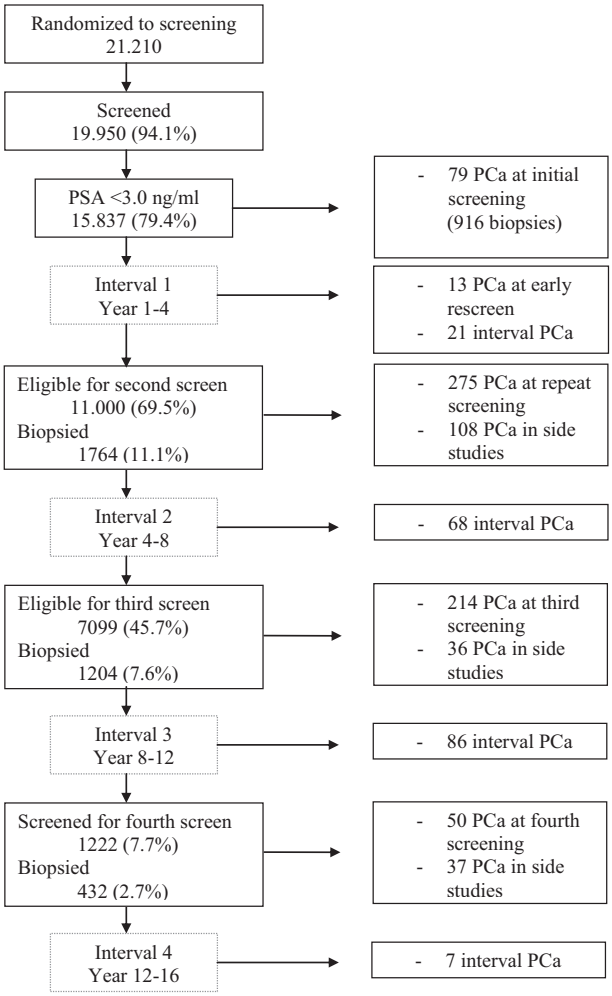

Figure 1 | Consort diagram showing prostate cancer detection during screening rounds and intervals of men initially presenting with PSA <3.0 ng/ml in the Rotterdam section of the ERSPC.

the study population at baseline PSA measurement was 62.3 years of age. Study population characteristics are provided in table 1.

Median baseline PSA level was 1.8 (25-75p: 1.2-2.4) for men who developed PCa and 1.0 (25-75p: 0.6-1.6) for men who did not (p <0.001). At diagnosis, the median PSA level for screen-detected cases (3.5, 25-75p: 2.9-4.6) and interval-detected cases (8.1, 25-75p: 4.7-18.0) differed significantly (p <0.001).

In this study population 5.8% (915 of 15.758) of all men were diagnosed with PCa at a median of 7.1 years after initial PSA screening. The risk of PCa diagnosis increased

Table 1 | Characteristics of study population classified by PSA-group

Characteristic	PSA (ng/ml)			Total study population
	<1.0	1.0-1.9	2.0-2.9	
Subjects, N	7126	6156	2476	15758
(%)	(45.2)	(39.1)	(15.7)	(100)
Med age at initial PSA test, years	61.2	62.8	64.3	62.3
Charlson score, N (%)				
0	5189 (72.8)	4579 (74.4)	1820 (73.5)	11.588 (73.5)
1	1638 (23.0)	1319 (21.4)	545 (22.0)	3502 (22.2)
2	266 (3.7)	208 (3.4)	93 (3.8)	567 (3.6)
Unknown	33 (0.5%)	50 (0.8)	18 (0.7)	101 (0.6)
PCa, N	129	415	371	915
(/ 1.000 LY)	(1.7)	(6.4)	(14.5)	(5.5)
Aggressive PCa*, N	27	61	50	138
(/ 1.000 LY)	(0.36)	(0.94)	(1.95)	(0.83)
Med age at diagnosis, years	69.5	68.9	68.2	68.8
Med time to diagnosis, years	8.3	8.1	4.2	7.1
Overall deaths, N	1560	1365	610	3535
(/ 1.000 LY)	(20.8)	(21.1)	(23.8)	(21.4)
PCa deaths, N	3	11	9	23
(/ 1.000 LY)	(0.04)	(0.17)	(0.35)	(0.14)

PSA, prostate-specific antigen; PCa, prostate cancer; LY, life years
**defined as: clinical stage ≥T2c, Gleason-score ≥8, PSA >20 ng/ml, positive lymph nodes or distant metastasis at diagnosis*

from 1.7 per 1000 LY in men with PSA levels <1.0 ng/ml to 14.5 per 1.000 LY in men with PSA levels 2.0-2.9 ng/ml. The cumulative hazard of being diagnosed with PCa showed a 4.0- and 10.3-fold increased risk for PSA groups 1.0-1.9 and 2.0-2.9 ng/ml, respectively, compared to PSA group <1.0 ng/ml (p <0.001) (figure 2). Aggressive cancer was present in 138 cases at diagnosis. Clinical stage and Gleason score were unknown in 5 and 41 cases, respectively. Tumor characteristics classified by PSA group are listed in table 2. The cumulative hazard of being diagnosed with aggressive PCa was found to be statistically different (p <0.001), showing 2.7- and 6.2- increased risk for PSA groups 1.0-1.9 and 2.0-2.9 ng/ml, respectively, compared to PSA group <1.0 ng/ml (figure 3). To evaluate the influence of biopsied men per category, we corrected for the percentage of men per PSA group that were actually biopsied. This resulted in hazard ratios (HRs) of 2.1 and 3.3 for PCa incidence and 2.0 and 3.3 for aggressive PCa in the 1.0-1.9 and 2.0-2.9 ng/ml PSA groups, respectively, preserving their highly significant outcome.

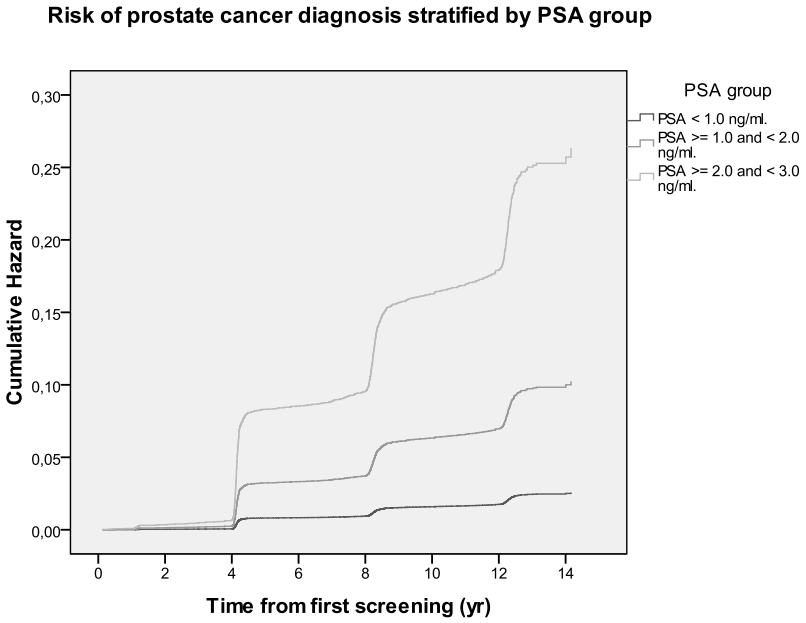

Figure 2 | Risk of prostate cancer diagnosis, corrected for age and stratified by PSA group.

Table 2 | Tumour characteristics classified by PSA group

PSA (ng/ml)	**Men** N (%)	**PCa** N (% of PSA group)	**≤T1C** N (% of PCa)	**≥ T2** N (% of PCa)	**GS ≤ 6** N (% of PCa)	**GS ≥ 7** N (% of PCa)	**Aggressive PCa***, N (% of PCa)
< 1.0	7126 (45.2)	129 (1.8)	83 (64.3)	42 (32.6)	76 (58.9)	47 (36.4)	27 (20.9)
1.0 – 1.9	6156 (39.1)	415 (6.7)	276 (66.5)	132 (31.8)	310 (74.7)	89 (21.4)	61 (14.7)
2.0 – 2.9	2476 (15.7)	371 (15.0)	243 (65.5)	122 (32.9)	279 (75.2)	73 (19.7)	50 (13.5)
Total	15758 (100)	915 (5.8)	602 (65.8)	296 (32.3)	665 (72.7)	209 (22.8)	138 (15.1)

PSA, prostate-specific antigen; PCa, prostate cancer

**defined as: clinical stage ≥T2c, Gleason-score ≥8, PSA >20 ng/ml, positive lymph nodes or distant metastasis at diagnosis*

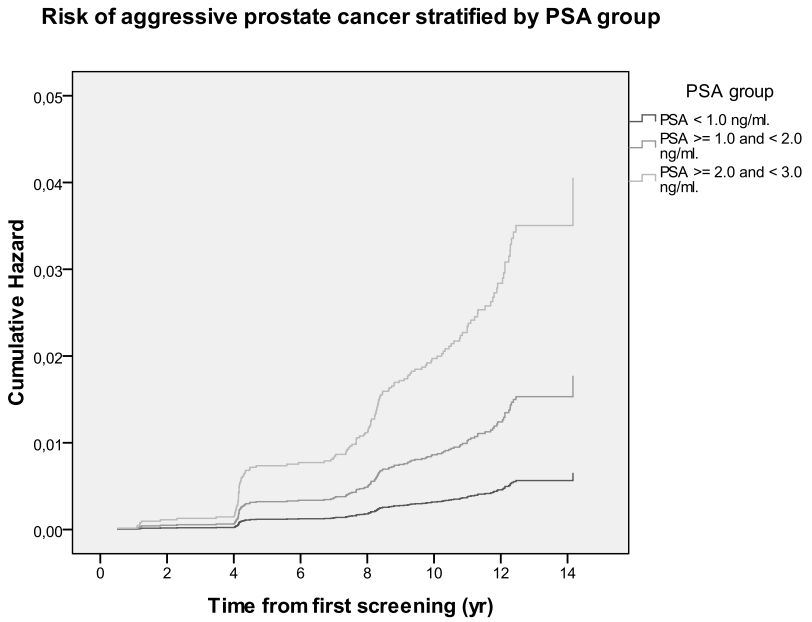

Figure 3 | Risk of aggressive prostate cancer, corrected for age and stratified by PSA group.

Table 3 | Hazard ratios for prostate cancer (PCa), aggressive PCa and disease-specific mortality, adjusted for age and co-morbidity score

PSA (ng/ml)	PCa (95% CI)	Aggressive PCa (95% CI)	Overall mortality (95% CI)	PCa mortality (95% CI)
< 1.0	*	*	*	*
1.0 – 1.9	4.0 (3.3 – 4.9) (*P* <0.001)	2.7 (1.7 – 4.3) (*P* <0.001)	0.9 (0.9 -1.0) (*P* =0.026)	4.0 (1.1 – 14.2) (*P* =0.035)
2.0 – 2.9	10.3 (8.4 – 12.5) (*P* <0.001)	6.2 (3.9- 10.0) (*P* <0.001)	0.9 (0.8 - 1.0) (*P* = 0.068)	7.6 (2.0 – 28.3) (*P* =0.003)

PSA, prostate-specific antigen; PCa, prostate cancer; CI, confidence interval
** reference group*

Interval-detected PCa cases were aggressive more often (72 of 182; 39.6%), compared to screen-detected cases (66 of 733; 9.0%) (p <0.001) (table 4). Of the interval-detected cases, 39 (21.4%) subjects were 75 years of age or older.

The number of overall deaths and disease-specific deaths classified by PSA group is outlined in table 1. After a 15-year period, an overall mortality of 21.4 men per 1000 LY was observed (3.535 of 15.758; 22.4%), while PCa specific mortality reached 0.14 per 1.000 LY (23 of 15.758; 0.15%). The risk of PCa specific mortality increased with higher initial

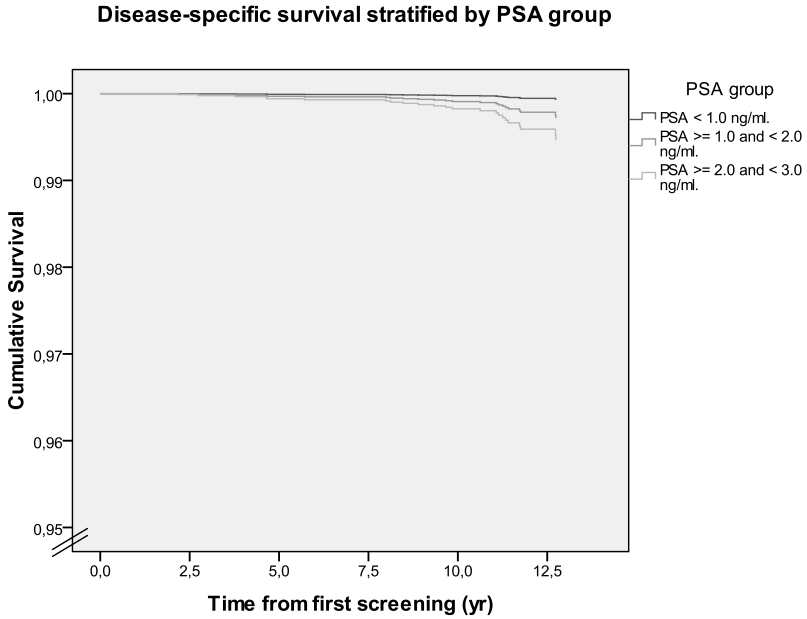

Figure 4 | Cumulative disease-specific survival, corrected for age and co-morbidity and stratified by PSA group.

Table 4 | Number of prostate cancer (PCa), aggressive PCa and disease-specific deaths in screen-detected and interval detected cases classified by PSA group

PSA (ng/ml)	**Men** N (%)	**PCa** N (% of PSA group)		**Aggressive PCa*** N (% of screen or interval detected PCa)		**PC deaths** N (% of screen or interval detected PCa)	
		Screen	**Interval**	**Screen**	**Interval**	**Screen**	**Interval**
< 1.0	7126 (45.2)	92 (1.3)	37 (0.5)	11 (12.0)	16 (43.2)	0 (0)	3 (8.1)
1.0 – 1.9	6156 (39.1)	345 (4.8)	53 (0.7)	29 (8.4)	32 (60.4)	4 (1.2)	7 (13.2)
2.0 – 2.9	2476 (15.7)	296 (4.2)	48 (0.7)	26 (8.8)	24 (50.0)	1 (0.3)	8 (16.7)
Total	15758 (100)	733 (4.7)	182 (2.6)	66 (9.0)	72 (39.6)	5 (0.7)	18 (9.9)

PSA, prostate-specific antigen; PCa, prostate cancer
**defined as: clinical stage ≥T2c, Gleason-score ≥8, PSA >20 ng/ml, positive lymph nodes or distant metastasis at diagnosis*

PSA levels, from 0.04 per 1.000 LY in the PSA range <1.0 ng/ml to an incidence of 0.35 per 1.000 LY in the range 2.0-2.9 ng/ml. PCa specific survival stratified by PSA group and corrected for age and co-morbidity is shown in figure 4. There was a significant increase in risk of PCa death which was 4.0 and 7.6 times higher for the PSA group 1.0-1.9 and 2.0-

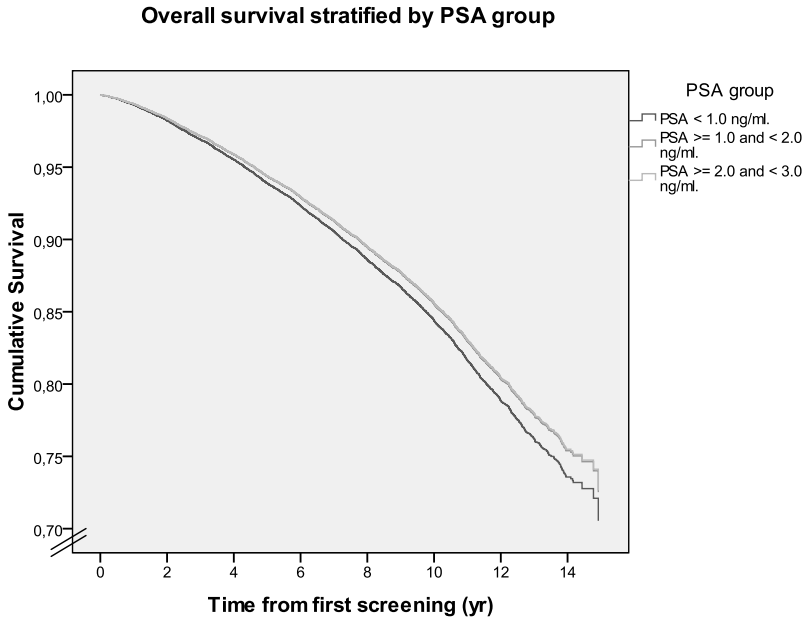

Figure 5 | Cumulative overall survival, corrected for age and co-morbidity and stratified by PSA group.

2.9 ng/ml, respectively, than for the group PSA <1.0 ng/ml. Disease-specific mortality occurred in 5 of 733 (0.7%) screen-detected cases and 18 of 182 (9.9%) interval-detected cases (p <0.001) (table 4). OS was higher in men with initial PSA levels 1.0-1.9 ng/ml (HR: 0.9; p = 0.026), compared to the lowest PSA range (figure 5). All HRs are provided in table 3. For our cohort, the 5-year, 10-year and 15-year OS rates were 92.7%, 82.2% and 67.9%, respectively; the PCa-specific survival rates were 100%, 99.9% and 99.7%, respectively.

DISCUSSION

Results of the ERSPC have shown that early detection by PSA-based screening can decrease PCa mortality up to 30% after a median follow-up of 9 years [6, 8]. The Göteborg screening study, which is part of ERSPC, recently showed even more favorable results after 14-year follow-up [13]. However, it is also known that PCa is prevalent in men with PSA levels below commonly used thresholds, with PSA lacking specificity, especially in these lower ranges [9]. This study was set up to quantify the predictive value of a negative result in PSA-based screening, to evaluate the risk of postponing PCa diagnosis in screening by applying a PSA cut-off $\geq$3.0 ng/ml and to contribute to the understanding of the natural history of PCa present in the low PSA ranges.

We identified a significant increase in PCa incidence in men with initial PSA 1.0-1.9 ng/ml and 2.0-2.9 ng/ml of 4.0- and 10.3-fold, respectively, compared to men with initial PSA <1.0 ng/ml. Similar results were observed for aggressive PCa, which showed a 2.7- and 6.2-fold increased risk in these groups, respectively. When we examined alternative definitions of aggressive PCa (i.e. Gleason score ≥8 or PSA at diagnosis >20 ng/ml), the overall patterns held with higher PSA levels being associated with higher risk. If we apply the PPV of 21.9%, as was reported from the control arm of the Prostate Cancer Prevention Trial [9] in 5587 biopsied men with initial PSA ≤3.0 ng/ml (aged ≥55 years), receiving biopsies upon indication (PSA >4.0 ng/ml or abnormal DRE) or at the end of a 7-year study, a total of 3468 PCa would be expected in 15.837 men. This conclusion indicates that 2474 PCa cases were not (yet) diagnosed in our cohort. The absence of PSA and clinical progression after 11 years of follow-up is re-assuring, but longer observation periods are needed to judge on the natural history of these biopsy detectable cancers. Our data show that in particular, subjects with PSA values close to the PSA cut-off have a high probability of being diagnosed with PCa in subsequent rounds. Previous studies confirm the association of PSA ranges and PCa, by showing a gradual increase in the odds of cancer during follow-up with higher baseline PSA measurements [14, 15].

In total, 3535 subjects died, resulting in an overall mortality rate of 21.4 per 1000 LY. The slightly higher OS in the group with an initial PSA level 1.0-1.9 ng/ml compared to the PSA <1.0 group remains unexplained. The overall risk of PCa death in our study cohort was limited, with a death rate equal to 0.14 per 1000 LY, compared to 1.55 per 1000 LY (p <0.001) for men with an initial PSA ≥3.0 ng/ml (11-fold higher) and 0.49 per 1000 LY in the overall cohort. A significant increase in risk of PCa related death was observed with increasing initial PSA, leading to 4.0- and 7.6-fold higher risks in the 1.0-1.9 ng/ml and 2.0-2.9 ng/ml PSA groups, respectively. Interval-detected PCa had a substantial part in the incidence of aggressive PCa and disease-specific deaths. Further study on how to prevent these interval cases is warranted, because shortening of the screening interval does not seem to solve this matter, but is rather likely to increase overdiagnosis, as was previously shown [16].

Our results are consistent with previous studies, showing PSA to be a predictor of death from PCa, even at moderate PSA levels [17, 18]. Vickers et al. [19] reported comparable findings to ours from their cohort of unscreened men, showing that PCa deaths among men with initial PSA levels <1.0 ng/ml are rare. Results of the current study strengthen the justification of the use of PSA in risk stratification for screening purposes. The favorable outcome in men with PSA <1.0 ng/ml supports the result of a previous study [20] to prolong the screening interval to 8 years in this group. To contribute to decreasing PCa mortality by means of screening, a large number of PCa deaths would need to be prevented, which cannot be found in the low PSA ranges. More aggressive screening would

lead to an unacceptable number needed to investigate (NNI) and number needed to treat (NNT). In line with this conclusion, a recent study [21] shows an NNI of 24.642 and an NNT of 724 for PSA <2.0 ng/ml, and in addition reveals excessive overdiagnosis and minor profit in PCa mortality of only 0.005 per 1000 LY between a screening cohort and a population-based cohort. Our results support the justification of a PSA threshold for screening based on current knowledge. Further effort should focus on the 2.0-2.9 ng/ml PSA range. Obviously, mechanisms to selectively detect aggressive cancers are needed, because the increase in the PCa detection rate with higher baseline PSA values does not alter the fact that the greater part of cases does not harbor aggressive disease. Already now, risk stratification instruments are available that avoid unnecessary biopsies and decrease overdiagnosis by incorporating clinically available risk modifiers and, once potentially indolent cancers are diagnosed, unnecessary treatments [22, 23]. In addition, further study on molecular and genetic markers selectively identifying aggressive disease is warranted.

CONCLUSION

This study provides insight into the natural history of PCa cases that remain undetected and the fate of screen- and interval-detected PCa in men with initial PSA values <3.0 ng/ml. It was shown that the risk of developing PCa, aggressive PCa, as well as PCa specific death in men participating in a screening trial with an initial PSA value <3.0 ng/ml, significantly increases in patients with higher initial PSA values. Interval detected cancers more often have aggressive characteristics and a substantial influence in causing disease-specific death, although the overall risk of PCa death in this cohort is low compared to men with initial PSA values $\geq$3.0 ng/ml (11-fold higher) and compared to the risk of other causes of death (150-fold higher). These results contribute to the risk stratification and individual management of men in PSA-based screening programs.

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6 Outcomes of initially expectantly managed patients with low- or intermediate-risk screen-detected localized prostate cancer

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ABSTRACT

Objective

To assess longer-term feasibility of active surveillance, we aimed to evaluate outcomes of patients with screen-detected localized prostate cancer (PCa) who initially elected to withhold radical treatment for either low- or intermediate-risk disease.

Patients and methods

All men underwent screening for PCa in the Rotterdam and Helsinki arms of the European Randomized Study of Screening for Prostate Cancer (ERSPC); eligible men were diagnosed with PCa prior to the establishment of the ERSPC affiliated Prostate Cancer Research International: Active Surveillance (PRIAS) study (1994-2007) and were initially expectantly managed in the absence of a fixed follow-up protocol. Low-risk PCa was defined as: clinical stage T1/T2, PSA $\leq$10 ng/ml, PSA density <0.2 ng/ml/ml, Gleason score $\leq$6, and maximum 2 positive biopsy cores, whereas PSA 10-20 ng/ml, Gleason score 7, and 3 positive biopsy cores were considered intermediate-risk features. Disease-specific-, overall-, and treatment-free survival were analysed using the Kaplan-Meier and competing risks methods.

Results

In all, 509 patients with PCa were eligible, of whom 381 were considered low-risk and 128 intermediate-risk. During a median follow-up of 7.4 years, a total of 221 patients (43.4%) switched to deferred treatment after a median of 2.6 years. The calculated 10-year disease-specific survival rates were 99.1% and 96.1% for low- and intermediate-risk patients, respectively ($p = 0.44$), and for overall survival 79.0% and 64.5%, respectively ($p = 0.003$). Competing risks analysis showed similar results.

Conclusion

Withholding radical treatment in men with low- to intermediate-risk, screen-detected PCa leads to a substantial delay or even avoidance of radical treatment and its potential side-effects in a majority of patients. Disease-specific outcomes at 7.4 years of follow-up are favorable in low- as well as intermediate-risk patients. This confirms the feasibility of active suveillance according to contemporary criteria, and also suggests a potential role for active surveillance in selected men with intermediate-risk features.

INTRODUCTION

The incidence of indolent prostate cancer (PCa) has increased substantially over the last two decades due to the widespread use of prostate-specific antigen (PSA) as a marker for the early detection of PCa [1]. In response to the increasing overdetection that followed the rising incidence of PCa [2], active surveillance (AS) evolved as a treatment strategy for low-risk PCa [3]. AS aims to prevent or at least delay treatment of presumed indolent tumors, thereby reducing potential side-effects from treatment and maintaining quality of life for these patients. AS programs aim to select patients with low-risk PCa by applying pre-defined inclusion criteria and a strict follow-up schedule, leaving the opportunity open to switch to deferred active therapy in case of risk reclassification or signs of tumor progression without compromising the window of opportunity for curative treatment.

Most AS studies do not yet have long-term results available and in particular outcomes after expectant management for men with screen-detected disease and more adverse features have not been widely reported. Information on the long-term outcomes of patients with expectantly managed PCa can contribute to expanding our knowledge and assessing the feasibility of AS as a treatment strategy for low- and intermediate-risk PCa in an era of widespread use of PSA testing for screening and early detection. We aimed to evaluate the outcomes in a cohort of patients with screen-detected PCa who initially elected to withhold radical treatment, and assessed differences in the outcomes of men who are assumed to be low-risk according to AS criteria [4] and men with intermediate-risk disease. Data on disease-specific mortality and risk of death from competing causes, active therapy-free survival, and metastases-free survival were recorded.

PATIENTS AND METHODS

All patients underwent screening for PCa between 1993 and 2007 in the Rotterdam or the Helsinki arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC) and, after PCa diagnosis, initially elected a strategy of expectant management.

Men aged 50-75 years were invited for PSA screenings at 4-year intervals. A PSA threshold of 3.0 or 4.0 ng/ml was used as an indication for biopsy, and also dependent on the centre, as was the additional use of findings at DRE and transrectal ultrasound [5, 6]. In the case of abnormal findings, a lateralized sextant biopsy was performed that was assessed by expert genitourinary pathologists in both centers. In 2002, the Finnish centre changed its biopsy schedule to 10 or 12 cores [6]. Men in whom PCa was diagnosed were referred to the regular medical circuit for further management of their disease. Since all men were diagnosed prior to the establishment of the ERSPC affiliated Prostate Cancer

Research International: Active Surveillance (PRIAS) study [7], no fixed follow-up protocol was applied regarding PSA measurements, repeat biopsies and recommendations on when to switch to deferred radical therapy. Instead, the timing and method of follow-up was at the treating physician's discretion. Data on baseline characteristics, deferred treatment, distant metastases, and causes of death were recorded. Deferred therapies were divided into 3 groups; radical prostatectomy (RP), radiation therapy, and hormonal therapy. Therapies applied for benign prostatic hyperplasia were not considered as active treatment in the context of this paper.

Patients were considered low-risk when contemporary PRIAS criteria were met: clinical stage T1C/T2, PSA $\leq$10 ng/ml, PSA density <0.2 ng/ml/ml, Gleason score $\leq$6 and maximum 2 positive biopsy cores. These criteria aim to select small, localized, well-differentiated PCa [7]. Men with known positive lymph nodes or distant metastases at the time of diagnosis were not considered eligible. Men with PSA 10-20 ng/ml and/or Gleason score 7 and/or 3 positive biopsy cores were considered intermediate-risk patients. Follow-up data were retrieved by chart review and mortality data were obtained by linkage with the national cancer registries. Causes of death were determined by an independent committee (Rotterdam), or either by death certificates or an independent committee (Helsinki).

Active therapy-free survival, metastases-free survival, disease-specific survival, and overall survival were analysed using the Kaplan-Meier method. In addition, to avoid overestimation of disease-specific mortality, non-parametric competing risks regression analysis was performed [8]. Comparisons between the low- and higher risk groups were made using the Mann-Whitney U-test (continuous data) and the Chi-square-test (nominal data). Statistical analyses were performed using SPSS statistical software (version 17.0; SPSS Inc, Chicago, IL, USA) and STATA version 11.0 software (College Station, TX, USA). All statistical tests were 2-sided with a p <0.05 considered to be statistically significant.

RESULTS

The overall cohort consisted of 509 patients, of whom 381 were considered low-risk (median age 67.6 years) and 128 were considered intermediate-risk (median age 67.4 years). Patients with low-risk features had a lower PSA level, larger prostate volume, lower PSA density, more favorable T stage, lower Gleason score and fewer positive cores at diagnosis than intermediate-risk patients. Study group characteristics at diagnosis are shown in table 1.

Table 1 | Study group characteristics at diagnosis for 509 screen-detected prostate cancer patients who were initially expectantly managed

	Low-risk (n=381)	**Intermediate-risk (n=128)**	***p* value**	**Total (n=509)**
	Median (25-75p)	***Median (25-75p)***		
Age, years	67.6 (64.2-71.3)	67.4 (64.7-72.1)	0.52	67.6 (64.4-71.4)
PSA, ng/ml	4.1 (3.2-5.0)	5.3 (4.0-7.6)	<0.001*	4.3 (3.4-5.5)
Prostate volume, ml	41 (33-51)	31 (25-41)	<0.001*	39 (30-49)
PSA density, ng/ml/ml	0.10 (0.07-0.13)	0.20 (0.12-0.25)	<0.001*	0.11 (0.08-0.15)
T stage	***N (%)***	***N (%)***	0.04*	
T1C	325 (85.3)	104 (81.3)		429 (84.3)
T2A	48 (12.6)	19 (14.8)		67 (13.2)
T2B	3 (0.8)	5 (3.9)		8 (1.6)
T2C	5 (1.3)	0 (0)		5 (1.0)
Gleason score			<0.001*	
≤6	381 (100)	99 (77.3)		480 (94.3)
3+4	0 (0)	25 (19.5)		25 (4.9)
4+3	0 (0)	4 (3.1)		4 (0.8)
Positive biopsy cores			<0.001*	
1	292 (76.6)	54 (42.2)		346 (68.0)
2	89 (23.4)	35 (27.3)		124 (24.4)
3	0 (0)	39 (30.5)		39 (7.7)
Number of biopsy cores, mean (range)	6.9 (3-13)	7.1 (3-14)	0.11	7.0 (3-14)

PCa; prostate cancer, PSA; prostate-specific antigen
** significant value (p <0.05)*

Median follow-up was 7.4 years (25-75p: 5.0-9.6 years) after PCa diagnosis. A total of 221 (43.4%) patients switched to deferred active therapy after a median of 2.6 years, while treatment was avoided, at least until last known follow-up, for a median of 6.8 years (25-75p: 4.5-9.1 years) in the other 288 men (56.7%). In the low-risk group 152 patients (39.9%) underwent treatment, while in the intermediate-risk group 69 patients (53.9%) were eventually treated (p = 0.006). The number of patients per deferred treatment option is shown in table 2. Men in the low-risk group received significantly more radiation therapy (p = 0.01) and less hormonal therapy (p = 0.01) than the intermediate-risk group. The 10-year active therapy-free survival rate was 49.7% and 30.3% in the low- and intermediate-risk groups, respectively (log-rank p = 0.005; figure 1).

Distant metastases were found in 1 low-risk patient and 3 intermediate-risk patients, leading to 10-year metastases-free survival rates of 99.7% and 96.4%, respectively (log-rank p = 0.03).

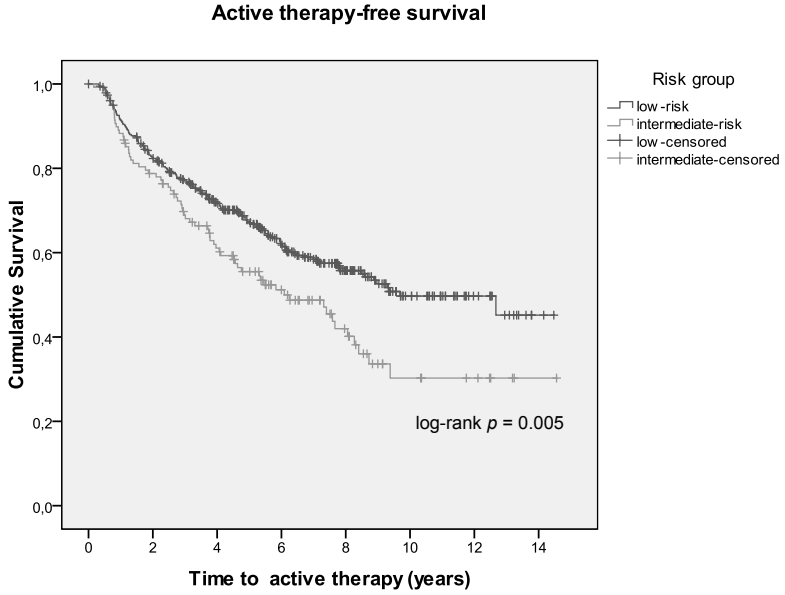
Table 2 | Study group characteristics during follow-up for 509 screen-detected prostate cancer patients who were initially expectantly managed

	Low-risk (n=381)	Intermediate-risk (n=128)	*p* value	Total (n=509)
	N (%)	***N (%)***		***N (%)***
Deferred active therapy	152 (39.9)	69 (53.9)	0.006*	221 (43.4)
Radical prostatectomy	32 (21.1)	18 (26.1)	0.41	50 (22.6)
Radiotherapy	104 (68.4)	35 (50.7)	0.01*	139 (62.9)
Hormonal therapy	16 (10.5)	16 (23.2)	0.01*	32 (14.5)
Distant metastases	1 (0.3)	3 (2.3)	0.02*	4 (0.8)
Overall death	60 (15.7)	38 (29.7)	0.001*	98 (19.3)
PCa death	3 (0.8)	2 (1.6)	0.44	5 (1.0)
	Median (25-75p)	***Median (25-75p)***		***Median (25-75p)***
Follow-up time, years	7.5 (4.9-9.6)	7.2 (5.3-9.9)	0.69	7.4 (5.0-9.6)
Follow-up PSA measurements, N	10 (6-14)	10 (6-15)	0.57	10 (6-14)
Time to active therapy, years	2.5 (1.2-4.9)	2.7 (1.1-4.6)	0.90	2.6 (1.1-4.8)
Time to metastases, years	3.5 (-)	8.4 (7.4-11.7)	0.18	7.9 (4.4-10.8)
Time to overall death, years	5.3 (3.1-8.6)	6.8 (4.7-8.9)	0.05	6.0 (3.6-8.6)
Time to PCa death, years	2.9 (0.4-5.8)	8.1 (7.5-8.6)	0.08	5.8 (1.7-8.1)

PCa; prostate cancer
** significant value (p <0.05)*

Overall 98 patients (19.3%) died during follow-up, of whom 5 (1.0%) died of PCa. The overall death rate was higher in the intermediate-risk group (29.7% vs. 15.7%; p = 0.001). PCa was considered the cause of death in 3 men in the low-risk group and 2 in the intermediate-risk group (p = 0.44). Study group characteristics during follow-up and a case description of patients in whom PCa was recorded as the cause of death are shown in table 2 and 3, respectively.

The 10-year overall survival rate was 75.1% in the complete study cohort, and 79.0% and 64.5% in the low-and intermediate risk group, respectively (p = 0.003, figure 2). The 10-year disease-specific survival rate overall was 98.4%; this rate was 99.1% and 96.1% in the low- and intermediate risk group, respectively (p = 0.44, figure 3). The cumulative incidence function (CIF) for PCa and other cause mortality, computed using competing risks analysis, showed similar results to the Kaplan-Meier method. The CIF after 10 years for disease-specific mortality in low- and intermediate-risk patients was 0.9% and 2.9% (p = 0.80), respectively (overall 1.5%). The CIFs in these groups were 20.1% and 32.5% (p = 0.06) for other cause mortality, respectively (overall 23.5%).



Number at risk								
Years	0	2	4	6	8	10	12	14
Low-risk	381	302	231	157	90	41	16	2
Intermediate-risk	128	99	69	42	24	9	6	1

Figure 1 | Kaplan-Meier curve showing active therapy-free survival, stratified by risk group.

Table 3 | Case description of 5 patients in whom prostate cancer was recorded as their cause of death

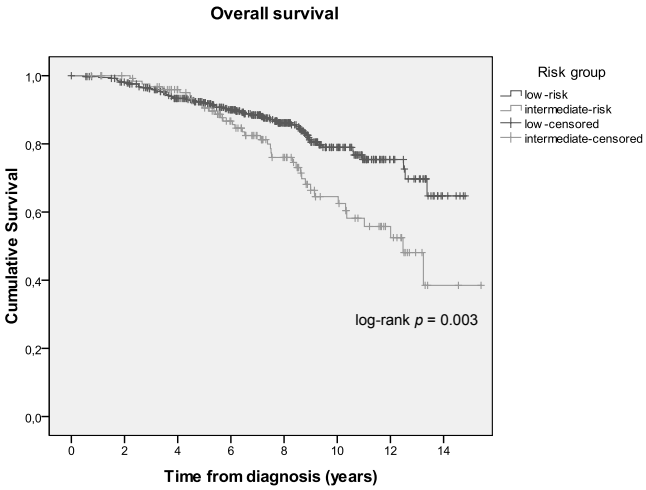
Patient	Tumour characteristics at diagnosis							Time to active treatment, years (therapy type)	Time to PCa death, years
	Age, years	Clinical stage	PSA, ng/ml	Prostate volume, ml	Biopsy result, positive/ total cores	Gleason score	Risk group		
1	68	T1C	3.8	25	2/6	3+3	Low	-	0.5*
2	63	T1C	3.1	40	2/6	3+3	Low	0.8 (RTx)	5.8
3	71	T1C	7.8	57	1/12	3+3	Low	0.3 (HTx)	2.9**
4	74	T2B	4.3	31	3/6	3+3	Intermediate	7.3 (HTx)	8.6***
5	63	T1C	4.0	unknown	1/6	3+3	Intermediate	2.7 (RTx)	7.5

PSA, prostate-specific antigen; RTx, radiotherapy; HTx, hormonal therapy; PCa, prostate cancer

** died during treatment of an abdominal aneurysm that was coincidentally found during the work-up for prostate cancer*

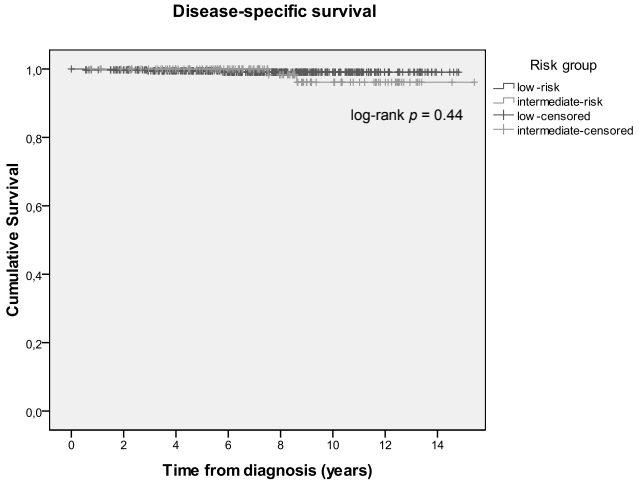
*** received initial expectant management because of co-morbidity, received hormonal therapy due to urinary retention, and despite no clinical evidence of progressive disease at time of death prostate cancer was recorded on his death certificate*

**** received initial expectant management because of co-morbidity*



Number at risk								
Years	0	2	4	6	8	10	12	14
Low-risk	381	363	313	249	164	83	31	5
Intermediate-risk	128	124	109	84	56	32	17	2

Figure 2 | Kaplan-Meier curve showing overall survival, stratified by risk group.



Number at risk								
Years	0	2	4	6	8	10	12	14
Low-risk	381	363	313	249	164	83	31	5
Intermediate-risk	128	124	109	84	56	32	17	2

Figure 3 | Kaplan-Meier curve showing prostate cancer-specific survival, stratified by risk group.

DISCUSSION

We assessed the outcomes of patients initially managed expectantly with either low- or intermediate-risk PCa to evaluate long-term feasibility of AS in a screen-detected population. Compared to men with low-risk PCa at diagnosis, intermediate-risk men, by definition, had more unfavorable disease characteristics at diagnosis. Deferred therapy, distant metastases, and overall deaths occurred more often in the group with intermediate-risk features. However, withholding radical treatment in low- and intermediate-risk screen-detected PCa leads to a substantial delay or even avoidance of therapy in a majority of men. Eventually, 43.4% of all patients received deferred treatment after a median of 2.6 years, while active therapy was avoided in 56.6% for a median of at least 6.8 years. Moreover, no difference was found in disease-specific survival between the two groups. The overall PCa-specific mortality was low, with a 10-year disease-specific survival rate of 98.4% for the entire cohort, despite a significant share (25.1%) of intermediate-risk patients. After accounting for other cause mortality, competing risks analysis showed comparable results for overall and disease-specific mortality.

Previously, other studies have shown favorable outcomes of conservatively managed patients with low- and intermediate-risk disease. A recent report from a population-based nationwide cohort study in Sweden [9] showed a 10-year disease-specific mortality of 3.6% in a group of 2021 expectantly managed men (i.e. including both AS and watchful waiting) who had a mean age of 64.7 years and who were followed for a median of 8.2 years. The 10-year disease-specific mortality rates for low- and intermediate-risk men in that cohort were 2.4% and 5.2%, respectively, while the overall mortality rate reached 20.4%. The corresponding rates for 10-year disease-specific mortality in our cohort are even more favorable; 0.9% and 3.9% for low- and intermediate risk disease and 1.6% for the overall cohort, which might be due to the small number of events in both studies, the more stringent definition of low- and intermediate-risk PCa we applied, or the difference in the amount of screen-detected cases. Moreover, only 2 patients who died of PCa received deferred treatment with curative intent and potentially missed the window of curability because of initial expectant management, which is only 0.4% of our cohort and 2% of the overall deaths.

Another study presented results from the Surveillance, Epidemiology, and End Results (SEER) program [10] of men who had a median age of 78 years with T1 or T2 PCa in whom curative therapy was not attempted and of whom 42% had received androgen deprivation therapy. The 10-year disease-specific mortality was 8.3-9.1% for well- and intermediate-differentiated tumors, while the overall mortality rate was 51.7% after a median follow-up of 8.3 years. Although these data were obtained in the PSA era and already show substantially lower mortality rates compared to the control arm of the

Scandinavian Prostate Cancer Group 4 (SPCG-4) study [11, 12], the overall health and the age of the patients in this study are not representative for the majority of patients who opt for AS in contemporary practice. Recently, results from the randomized Prostate cancer Intervention Versus Observation Trial (PIVOT) were presented [13], showing that RP did not reduce disease-specific survival more than observation in patients with low-risk PCa after 10 years, which also suggests a favorable natural course of disease in patients who are considered to be at low-risk.

Because AS is a relatively new treatment strategy, most prospective studies on the subject do not have data on long-term outcomes available. Klotz et al. [14] did publish results of an AS cohort comprising low- and intermediate-risk PCa cases (71% vs. 29%) with a median follow-up of 6.8 years in men with a median age of 70.3 years. They described a 10-year disease-specific survival rate of 97.2%, while the 10-year overall survival rate was 68%. These survival rates are quite comparable, but slightly lower than the rates in our cohort, which is most probably due to the higher median age in their series. The median follow-up of other prospective AS studies is still too short to evaluate disease-specific outcomes. The proportion of patients switching to deferred treatment in contemporary prospective AS cohorts varies between 14 and 35% [4, 14-18]; the higher proportion of patients undergoing active therapy in our cohort might result from the lack of a follow-up protocol. Nevertheless, it was shown that the majority of treated patients switch to active treatment during the first 3 years after diagnosis, which is a common observation in most AS series and can, at least partly, be explained by risk reclassification of the disease [19].

Outcomes in intermediate-risk patients in our cohort were quite favorable, showing similar disease-specific survival rates compared with the low-risk cohort, despite less favorable baseline characteristics. Previously, Cooperberg et al. [15] also found favorable results in their AS cohort (n=466) of patients with low-risk and intermediate-risk PCa; although intermediate-risk patients had more adverse features at diagnosis, they did not undergo more active therapy or experience more progression. None of the men undergoing deferred RP were node positive and none experienced biochemical progression within 3 years. These results show that selected candidates with intermediate-risk features can be followed on AS, preserving favorable long-term prognosis. In addition, in the current cohort, Cox regression analysis correcting for curative treatment (RP or radiation therapy), showed no difference between the risk groups regarding PCa mortality (data not shown). Moreover, it should be noted that no distinction could be made between men on watchful waiting and men on AS. In watchful waiting no follow-up protocol is used and the intent for curative treatment, if necessary, is lacking. Therefore, it can be expected that a true AS cohort with strict follow-up of their PSA kinetics and

tumor characteristics with deferred active treatment on indication, might show even better outcomes than the ones presented here.

To identify low-risk PCa, we used PRIAS study criteria [4, 7]. We believe the favorable results in this report confirm the feasibility of AS according to these criteria, but we are aware of the fact that inclusion and follow-up criteria still need further validation through outcome data with longer follow-up. Furthermore, we found that selected men with intermediate-risk PCa may be appropriate candidates for AS as well. The higher overall mortality rate and use of hormonal therapy in the intermediate-risk group indicates that the overall health in this group was worse than in the low-risk group. And although the life expectancy in our cohort (median age 67 years) is longer than our median follow-up, the low number of adverse events over a 10-year time frame in the intermediate-risk group supports the idea of less stringent criteria for AS in screen-detected men over 70 years or with significant co-morbidities. Moreover, even in case of deferred treatment, quality of life is likely to be maintained by prolonged therapy-free survival [20, 21] and patients might profit from improved treatments or other potential advances in medical care.

This study has some limitations. Since no protocol was applied for surveillance, follow-up might have been less strict than in contemporary AS cohorts and patients who were actually candidates for watchful waiting very probably also form part of this cohort. However, more frequent follow-up such as is applied in contemporary AS protocols might have led to earlier detection of progression and even better outcomes in some men. Furthermore, potential variation in pathology reporting over time could have occurred due to the shift in Gleason scores [22, 23], which could have influenced clinical outcomes. Follow-up was limited to 7.4 years and regarding the median life expectancy for men in our cohort, longer follow-up remains useful to confirm our findings.

In conclusion, withholding radical treatment in men with low- or intermediate-risk screen-detected localized PCa may lead to a substantial delay or even avoidance of radical treatments and their side-effects. Favorable disease-specific outcomes over a 10-year period confirm the feasibility of AS for low-risk PCa and also open the way for implementation of this method for intermediate-risk disease for selected patients. The choice of therapy should always take co-morbidity, patient age and patient preferences into account. Regarding the considerable difficulties in implementing trials randomizing for radical treatment and AS, answers to important questions on long-term mortality, and inclusion and follow-up criteria for AS are more likely to come from prospective AS studies such as PRIAS.

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III | Risk calculator

7 Updating the prostate cancer risk indicator for contemporary biopsy schemes

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ABSTRACT

Introduction and Objective

The prostate cancer risk indicator is a validated tool for predicting the chance of a screen detected prostate cancer to be classified as indolent, partially based on lateralized sextant biopsies. Our objective is to extract correction factors for adjustment of the model, addressing contemporary extended biopsy schemes.

Materials and Methods

Post-mortem 18-core biopsy results of men who died of unrelated causes, but were diagnosed with prostate cancer post-mortem were used to provide details on prostate biopsies and whole mount specimens. For each of the 18-core biopsies showing cancer, Gleason-score, number of positive cores, location in the gland and percentage of cancer involvement were determined and correlated to final pathology. Total length of cancer tissue in a 6-core scheme was related to the length in 12 and 18-core schemes to compute correction factors. Furthermore, upgrading on extended biopsies and final pathology was evaluated.

Results

Data from 33 autopsied men were included. The 18 and 12-core biopsies showed 192.72mm and 143.76mm of prostate cancer, compared to 70.80mm with lateralized sextant biopsy, resulting in correction factors of 2.72 and 2.03 for 18 and 12-core schemes, respectively. Upgrading in Gleason score on extended biopsy regimens compared to lateralized sextant biopsy occurred in 33% (11/33) of the cases.

Conclusion

Based on autopsy data, the present correction factors provide a support in the adjustment of the prostate cancer risk indicator towards more extended contemporary biopsy schemes, eventually leading to a more accurate prediction of the probability of indolent cancers and assisting patients and clinicians to make appropriate choices in daily practice.

INTRODUCTION

Screening with serum prostate-specific antigen (PSA) was shown to reduce the rate of death from prostate cancer by 20% in the European Randomized Study of Screening for Prostate Cancer (ERSPC) [1]. This rate could even be improved when it was adjusted for non-compliance and contamination [2]. In contrary, the first results of the Prostate, Lung, Colorectal and Ovarian (PLCO) screening study did not show a decrease in mortality [3], but selective use of PSA screening for men in good health was found to reduce the risk of disease-specific mortality in this trial [4]. However, concerns have been raised on overdiagnosis [1, 5, 6] and overtreatment of tumors which may not be harmful. Men with low-grade prostate cancer often die of other causes before these tumors become harmful [7] and radical treatment is associated with serious side-effects [8, 9]. The percentage of prostate cancer detected during screening in men who would not otherwise have clinical symptoms during their lifetime, has been estimated to be as high as 50% [10].

Prognostic models have been designed to predict indolent prostate cancer [11]. Steyerberg et al. [12] updated and validated a nomogram, that is now applied in level 6 of the prostate cancer risk indicator, www.prostatecancer-riskcalculator.com, figure 1. This

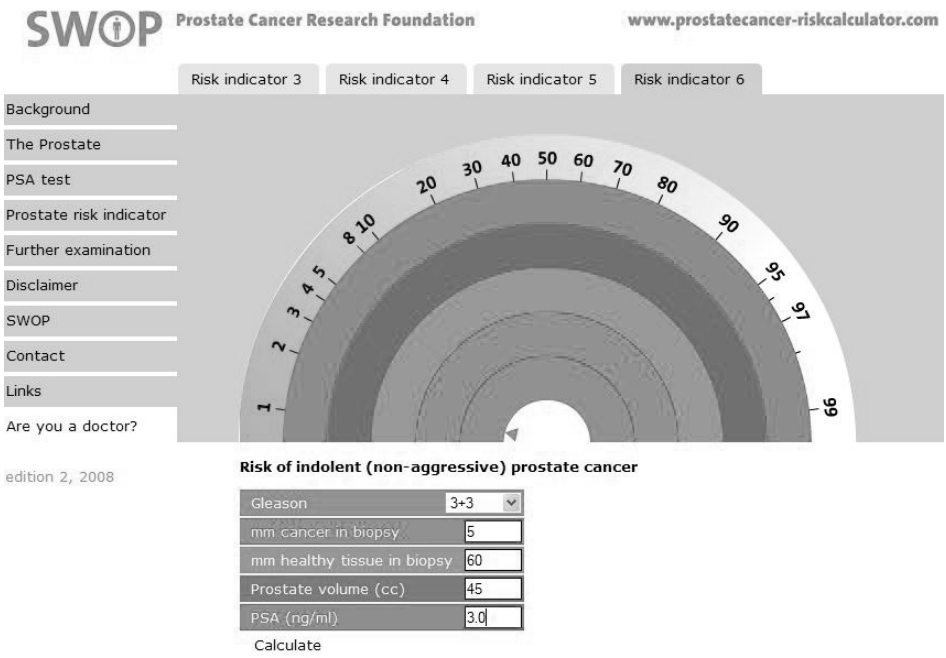

Figure 1 | Prostate Cancer Risk indicator, level 6. The boxes under the graph can be completed with GS, PSA, prostate volume and length of cancerous and healthy tissue in the biopsy in order to predict the probability of indolent PC.

nomogram predicts the probability of clinically indolent prostate cancer (i.e. prostate cancer not causing any co-morbidity or mortality based on favorable tumor characteristics, irrespective of patient related factors) detected by screening and can support patients and clinicians when considering different treatment options. These predictions are based on the length (in mm) of prostate cancer sampled in sextant biopsies (from the Rotterdam arm of the ERSPC), which limits its applicability for contemporary practice where often extended biopsy regimens are used. In order to allow predictions based on 12-18 core biopsy regimens we analyzed the data of recently published autopsy studies [13, 14], after establishing co-operation which allowed access to the original data, and extracted adjustment factors for specific biopsy schemes.

MATERIALS AND METHODS

We analyzed the percentage of tumor involvement per biopsy core from two autopsy studies investigating the true sensitivity and specificity of 6, 12 and 18-core biopsies [13, 14], to allow predictions based on contemporary 12 to 18 core biopsy regimens by deriving adjustment factors for specific biopsy schemes. In these studies 18-core needle biopsies were performed on prostates (ex vivo) obtained at autopsies of men who died of unrelated causes (n=212) and of whom only age, race and cause of death were recorded. All biopsies were performed in a manner that mimicked clinical biopsy under the direction of a urologist. Biopsies were taken with a standard 18F spring-loaded biopsy gun (Bard Maxcore, C.R. Bard, Covengton, GA, USA). The biopsy gun needle was inserted through the posterior surface of the hand-held gland and bilateral samples were taken from the apex, mid gland and base. Six-core biopsies were taken from the mid peripheral zone, the lateral peripheral zone and the central zone. For each biopsy showing cancer, Gleason-score, the number of tissue cores containing cancer, the percentage of cancer involvement in each core and the location of the tumor in the gland were determined. The Gleason score on biopsy was correlated to the Gleason score on final pathology of the prostates. Each tumor focus was graded according to the modified Gleason-grading system [15]. The lateralized sextant biopsy regimen of the ERSPC (red circles, figure 2) was compared to the 12 (red and blue circles) and 18-core (all circles) regimens of the autopsy study. The length (in mm) of cancer tissue in each biopsy core was recorded. The total length of cancer tissue found with the sextant biopsy approach was related to the 12 and 18-core biopsy scheme. Gleason score and possible upgrading per biopsy regimen were evaluated. Furthermore, the nomogram probability of indolent disease was evaluated in the case of a 6, 12 or 18-core regimen, with and without making use of the correction factors, respectively. For the purpose of this study, all prostate cancer cases were considered to be indolent, as none of the subjects were diagnosed with prostate

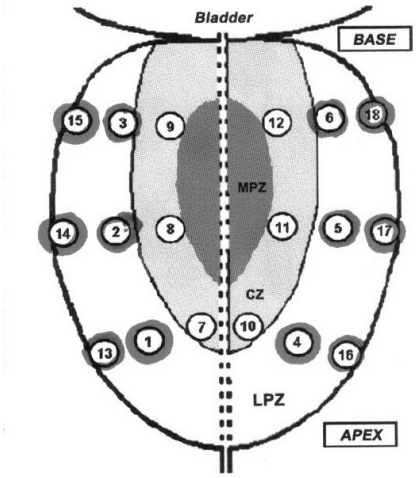

Figure 2 | Biopsy scheme autopsy study. Biopsy scheme for the 18-core needle biopsies with the red circles representing the sextant biopsy regimen of the ERSPC and the red and blue circles together representing the 12-core regimen.

cancer during life, nor died of the disease. A nomogram predicted chance ≥70% for indolent disease was used as a cut-off value, because of a good sensitivity-specificity trade-off with detection of 94% of clinically important prostate cancer [12].

RESULTS

Prostate cancer was found on whole mount sections in 59 of 212 men (28%). Prostate biopsies detected cancer in 33/59 patients (56%). In all of these patients, detailed information on percentage tumor involvement per single biopsy core was known. Median age was 72 years (range 49-92 years). Median prostate volume was 50cc (range 23-95cc). The mean length of the biopsy cores in the 33 autopsy cases was 12 mm per core, which is similar to the mean length in the ERSPC [1]. The 18-core and 12-core biopsy regimen sampled a total of 192.72mm and 143.76mm of prostate cancer, respectively. The lateralized 6-core regimen (biopsy technique of the ERSPC) sampled 70.80mm prostate cancer tissue. These data translate into correction factors of 2.72 (192.72/70.80) if a biopsy scheme of 18 cores is used and of 2.03 (143.76/70.80) with a 12-core biopsy scheme. The total length in mm of benign tissue can be multiplied by 2 or 3 in case of a 12 or 18-core biopsy scheme, respectively.

Upgrading in Gleason score on extended biopsy regimens compared to lateralized sextant biopsy is depicted in table 1. There was undergrading on sextant biopsy in 33% (11/33) of cases. The biopsy results are compared to final pathology in table 2. In one case, prostate cancer was detected with biopsy, but could not be located in the whole

mount specimen. The concordance rate was 70% (23/33) in total and 52% (17/33) for the prostate cancer diagnosed with a sextant regimen. The undergrading rates were 18% (6/33) and 39% (13/33), respectively.

Table 1 | Upgrading (bold) in Gleason score on extended biopsy regimens (12 or 18-core) compared to lateralized sextant biopsy

		Gleason score on extended biopsy regimens			
Gleason score on lateralized sextant biopsy		3+3	3+4	4+4	4+5
	3+3	18			
	3+4		3	**1 (12)**	**1 (12)**
	4+4			1	
	No PCa	**5 (12)** **1 (18)**	**2 (12)**	**1 (12)**	

PCa, prostate cancer

Table 2 | Overall biopsy results as well as lateralized sextant biopsy results compared to upgrading (bold) in final pathology

		Gleason score on extended biopsy				**Gleason score on lateralized sextant biopsy**				
Gleason score on final pathology		6	7	8	9	6	7	8	9	No PC
	6	18		1		14	1			**4**
	7	**5**	5	1		**3**	3	1		**4**
	8				1		**1**			
	9			**1**						**1**
	No PCa	1				1				

PCa, prostate cancer

DISCUSSION

Prostate cancer is the most common (non-cutaneous) cancer in US males and the second most important cause in cancer related deaths with estimated numbers of 192.280 and 27.360 in 2009 [16] and numbers of 382.000 and 89.000 in Europe in 2008, respectively [17]. Due to PSA-based screening, the time of diagnosis of prostate cancer has advanced considerably and a substantial overdiagnosis is observed in up to 50% of the cases, meaning that half of the men screened would not have ever been diagnosed with prostate cancer in their lifespan in the absence of screening [10]. With these prostate cancers being detected, improvement of outcome predictions by proper staging is a major issue. In order to predict indolent prostate cancer and to subsequently reduce unnecessary radical treatment, nomograms that predict the chance of potentially indolent disease can be used, for example level 6 of the prostate cancer risk indicator. This nomogram

[12] was validated and updated with 247 patients from the ERSPC who were treated with radical prostatectomy and contains the following predictive characteristics: serum PSA, ultrasound prostate volume, clinical stage, biopsy Gleason score and total length of cancerous and noncancerous tissue in biopsy cores. Indolent disease was defined as a combination of a total tumor volume less than 0.5ml, no extracapsular extension and no Gleason score 4 or 5. Selection criteria for the 247 patients were: age group 55-74 years, clinical stage T1c/T2a, PSA $\leq$20 ng/ml, primary or secondary Gleason score $\leq$3, 50% or less positive cores, 20mm or less total cancer in biopsy cores and at least 40mm benign tissue in all cores. When applying both the Kattan nomogram [11] and the Steyerberg nomogram [12] to a recent, clinical population, the resulting AUC of the ROC curve for predicting indolent disease were 0.779 and 0.777, respectively, indicating good and comparable discrimination for both models [18].

In this manuscript we proposed a correction factor for contemporary 12 and 18-core biopsy regimens based on autopsy data, to support future conversion of the risk indicator to predict the probability of indolent cancers on a more accurate prostate sampling. Correction factors of 2 and 3 for benign tissue and 2.03 and 2.72 for malignant tissue, respectively for 12 and 18-core biopsy regimens were calculated. These values are indicative, but still have to be validated before they can be used to predict a more precise outcome for extended biopsy regimens than the sextant biopsy on which the risk indicator was originally based. These results accentuate that it is inaccurate to use default correction factors of 2 and 3 for 12 and 18 cores, respectively. The calculated correction factors implicate that the length of prostate cancer tissue would be divided by 2.03 and 2.72 with biopsy regimens of 12 and 18-cores, respectively. Although not yet validated, these findings give direction to the improvement of the clinical applicability of the risk indicator, because changes in clinical practice have led to the use of larger numbers of biopsies often compatible with the 12 and 18 cores applied in our autopsy series.

Extended biopsy regimens result in significantly higher detection rates as compared to earlier sextant protocols [19]. The incidence of prostate cancer is not equally distributed throughout the prostate, with the peripheral zone being affected more often [20, 21]. In this study lateralized sextant biopsy detected 24/33 (73%) patients with prostate cancer. The 9 prostate cancers that were not diagnosed based on lateralized sextant biopsy, were detected on 12-core biopsy in 4 cases, on 18-core biopsy in 1 case and on a combination of both in 4 cases. This implies that 97% (32/33) of prostate cancer cases were detected on 12-core biopsy. Scattoni et al. state that the 12-core sample seems reasonable to consider as an initial prostatic biopsy, with saturation techniques not demonstrating to improve cancer detection, but with significantly superior results compared to the standard sextant biopsy [19]. Schröder et al. [22] found lateralized sextant biopsy to be an adequate and safe regimen if *repeated* screening is applied.

Furthermore, they stated that, based on a review of literature, lateralized sextant biopsy would miss 19% of cancers detectable with more extensive schemes. This is a smaller amount than the 27% we found in this study. In the screening study of the Rotterdam section of the ERSPC, missed or delayed diagnosis did not appear to result in increased progression or cancer specific mortality [22].

Three of the patients with cancer on sextant biopsy showed an upgrading of Gleason score with the extended biopsy regimens, resulting in an underestimation of Gleason score by sextant biopsy in 8.3% of the cases. Noteworthy is all three of these patients would not have fitted the active surveillance protocol we use at our centre [23] following any of the biopsy regimens and would thus have had the advice for radical treatment. Prediction of the final Gleason score in this cohort by biopsy results for the sextant regimen and the 18-core regimen showed 52-70% concordance rates, respectively. In literature [19] similar concordance rates have been reported of 28-48% and 63-72%, respectively.

Besides Gleason score, we did not further compare the predicted outcome of the risk indicator to the final outcome on pathology, because all the cancers were by definition clinically insignificant as none of them were diagnosed during life. Also, the age and PSA distribution of this cohort deferred of that of the cohort on which the nomogram was validated and no information on clinical stage was available for the autopsy specimens.

Limitations of this study include the small number of patients and the lack of validation of the results. Additionally, the calculated correction factors are restricted to 12 and 18-core biopsy schemes with a mean length of 12mm per core. Not all pathologists may report on the exact length of cores and cancerous tissue, which potentially makes it a more difficult value to acquire. This study population does not exactly match the population used to create level 6 of the risk indicator concerning the selection criteria mentioned above, thus caution should be used when interpreting these results. Previous negative biopsies during lifetime would represent a selection bias and could not be excluded in the autopsy series.

CONCLUSION

The outcome of this study contributes to the improvement of the prostate cancer risk indicator, providing a support in the adjustment towards more extended biopsy schemes, eventually leading to a more accurate prediction of the probability of indolent cancers, which will enable its use with the extended biopsy regimens in contemporary practice. As a result, patients and clinicians can be assisted in making more appropriate treatment decisions. Further validation of these results is needed to justify the use of these correction factors in contemporary practice.

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IV | Active Surveillance

8 Predictors of unfavourable repeat biopsy results in men participating in a prospective active surveillance program

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ABSTRACT

Background

Active surveillance (AS) protocols for low-risk prostate cancer (PCa) generally include repeat prostate biopsies at predefined follow-up intervals.

Objective

To study the outcome of routinely obtained 1-year repeat biopsies and factors predicting reclassification to higher risk, to contribute to risk stratification for men on AS.

Design, setting and participants

We analysed men with low-risk PCa (clinical stage <T2, prostate-specific antigen (PSA) <10 ng/ml, PSA density <0.2 ng/ml/ml, 1 or 2 positive biopsy cores and Gleason score <6) who had been included in a prospective AS protocol.

Interventions

PSA was measured 3-monthly and the first, volume-dependent repeat biopsy was scheduled 1 year after diagnosis, independent of PSA doubling time (PSA-DT). Reclassification to higher risk disease on repeat biopsy was defined as Gleason score >7 or >3 positive cores.

Measurements

We analysed whether baseline patient characteristics and PSA-DT were associated with reclassification to more aggressive PCa on repeat biopsy.

Results and limitations

A first repeat biopsy was taken in 757 patients after median follow-up of 1.03 years. The results of repeat biopsies were favorable (no or low-risk PCa) in 594 patients (78.5%) and led to reclassification of risk in 163 (21.5%). Analysis showed that reclassification to higher risk was significantly influenced by the number of initial positive cores (2 vs. 1) (odds ratio [OR] =1.8; p =0.002) and higher PSA density (OR =2.1; p =0.003). The outcome was not significantly influenced by age, clinical stage, total number of biopsy cores, or PSA. Adding PSA-DT at time of repeat biopsy to the model showed PSA-DT <3 years to be significantly associated with reclassification to higher risk (OR =1.7; p =0.015). Data on tumor involvement per biopsy core was not available.

Conclusions

Clinical features at baseline and during follow-up in our AS cohort are significantly associated with short-term reclassification to higher risk on repeat biopsy. These characteristics can potentially be used for risk stratification of men with PCa who are apparently at favorable risk.

INTRODUCTION

In addition to contributing to a reduction in prostate cancer (PCa) mortality over recent decades [1, 2], prostate-specific antigen (PSA)-based screening has led to considerable overdetection of cancer that would not have been diagnosed during lifetime in the absence of screening, in up to 50% of cases [3]. Subjecting all men with low-risk disease to invasive therapy would lead to many unnecessary side-effects of treatment, such as impotence and incontinence [4, 5], without improving their survival rate.

Active surveillance (AS) for low-risk PCa aims to prevent, or at least delay, invasive therapy and its potential side-effects in carefully selected men, mainly those with screen-detected disease. The idea of AS is to preserve the opportunity to switch to curative treatment in case of reclassification to a more aggressive cancer during follow-up. Bearing in mind that most PCa is slow-growing with a long lead-time advanced by screening [3], and most 'progression' in AS series occurs 1-2 years after diagnosis [6-8], it is more likely that most of these tumors have not truly progressed over a relatively short period of time, but were understaged and/or undergraded at diagnosis. Repeat biopsies at predefined time intervals are a common part of AS protocols, and are intended to detect men who are considered to have unfavorable disease and should be offered radical therapy, despite seemingly low-risk features at diagnosis. However, the optimal strategy with regard to the exact timing and indications for repeat biopsy has not yet been established.

Prostate Cancer Research International: Active Surveillance (PRIAS) is a prospective, observational study, which originated from the European Randomized Study of Screening for Prostate Cancer (ERSPC) [1]. It provides a protocol for the inclusion and follow-up of low-risk PCa patients that is being used by urologists worldwide via a web-based instrument (www.prias-project.org). This protocol schedules a first repeat biopsy one year after diagnosis to evaluate potential reclassification of the tumor to higher risk disease. In order to contribute to risk stratification for men on AS, we studied the outcome of repeat biopsies and predictive factors for risk reclassification to more aggressive disease.

METHODS

Inclusion for the international PRIAS study started in December 2006 and follow-up for this study was complete until October 2010. For analysis, we used patients with low-risk PCa who met all of the inclusion criteria (clinical stage <T2, PSA <10 ng/ml, PSA density [PSA-D] <0.2 ng/ml/ml, 1 or 2 positive biopsy cores, and Gleason score <6). PSA was

measured 3-monthly and the first repeat biopsy was scheduled after 1 year. Volume-dependent biopsies were recommended according to protocol (prostate volume <40cc: 8 biopsy-cores, 40-60cc: 10, and >60cc: 12). Risk reclassification as high risk on repeat biopsy was defined as three or more positive biopsy cores or Gleason score >7. PSA doubling time (PSA-DT) was calculated at the time of repeat biopsy, and outcomes were subdivided into 4 different groups: negative values, >10 years, 3-10 years or <3 years. For analysis, the most favorable PSA-DT groups, with either negative values or values >10 years, were used as a reference group. For each patient we recorded age, prostate volume, PSA, PSA-D, total number of cores, clinical stage, number of positive cores and Gleason score at diagnosis, as well as time to follow-up and PSA-DT at repeat biopsy. Because of small numbers, clinical stage T2 was not further subdivided into specific categories. PSA-D was calculated as PSA divided by total prostate volume. The odds ratio (OR) for PSA-D was reported per 0.10 units increase to prevent very high and unrealistic outcomes.

Multivariate logistic regression analysis was performed to evaluate the association of all baseline characteristics and PSA-DT with risk reclassification towards high risk on repeat biopsy. Clinical stage and PSA-DT were stratified into groups; other characteristics were used as continuous variables. P values were calculated using the Mann-Whitney U test (continuous variables) and the Chi-square test (categorical variables). Statistical analyses were performed using SPSS statistical software v.17.0 (SPSS Inc, Chicago, IL, USA). All statistical tests were 2-sided with $p < 0.05$ considered to be statistically significant.

RESULTS

A first repeat biopsy was taken in 757 men at a median age of 65.2 years (25-75p: 60.5-70.0) and after a median follow-up of 1.03 years (25-75p: 1.00-1.08). Figure 1 shows the number of repeat biopsies per participating country. The median number of biopsy-cores at diagnosis, as well as at repeat biopsy was 10 (25-75p: 8-12). At diagnosis 743 patients (98.2%) had clinical stage <T2a. Favorable repeat biopsy results, that is no PCa or PRIAS suitable PCa, were observed in 277 patients (36.6%) and 317 patients (41.9%), respectively. An upgrade in Gleason score was seen in 67 men (8.9%) and 130 men (17.2%) showed an increase in positive biopsy-cores more than two; 34 men (4.5%) met both conditions. This resulted in a total number of favorable outcomes in 594 patients (78.5%) and unfavorable outcomes in 163 patients (21.5%).

Table 1 shows the study group characteristics at baseline stratified by outcome. Characteristics at repeat biopsy and the value of PSA-DT are depicted in table 2.

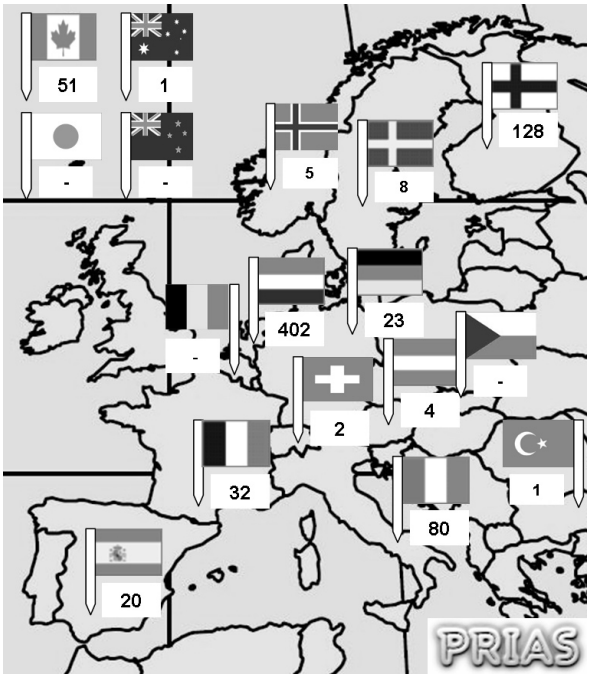

Figure 1 | The number of repeat biopsies per participating country in the PRIAS study.

Table 1 | Study group characteristics at diagnosis, divided by repeat biopsy outcome

	Favorable biopsy outcome (N=594)		Unfavorable biopsy outcome (N=163)		
	Median	***25-75 percentile***	***Median***	***25-75 percentile***	***p* value**
Age (years)	65.2	60.2-69.8	65.3	60.9-70.6	0.65
Volume (ml)	44.9	35.0-58.2	40.0	33.0-52.0	0.01*
PSA (ng/ml)	5.5	4.1-6.8	5.3	4.3-6.8	0.94
PSA-D (ng/ml/ml)	0.12	0.09-0.16	0.13	0.10-0.16	0.01*
Total cores	10	8-12	10	8-12	0.75
Clinical stage	***Number***	***% of total***	***Number***	***% of total***	0.44
≤T1c	503	79.0	134	21.0	
T2	91	75.8	29	24.2	
Positive cores					<0.001*
1	434	81.9	96	18.1	
2	160	70.5	67	29.5	
Gleason score					0.69
3+3=6	552	78.7	149	21.3	
Lower	42	75.0	14	25.0	

PSA, prostate-specific antigen; PSA-D, PSA density (PSA/prostate volume)

** significant result (p <0.05)*

Table 2 | Study group characteristics at first repeat biopsy, divided by repeat biopsy outcome

	Favorable repeat biopsy outcome (N=594)		Unfavorable repeat biopsy outcome (N=163)		
	Median	***25-75 percentile***	***Median***	***25-75 percentile***	***p* value**
Follow-up (years)	1.03	1.00-1.08	1.03	0.99-1.07	0.10
Age (years)	66.4	61.3-70.8	66.3	62.0-71.8	0.71
PSA (ng/ml)	5.3	3.5-7.4	6.0	4.3-7.8	0.004*
Total cores	10	8-12	10	8-12	0.70
PSA-DT (years)	***Number***	**%**	***Number***	**%**	0.03*
Negative	269	45.3	55	33.7	
0-3	132	22.2	49	30.1	
3-10	133	22.4	42	25.8	
>10	60	10.1	17	10.4	
Positive cores					<0.001*
≤2	594	100	33	20.2	
≥3	0	0	130	79.8	
Gleason score					<0.001*
≤6	594	100	96	58.9	
7	0	0	62	38.0	
≥8	0	0	5	3.1	

PSA, prostate-specific antigen; PSA-DT, PSA doubling time
** significant result (p <0.05)*

Multivariate logistic regression showed a significant relation for higher PSA-D (p =0.003) and having two positive cores at diagnosis instead of one (p =0.002) with eventual risk reclassification. Age, PSA value, clinical stage and total number of biopsy cores showed no association with unfavorable outcome on repeat biopsy. Adding PSA-DT to the multivariate model, showed a significant association of PSA-DT values <3 years with risk reclassification (p =0.015), while unabated significant results for PSA-D and number of positive cores remained (table 3).

Table 4 describes the association between patient characteristics and reclassification to higher risk, stratified by the different unfavorable outcome measures on repeat biopsy (more than two positive biopsy cores, Gleason score >6, or both conditions).

DISCUSSION

Current results show a higher risk of reclassification to more aggressive disease on repeat biopsy in 21.5% of men after a median follow-up of 1 year within a protocol-based

Table 3 | Multivariate analysis of association between patient characteristics and risk reclassification on repeat biopsy

	Baseline characteristics		Baseline characteristics and PSA-DT at repeat biopsy	
	OR (95% CI)	***p value***	***OR (95% CI)***	***p value***
Age at diagnosis	1.0 (0.98-1.04)	0.39	1.0 (0.98-1.04)	0.46
PSA	0.9 (0.82-1.02)	0.10	0.9 (0.82-1.03)	0.14
PSA-D†	2.1 (1.29-3.42)	0.003*	2.1 (1.29-3.46)	0.003*
Clinical stage				
≤T1c	**	**	**	**
T2	1.1 (0.68-1.76)	0.72	1.1 (0.71-1.86)	0.59
Total biopsy cores	1.0 (0.93-1.08)	0.95	1.0 (0.93-1.09)	0.88
Positive cores				
1	**	**	**	**
2	1.8 (1.25-2.62)	0.002*	1.8 (1.21-2.54)	0.003*
PSA-DT				
negative / >10 yr		-	**	**
3-10 yr			1.4 (0.92-2.23)	0.11
<3 yr			1.7 (1.11-2.61)	0.015*

PSA-DT, PSA doubling time; OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen; PSA-D, PSA density (PSA/prostate volume)

† OR for PSA-D is reported per 0.10 units increase

** significant result (p <0.05)*

*** reference group*

AS setting. It was demonstrated that a higher PSA-D and having 2 positive biopsy cores instead of 1 at diagnosis are significant, independent predictors of adverse histological features on repeat biopsy. A short PSA-DT at the time of repeat biopsy is also associated with adverse characteristics. Subdividing possible unfavorable outcomes showed PSA-D to be predictive for a Gleason score >6, as well as for more than two positive cores on repeat biopsy.

Several AS studies are being conducted [7, 9-12], that all use their individual protocol to monitor their patients intensively by means of PSA testing, physical examination and repeat biopsies. These strict follow-up schedules aim to evaluate potential reclassification to higher risk disease (i.e. based on repeat biopsy, revealing more aggressive characteristics that make understaging and/or undergrading at diagnosis most likely) or evidence of true disease progression, for which active therapy is recommended to preserve the window of opportunity for cure.

However, there are no validated criteria for the inclusion and follow-up for expectantly managed patients with low-risk PCa. This study aimed to shed light on the risk stratifica-

Table 4 | Association of patient characteristics with risk reclassification subdivided by: >2 positive biopsy cores, Gleason score >6 or both on repeat biopsy

	>2 positive cores (N=130)		GS >6 (N=67)		>2 cores and GS >6 (N=34)	
	OR (95% CI)	***p value***	***OR (95% CI)***	***p value***	***OR (95% CI)***	***p value***
Age at diagnosis	1.0 (0.98-1.05)	0.41	1.0 (0.99-1.07)	0.21	1.1 (1.00-1.11)	0.08
PSA	0.9 (0.80-1.02)	0.11	0.9 (0.78-1.08)	0.31	0.9 (0.69-1.07)	0.17
PSA-D†	1.9 (1.10-3.17)	0.02*	2.5 (1.24-5.08)	0.01*	2.4 (0.93-6.11)	0.07
Clinical stage						
≤T1c	**	**	**	**	**	**
T2	1.4 (0.83-2.27)	0.23	1.1 (0.55-2.14)	0.82	1.8 (0.88-4.01)	0.17
Total biopsy cores	1.0 (0.95-1.12)	0.42	1.0 (0.87-1.08)	0.57	1.0 (0.89-1.19)	0.71
Positive cores						
1	**	**	**	**	**	**
2	1.8 (1.23-2.73)	0.003*	1.2 (0.73-2.14)	0.43	1.3 (0.61-2.60)	0.54
PSA-DT						
negative / >10 yr	**	**	**	**	**	**
3-10 yr	1.6 (0.99-2.55)	0.054	1.1 (0.59-2.20)	0.69	1.5 (0.65-3.38)	0.35
<3 yr	1.5 (0.92-2.36)	0.11	1.6 (0.87-2.87)	0.14	1.1 (0.44-2.57)	0.89

GS, Gleason score; OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen; PSA-D, PSA density (PSA/prostate volume); PSA-DT, PSA doubling time

† OR for PSA-D is reported per 0.10 units increase

** significant result (p <0.05)*

*** reference group*

tion of patients on AS, regarding the likelihood of reclassification to more aggressive disease on repeat biopsy.

A study by Berglund et al. [13] showed 27% (28 of 104) unfavorable results (defined as any Gleason pattern >4, more than three positive biopsy cores, or >50% core involvement) on repeat biopsy, performed in men suitable for AS within 3 months after diagnosis. Compared to our results, the amount of reclassification in both studies is comparable, irrespective of whether biopsies were performed after 3 months or after 1 year. This strengthens the idea of misclassification of risk at diagnosis instead of real upgrading and/or upstaging of the tumor as a result of biological progression during follow-up.

Several other studies have described reclassification rates, varying from 18% to 55% of cases [8, 13-22]. Inclusion criteria and duration of follow-up, as well as the exact definition of adverse histological features on repeat biopsy varied between studies (table 5). The association between repeat biopsy results and clinical baseline and follow-up characteristics reported in these papers are also defined in the table.

Table 5 | Overview of studies assessing the association between clinical characteristics at baseline and during follow-up with unfavourable repeat biopsy results

Study	N	Median follow-up, years	Inclusion criteria	Reclassification criteria	% reclassification (N)	Baseline predictors for reclassification	Follow-up predictors for reclassification
Kotb et al. 2010 [14]	101	5.1 (mean)	Not defined	GS ≤6 to GS ≥7, any new GS ≥4	18 (18/101)	PSA-D >0.15ng/ml/ml	
Ventikaraman et al. 2007 [15]	119	1.7	T1/2a, PSA <15ng/ml, GS ≤3+4, ≤50% positive cores	GS ≤6 to GS ≥7, primary GS ≥4, >50% positive cores	28 (33/119)	PSA-D, % positive cores	
Whitson et al. 2011 [16]	241	0.8	T1/2, PSA <10ng/ml, GS ≤6, ≤33% positive cores (min. 6), ≤50% invasion any core	GS ≥7, >33% positive cores, >50% invasion any core	23 (55/241)	Age, prostate volume	
San Francisco et al. 2011 [17]	120	2.4	T1c/2a, GS ≤6, ≤2 positive cores, ≤50% invasion any core	GS ≥7, >2 positive cores, >50% invasion any core	30 (36/120)	PSA-D >0.08ng/ml/ml, family history	PSA-V
Tseng et al. 2010 [18]	376	5.6	T1c, PSA-D <0.15ng/ml/ml, GS ≤6, ≤2 positive cores, ≤50% invasion any core	Any GS ≥4, ≥2 positive cores, >50% invasion any core	33 (123/376)	% free PSA, % invasion any core	Cancer presence and PSA-D at initial surveillance biopsy*
Adamy et al. 2011 [19]	238	1.8	T1/2, PSA <10ng/ml, any GS ≤4, ≤3 positive cores (min 10), ≤50% invasion any core, confirmatory biopsy	GS ≥7, >3 positive cores, >T2a, >50% invasion any core, PSA ≥10ng/ml**	13-26 (32-61/238)**	PSA, positive confirmatory biopsy**	
Ng et al. 2008 [20]	199	≥2	T1/2a, PSA <15ng/ml, GS ≤7, primary GS ≤3, ≤50% positive cores	GS ≤6 to GS ≥7, primary GS ≥4, >50% positive cores	27 (53/199)	PSA-D, % invasion any core	PSA-V, PSA-DT
Al Otaibi et al. 2008 [8]	92	6.3	Not defined	Primary GS ≥4, ≥T2b, ≥3 positive cores, >50% invasion any core	36 (34/92)		PSA-DT <67 months

Table 5 | Overview of studies assessing the association between clinical characteristics at baseline and during follow-up with unfavourable repeat biopsy results

Study	N	Median follow-up, years	Inclusion criteria	Reclassification criteria	% reclassification (N)	Baseline predictors for reclassification	Follow-up predictors for reclassification
Ross et al. 2010 [21]	290	2.9	PSA-D <0.15ng/ml/ml, GS ≤6, ≤2 positive cores, ≤50% invasion any core	GS ≥7, ≥3 positive cores, >50% invasion any core	35 (102/290)		PSA-V (marginally ; *P= .06)*
Isharwal et al. 2010 [22]	71	3.7	T1c, PSA-D <0.15ng/ml, GS ≤6, ≤2 positive cores, ≤50% invasion any core	GS ≥7, ≥3 positive cores, >50% invasion any core	55 (39/71)	Serum phi ratio, biopsy tissue DNA content	

GS, Gleason score; PSA, prostate specific antigen; PSA-D, PSA density; PSA-V, PSA velocity; PSA-DT, PSA doubling time

**cancer presence and PSA-D were associated with adverse histological features on subsequent surveillance biopsies*

***PSA >10ng/ml was included in the full progression criteria and excluded in the modified criteria, the highest percentage reclassification was seen using the full criteria, and only a positive confirmatory biopsy predicted for reclassification using the modified criteria*

PSA-D was repeatedly found to be significantly correlated with adverse histological findings on repeat biopsy. Kotb et al. [14] demonstrated PSA-D >0.15 ng/ml to be a significant predictor of upgrading, while San Francisco et al. [17] validated a PSA-D cut-off >0.08 ng/ml as predictor for subsequent progression. Also, PSA-D and biopsy pathologic findings have previously been shown to be predictive of insignificant PCa in the radical prostatectomy (RP) specimen [23-26]. Current results support the importance of PSA-D as a predictor for repeat biopsy outcome; however the ideal cut-off value remains to be determined. Also, it is important to realize that, because PSA does not predict for unfavorable repeat biopsy in our model, the effect of PSA-D is brought about by prostate volume. It was previously shown in RP series that smaller prostate volumes are associated with higher grade disease [27, 28]. However, recent results suggest that this observation might be biased and that the PSA performance characteristics for high grade PCa instead of true tumor biology are responsible for detection of more aggressive disease in smaller volume prostates [29]. Selection bias may also play a role in our study, because men with PSA-D values >0.2 ng/ml/ml were excluded. For PSA levels <10 ng/ml, PSA-D will only reach this threshold for prostate volumes <50ml (61% of our cohort). We therefore can not accurately differentiate with our data, whether the effect is actually based on PSA-D or solely on prostate volume. Although our results are in accordance with those of other studies, longer follow-up might better demonstrate the influence of these parameters on reclassification in the long run.

In our cohort, men with both 2 positive cores and PSA-D >0.15 have twice the risk of an unfavorable result on repeat biopsy (35%) compared with men without both features (17%); PSA-DT <3 years increases this chance even further (41%). It should be kept in mind, however, that most men will not show unfavorable results on repeat biopsy. Nevertheless, these results do facilitate risk stratification to assess the likelihood of unfavorable short-term repeat biopsy results in patients with assumed low-risk PCa managed by AS and caution is warranted in case of a combination of unfavorable characteristics.

PSA kinetics during follow-up for AS, used to predict unfavorable results either on repeat biopsy or after surgery are a frequently discussed topic in literature. Al Otaibi et al. [8, 29] found that PSA-DT <67 months was associated with an increased risk of disease progression on repeat biopsy. Local progression after RP in men on AS was found to be associated with PSA-DT in a study by Khatami et al. [30], with higher risk in those men with PSA-DT <4 years. Similar results were described by Klotz et al. [7], with an 8.5-fold increased risk of biochemical recurrence after RP in men with PSA-DT <3 years. However, other studies on PSA-DT have shown no association with subsequent adverse biopsy or RP findings [16, 21]. The current results show PSA-DT <3 years at the time of repeat biopsy to be associated with reclassification to higher risk on repeat biopsy. This finding therefore seems to support the PRIAS protocol in which men with shorter PSA-DT (3-10

years) undergo yearly repeat biopsies and men with PSA-DT <3 years are advised to undergo deferred radical treatment. Although it plays no role in our AS protocol, we found PSA velocity (PSA at repeat biopsy minus PSA at diagnosis divided by elapsed time in years) also to be predictive when it was used in the model instead of PSA-DT (OR: 1.1; p =0.002). However, it is not yet known whether biopsy outcome is a valid measure to predict aggressive disease. A report on the PRIAS RP results is expected shortly and will shed more light on this topic.

The rationale for AS is to select men with low-risk disease by means of favorable characteristics at diagnosis to subsequently prevent or delay invasive treatment with its possible side-effects. At least a quarter of patients with screen-detected PCa (prevalence screen) are eligible for AS according to PRIAS criteria [31]. However, some patients who are apparently at favorable risk, harbour more aggressive disease, which therefore justifies intensive monitoring to offer deferred treatment in a still curable stage if necessary. Reclassification of risk is not a rare phenomenon and repeat biopsies are an important part of follow-up protocols in AS to check for correct classification of disease and monitor for potential reclassification over time. Although postponing a repeat biopsy until after 1 year is not likely to cause progression of disease beyond curability, it seems advisable to offer repeat biopsy in an early stage to confirm eligibility, especially in men with a combination of characteristics predicting increased chance of risk reclassification. Our protocol recommends performing volume-based biopsies to reduce sampling errors and provide good risk assessment. Data on tumor involvement per biopsy core could provide additional information on the probability of insignificant PCa, but are not systematically recorded in this study to prevent reduction in general feasibility and participation in our protocol that is used in many different centres worldwide. Predominantly due to the lack of long-term outcome, the present study is inadequate to indicate an improved repeat biopsy scheme.

CONCLUSION

This study showed that routinely performing 1-year repeat biopsies in an AS cohort results in risk reclassification towards higher risk in 21.5% of men. Clinical features at baseline and during follow-up in men with apparently low-risk PCa can significantly predict short-term unfavorable repeat biopsy results. These variables can potentially be used for better selection and risk stratification of men on AS programs to either reassure them or to subject them to early repeat biopsy and curative intervention if necessary. Longer follow-up results from AS studies are essential for further improvement of criteria for inclusion and follow-up.

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9 Radical prostatectomy for low-risk prostate cancer following initial active surveillance: results from a prospective observational study

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ABSTRACT

Background

Little is known about the outcome of radical prostatectomy (RP) in men initially followed on active surveillance (AS) for low-risk prostate cancer (PCa).

Objective

Evaluate pathology findings after RP in our prospective AS cohort.

Design, Setting and Participants

All men participated in the Prostate Cancer Research International: Active Surveillance (PRIAS) study. Eligible men were initially diagnosed with low-risk PCa (clinical stage ≤T2, prostate-specific antigen [PSA] ≤10 ng/ml, PSA density <0.2 ng/ml/ml, one or two positive biopsy cores and Gleason score ≤6) and underwent RP between December 2006 and July 2011. The study protocol recommends RP in case of risk reclassification on repeat biopsy (Gleason score >6 and/or more than two positive cores) or a PSA doubling-time ≤3 years.

Measurements

Descriptive statistics were used to report on pathology findings for staging and grading.

Results and Limitations

Pathology results were available in 167 out of 189 RP cases (88.4%). Median time to RP was 1.3 years (25-75p: 1.1-1.9 years). Protocol-based recommendations led to deferred RP in 143 men (75.7%); 24 men (12.7%) switched because of anxiety and 22 men (11.6%) had other reasons. Pathology results showed 134 (80.8%) organ-confined cases and 32 (19.2%) cases with extracapsular extension. Gleason score of ≤6, 3+4, 4+3, and 8 were found in 79 (47.3%), 64 (38.3%), 21 (12.6%), and 3 (1.8%) cases, respectively. Unfavorable RP results (pT3-4 and/or Gleason score ≥4+3) were found in 49 patients (29%), of whom 33 (67%) had a biopsy-related reason for deferred RP.

Conclusions

RP results in men initially followed on AS show organ-confined disease and favorable Gleason grading in a majority of cases. Most men in our cohort had a protocol-based reason to switch to deferred RP. A main focus for AS protocols should be to improve the selection of patients at time of inclusion to minimize reclassification of risk and preserve the chance for curative treatment if indicated.

INTRODUCTION

The use of active surveillance (AS) as a treatment option for low-risk prostate cancer (PCa) is increasing in response to high rates of overdiagnosis in the contemporary prostate-specific antigen (PSA) era. AS protocols aim to select patients with favorable disease characteristics by applying strict criteria for inclusion and follow-up. Systematical monitoring of these men serves to provide timely identification of any risk reclassification or disease progression, so that radical treatment can be applied within the window of curability to those who need it and AS can be continued in those with persisting low-risk features. However, in the absence of markers selectively differentiating low-risk from significant disease, it remains challenging to exclusively select those men in whom PCa will never lead to symptoms, let alone death, which has led to a variation of criteria for eligibility and risk reclassification or disease progression in different AS studies [1-6]. In addition to tumor characteristics, competing risks for mortality should be considered when deciding on the best treatment for a patient [7]. Because AS is a fairly new treatment strategy, relatively few studies have long-term results available and criteria for inclusion and follow-up have not yet been validated.

Prevention of overtreatment by AS protocols should not be at the cost of potentially preventable unfavorable outcomes which can lead to poor prognosis in the case of delayed radical therapy. However, so far little is known about the outcome of radical prostatectomy (RP) in men initially followed on AS for low-risk PCa. To get better insight into the effectiveness of protocol-based active therapy recommendations and into the nature of the disease at RP after initial AS, we evaluated the reasons for deferred treatment and reported on the pathological outcome in patients who underwent RP in our prospective AS cohort.

METHODS

The Prostate Cancer Research International: Active Surveillance (PRIAS) study offers an AS protocol that is being used by urologists worldwide via a web-based instrument [8]. Eligible men were initially diagnosed with low-risk PCa (clinical stage $\leq$T2, PSA $\leq$10 ng/ml, PSA density <0.2 ng/ml/ml, one or two positive biopsy cores and Gleason score $\leq$6). PSA was measured 3-monthly and volume-based (<40ml, 8 cores; 40-60ml, 10 cores; >60ml, 12 cores) repeat biopsies were applied according to protocol (at least after 1, 4 and 7 years). Deferred radical treatment was advised in case of risk reclassification towards higher risk on repeat biopsy (Gleason score $\geq$7 or $\geq$3 positive biopsy cores) or a PSA doubling time (PSA-DT) $\leq$3 years. PSA-DT was calculated by plotting the base 2 logarithm of the PSA-value against the time since diagnosis; the DT can be calculated as the reciprocal

value of the slope of the regression line through these points. The PSA-DT was used for recommendation only after a minimum of 4 follow-up visits (i.e. the first protocol-based recommendation to switch to active treatment normally was after 1 year of follow-up). Men who underwent RP between December 2006 and July 2011 were eligible for this study. The reason for switching to RP was recorded on the PRIAS website [8]. Information on pathology findings on T stage, lymph node status, Gleason score, and surgical margins was requested from the attending physicians. A favorable RP result was defined as pT stage <2 and Gleason score <3+4; unfavorable disease was defined as pT stage 3-4 and/or Gleason score >4+3 [9, 10]. An observational descriptive analysis was performed to summarize data and to report absolute numbers, proportions and median values. Statistical analyses were performed using SPSS v.17.0 statistical software (IBM Corp, Armonk, NY, USA).

RESULTS

Of 2079 men that were included in PRIAS up to July 2011, 446 men (22%) underwent deferred treatment, of which 189 men (42%) underwent RP. Pathology results were available in 167 men (88.4%). Median follow-up for patients who remained on AS was 1.6 years (25-75p: 0.8-2.8 years). Median time to RP was 1.3 years (25-75p: 1.1-1.8 years) after diagnosis. Table 1 shows the clinical characteristics at time of diagnosis.

Table 1 | Baseline cohort characteristics (N=189)

Parameter	Median	25-75th percentile
Age, years	63.2	59.6 - 67.2
PSA ng/ml	5.8	4.8 - 7.1
Prostate volume, ml	41	34 - 59
PSA density, ng/ml/ml	0.14	0.10 - 0.17
Number of cores	10	8 - 12
	Number	**%**
Clinical T stage		
- T1C	162	85.7
- T2A	27	14.3
Number of positive cores		
- 1	118	62.4
- 2	71	37.6
Gleason score		
- lower than 6	19	10.1
- 6	170	89.9

PSA, prostate-specific antigen

Table 2 | Reason for deferred radical prostatectomy (N=189)

	Number	%	Time to surgery in years (25-75th percentile)
Protocol recommendation	143	75.7	1.3 (1.2 - 1.9)
Anxiety	24	12.7	0.7 (0.5 - 1.3)
Other*	22	11.6	1.0 (0.6 - 2.2)

**other reasons included; increase in PSA, increase in lower urinary tract symptoms, patient's desire and unknown reasons*

Table 3 | Radical prostatectomy results after initial active surveillance (N=167)

Parameter	**Median**	**25-75th percentile**
Time to surgery, years	1.3	1.1 – 1.8
	Number	**%**
Pathological T stage		
- HG-PIN	**1**	**0.6**
- All T2	**134**	**80.2**
- T2	6	3.6
- T2A	17	10.2
- T2B	13	7.9
- T2C	98	59.8
- All T3	**30**	**18.0**
- T3	7	4.2
- T3A	20	12.0
- T3B	3	1.8
- T4A	**2**	**1.2**
Gleason score		
- ≤3+3 = 6	79	47.3
- 3+4 = 7	64	38.3
- 4+3 = 7	21	12.6
- 8	3	1.8
Margin status		
- Negative	123	75.5
- Positive	40	24.5
of which T2	25	18.9
of which T3-4	15	51.6
Positive lymph nodes*	0	0
RP outcome**		
- Favourable	118	70.7
- Unfavourable	49	29.3

HG-PIN, high-grade prostatic intraepithelial neoplasia; RP, radical prostatectomy
** negative lymph nodes (N0) were reported in 45 cases, while an NX status was reported in 122 cases ** favourable outcome was defined as pT stage ≤2 and Gleason score ≤3+4; unfavourable outcome was defined as pT stage 3-4 and/or Gleason score ≥4+3*

Protocol-based recommendations led to deferred RP in 143 men (75.7%); 24 men (12.7%) switched because of anxiety and 22 men (11.6%) had other reasons (table 2). Pathology results showed 134 (80.8%) organ-confined cases and 32 (19.2%) cases with extracapsular extension. Gleason score of ≤6, 3+4, 4+3, and 8 were found in 79 (47.3%), 64 (38.3%), 21 (12.6%), and 3 (1.8%) cases, respectively (table 3). The latter group consisted of 2 patients with Gleason score 3+5 and 1 with Gleason score 5+3. Upgrading in the RP specimen compared to the last (repeat) biopsy was seen in 31%, while downgrading was present in 8%; 61% had an unchanged Gleason score (table 4). Negative lymph nodes were reported in 45 patients, while an NX status was reported in 122 cases.

Table 4 | Gleason score on last (repeat) biopsy compared to Gleason score on final pathology (N=167)

	Gleason score on RP				
Gleason score on last (repeat) biopsy*	**No PC**	**≤6**	**3+4**	**4+3**	**8**
No PCa	1	4		2	
≤6		67	32	7	2
3+4		7	28	4	1
4+3			2	7	
8			1	1	
9			1		

RP, radical prostatectomy; PCa, prostate cancer
** in 137 patients at least 1 repeat biopsy was taken, in 30 patients the biopsy at diagnosis was the last*

Unfavorable RP results (pT3-4 and/or Gleason score ≥4+3) were found in 49 patients (29%). Forty (82%) of these patients had a protocol-based reason for deferred RP; in 33 (67%) cases the reason was biopsy-related. Of the 118 cases (71%) with favorable RP results (pT2 and Gleason score ≤3+4), 88 (75%) had been given a protocol-based advice to undergo radical treatment. The number of favorable and unfavorable RP results per protocol-based reason is shown in table 5. Having more than three positive biopsy cores was the most frequent trigger to switch to RP while a combination of both biopsy-related features shows the highest percentage (52%) of unfavorable outcomes. In patients in whom anxiety was the trigger for RP, only 1 out of 17 (6%) had an unfavorable RP result. Pathology results for patients with biopsy-based indications for RP are shown again separately in table 6; the proportion of favorable and unfavorable RP outcomes in this subgroup was (71 of 104) 68.8% vs. (33 of 104) 31.7%, respectively.

Table 5 | Number of men with protocol-based reasons to switch to deferred radical prostatectomy with either favourable or unfavourable results

		Favorable RP outcome (N = 118) (pT2 and Gleason score ≤3+4)			**Unfavorable RP outcome (N = 49)** (pT3-4 and/or Gleason score ≥4+3)		
Protocol-based reason to switch to deferred RP†	**N**	**N**	**% of reason for RP**	**% of favourable RP outcome**	**N**	**% of reason for RP**	**% of unfavourable RP outcome**
Any protocol-based reason	128	88	69	75	40	31	82
1.) Only Gleason score ≥7 on repeat biopsy	23	18	78	15	5	22	10
2.) Only ≥3 positive cores on repeat biopsy	35	27	77	23	8	23	16
3.) Only PSA-DT ≤3yrs*	24	17	71	14	7	29	14
Combination 1 + 2	21	10	48	8	11	52	22
Combination 1 + 3	4	2	50	2	2	50	4
Combination 2 + 3	17	12	71	10	5	29	10
Combination 1 + 2 + 3	4	2	50	2	2	50	4

RP; radical prostatectomy; PSA-DT, prostate-specific antigen doubling time

† includes patients with the particular protocol-based reason in the absence of any other reason

** PSA-DT was used for recommendations only after a minimum of 4 follow-up visits*

Table 6 | Radical prostatectomy results after initial active surveillance and any biopsy-based reason for surgery (N=104)

Parameter	Median	25-75th percentile
Time to surgery, years	1.3	1.1 – 1.6
	Number	**%**
Pathological T stage		
- All T2	**81**	**77.9**
- T2	3	2.9
- T2A	9	8.7
- T2B	8	7.7
- T2C	61	58.7
- All T3	**22**	**21.2**
- T3	5	4.8
- T3A	16	15.4
- T3B	1	1.0
- T4A	**1**	**1.0**
Gleason score		
- ≤3+3 = 6	36	34.6
- 3+4 = 7	53	51.0
- 4+3 = 7	13	12.5
- 8	2	1.9
Margin status		
- Negative	73	73.7
- Positive	26	26.3
of which T2	15	18.5
of which T3-4	11	47.8
Positive lymph nodes*	0	0
RP outcome		
- Favourable	71	68.3
- Unfavourable	33	31.7

RP; radical prostatectomy
** negative lymph nodes (N0) were reported in 38 cases, while an NX status was reported in 66 cases*
*** favourable outcome was defined as pT stage ≤2 and Gleason score ≤3+4; unfavourable outcome was defined as pT stage 3-4 and/or Gleason score ≥4+3*

DISCUSSION

AS is emerging as a treatment option for low-risk PCa, but becauseof relatively short follow-up little is known about the outcome of RP after initially being followed on AS. In the present analysis we report on the largest prospective cohort of men receiving RP af-

ter initial AS. It was shown that most men switch to RP on the basis of the protocol. Most of their pathology results show organ-confined disease and favorable Gleason grading.

Regarding the short amount of time from diagnosis to surgery in the current study (median 1.3 years) and the slow growing nature of PCa, true disease progression is less likely than actual reclassification of risk due to understaging and/or undergrading at diagnosis. It is the basic principle of AS that patients with more aggressive disease will eventually be selected to undergo treatment. Timely identification of risk reclassification could attenuate the risk of a potentially worsened prognosis resulting from a delay in curative therapy. Early repeat biopsy potentially could have decreased the amount of unfavorable RP outcomes in this cohort by up to 67%, because 33 out of 49 patients with unfavorable disease had a biopsy-related reason to undergo RP. Thus, it is important to improve the selection of patients by means of extended biopsy schemes, immediate repeat biopsy, or risk stratification to prevent patients from being included in an AS program when they are probably better off receiving immediate treatment. Future studies on new biomarkers [11] will hopefully add to the selective identification of suitable patients.

One of the main questions in evaluating AS as a treatment strategy is what price has to be paid for delaying or avoiding radical treatment. In an attempt to address this issue, several previous studies examined oncologic outcomes in RP series comparing delayed to immediate therapy in men with low-risk features at diagnosis, which did not lead to significant differences in outcome between both cohorts in most series.

Dall'Era et al. [12] reported no difference in Gleason upgrading, positive surgical margins (PSM) or ECE between men undergoing primary RP and a surveillance cohort. Van den Bergh et al. [13] found similar results as well as comparable tumor volume and biochemical recurrence (BCR) rates in a similar setting. Warlick et al. [14] also showed that a >75% risk of 'non-curable' cancer was not significantly different for delayed and immediate intervention groups. Accordingly, in a Swedish study [15] among low- and intermediate-risk patients no difference was observed for any 1 or more of 3 adverse pathology features of Gleason score upgrading, positive PSM and ECE. Furthermore, two studies [16, 17] found no effect of treatment delay on biochemical progression rates in an RP cohort receiving surgery within 1 year after diagnosis. Also, a nationwide cohort study in the United States showed similar rates for PCa mortality among men with low-risk disease who opted for deferred treatment and those who were initially treated [18].

Conflicting results have been reported by others who showed increased rates of PSA progression [19, 20] and Gleason score upgrading in low-risk patients undergoing deferred therapy before or after 6 months, while no difference was found for ECE, PSM and positive lymph nodes [19]. However, both studies identified low-risk patients according

to the D'Amico classification, which results in less strict criteria to define low-risk disease than those used in most contemporary AS studies.

Although the aforementioned studies attempt to throw light on the risk of applying AS, it should be kept in mind that selection bias in the deferred treatment groups is very likely because reasons for switching from AS to active treatment often include signs of risk reclassification (e.g. on repeat biopsy). Another downside of these studies is their retrospective and non-randomized nature. To be able to evaluate whether a delay in treatment after risk reclassification or true disease progression will compromise cure, prospective randomised trials comparing AS to radical treatment are essential, but not yet available [21].

Other studies have evaluated the pathological RP outcomes of men who would have been eligible for AS [22-26]. Rates of upgrading in these studies varied between 21-36% with Gleason score 8-10 in 3-4%, ECE was found in 5-19%, PSA progression in 11-23% and PSM in 14-35%. These results show that a considerable amount of men who are thought to have low-risk PCa according to clinical features at diagnosis, harbor more aggressive disease on RP.

Compared to these immediate RP series in patients with AS suitable clinical features, the rate of unfavorable characteristics in RP specimens of this AS cohort might be considered relatively high. Again, this might be explained by the self-selection of men who start on AS and receive RP because of reclassification to higher risk during follow-up, which leaves the true low-risk patients undisturbed and singles out men at higher risk and worse prognosis among those selected for AS to undergo RP. It can also be argued that the follow-up protocol in this study is able to ensure that those with aggressive disease are not left untreated. This is also illustrated by the observation that all protocol-based reasons led to relatively high rates of unfavorable RP outcomes (table 5), especially when compared to the rate in patients switching to RP based on anxiety (1 of 17; 6%). Moreover, the majority of this cohort had a favorable RP outcome and as the number of unfavorable outcomes is only 3% of the original AS population which is still being followed on AS it still seems to be acceptable compared with upfront RP in all patients.

Prospective data on RP results after initial AS is scarce. Khatami et al. [27] presented the RP results of 70 patients who had initially been managed expectantly. They found upgrading in 21%, organ-confined disease in 86%, and PSM in 23%. PSA-DT was the only predictive factor of PSA relapse in their study, with no PSA relapses in cases with PSA-DT >4 years after a median follow-up of 63 months. However, inclusion and follow-up of patients in this cohort was not executed according to a strict AS protocol. Seiler et al. [28] reported 79% organ-confined cases, 56% Gleason score >6 and 31% PSM in

61 cases. They found more favorable results in patients fulfilling the Epstein criteria [29] for low-risk disease. In another study by Duffield et al. [30] a total of 48 RP cases after AS and progression on biopsy were evaluated. Mean time to RP was 29.5 months; organ-confined disease was present in 65%, of which 52% was Gleason score 6. Potentially clinically insignificant tumors (according to Epstein [29]) were found in 27%, while 71% showed at least one of the criteria of ECE, any Gleason score 4 or tumor volume >1 cm^3. Although no tumor volume was available in our study, we found a comparable rate of 28% with no ECE and no Gleason score 4 for the group with biopsy-related reasons for RP and even 41% for the complete cohort. This result indicates that at least a portion of these men was overtreated, but we would rather stay on the safe side as opposed to not treating men with higher risk disease. It should also be kept in mind that a vast majority of the total AS cohort has not received any treatment until now, contributing to the aim of AS: minimizing overtreatment.

Limitations of this study include the heterogeneity in medical centres participating in PRIAS and their surgery experience, which might also be reflected by the relatively high rate of PSM. It can be argued that this is more of a true reflection of PSM rates than those presented in most high-volume centres though. Furthermore, interobserver variations in pathologic diagnosis might have slightly affected pathologic outcomes, and data on tumor volume and localisation was not routinely reported. Because follow-up for prospective AS cohorts is still limited, adverse pathological features are often used as surrogate markers which do not necessarily translate to poorer outcomes instead of hard endpoints such as metastatic disease and PCa-specific death. Follow-up after RP in this cohort was too short to report clinically relevant details on BCR, metastatic disease and PCa death. Longer follow-up will provide essential insight into these outcome measures.

CONCLUSION

Pathology results in men who were initially followed with AS show organ-confined disease and favorable Gleason grading in a majority of cases; however, the amount of unfavorable outcomes could not be neglected. Therefore, it remains an important focus for AS protocols to improve the selection of patients at the time of inclusion to minimize reclassification of risk during follow-up; early repeat biopsy in this cohort could have identified up to 67% of the unfavorable PCa cases. Until biomarkers become available that reliably predict significant disease, strict follow-up of men on AS with repeated PSA tests and regular repeat biopsies is warranted to preserve the chance for curative treatment if indicated and to avoid side-effects of invasive treatment in those with persisting low-risk features.

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10 Active surveillance for low-risk prostate cancer worldwide: the PRIAS study

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ABSTRACT

Background

Overdiagnosis and subsequent overtreatment are important side-effects of screening and early detection of prostate cancer (PCa). Active surveillance (AS) is of growing interest as an alternative to radical treatment for low-risk PCa.

Objective

To update our experience in the largest worldwide prospective AS cohort.

Design, Setting and Participants

Eligible patients had clinical stage T1/T2 PCa, prostate-specific antigen (PSA) $\leq$ 10ng/ml, PSA density <0.2 ng/ml/ml, one or two positive biopsy cores and Gleason score $\leq$6. PSA was measured every 3-6 months and volume-based repeat biopsies were scheduled after 1, 4 and 7 years. Reclassification was defined as more than two positive cores or Gleason >6 at repeat biopsy. Recommendation for treatment was triggered in case of PSA doubling time <3 year or reclassification.

Outcome measurements and Statistical Analysis

Multivariate regression analysis was used to evaluate predictors for reclassification at repeat biopsy. Active therapy-free survival (ATFS) was assessed with a Kaplan-Meier analysis and Cox regression was used to evaluate association of clinical characteristics with active therapy over time.

Results and Limitations

In total, 2494 patients were included and followed for median 1.6 year. One or more repeat biopsies were performed in 1480 men, of whom 415 (28%) showed reclassification. Compliance with the first repeat biopsy was estimated to be 81%. During follow-up 527 (21.1%) patients underwent active therapy. ATFS at 2-year was 77.3%. Strongest predictors for reclassification and switching to deferred treatment were the number of positive cores (2 cores compared with one core) and PSA density. The disease-specific survival rate was 100%. Follow-up was too short to draw definitive conclusions about the safety of AS.

Conclusions

Our short-term data support AS as a feasible strategy to reduce overtreatment. Clinical characteristics and PSA kinetics during follow-up can be used for risk stratification. Strict monitoring is even more essential in men with high risk features to enable timely recognition of potentially aggressive disease and offer curative intervention. Limitations of using surrogate endpoints and markers in AS should be recognized.

INTRODUCTION

Prostate cancer (PCa) affects many men worldwide with over 900.000 diagnoses and over 258.000 deaths of the disease in 2008 [1]. Studies on PCa screening have shown a positive effect of screening with a reduction in disease-specific mortality of up to 21-30% [2, 3]. However, due to the increasing use of prostate-specific antigen (PSA) over the last two to three decades, the proportion of low-risk tumors in which early detection and treatment will not change prognosis has been rising [4]. Treatment of these so-called overdiagnosed cases will inevitably lead to overtreatment and its potential side-effects, thereby negatively impacting the patient's quality of life.

Over the last decade, active surveillance (AS) has evolved as an alternative to radical treatment of low-risk PCa. It focuses on the prevention of overtreatment by selecting patients with low-risk disease features and by strictly monitoring them over time to recognize any potential risk reclassification that would justify deferred radical treatment, still with curative intent. Several AS studies have been initiated worldwide, that show quite similar and favorable outcomes. However, follow-up in the majority of cohorts is still short and prospective validation of criteria for selecting low-risk disease therefore is still lacking. In 2006 the Prostate Cancer Research International: Active Surveillance (PRIAS) study was initiated to counteract overtreatment and contribute to prospective data collection. PRIAS aims to reflect daily practice by collecting data from affiliated centres worldwide using a web-based decision tool and PRIAS protocol. The first data on this study was reported on the first 500 patients in 2009 [5]. This study represents an update of our experience with nearly 2500 patients.

METHODS

The PRIAS study started including patients in December 2006 and recruitment is still ongoing. Over 100 medical centres in 17 countries worldwide contribute to the collection of data using a web-based tool for entering information on patients' baseline and follow-up characteristics (www.prias-project.org). This report is updated until May 2012. Eligible patients fulfilled the PRIAS inclusion criteria for low-risk PCa: clinical stage T1c/T2, PSA <10 ng/ml, PSA density (PSA-D) <0.2 ng/ml/ml, one or two positive biopsy cores, and Gleason score <6. The follow-up protocol scheduled PSA measurements every 3 months for the first two year and PSA measurements every 6 months thereafter. Repeat biopsies were scheduled after 1, 4 and 7 year, and in case of a PSA doubling time (PSA-DT) between 3 year and 10 year, yearly repeat biopsies were advised. Volume-dependent biopsies were recommended according to protocol (prostate volume <40cc: 8 biopsy-cores, 40-60cc: 10 biopsy-cores, and >60cc: 12 biopsy-cores). Risk reclassification at

repeat biopsy triggered a recommendation for active treatment and was defined as 3 or more positive biopsy cores and/or Gleason score >6. PSA-DT was calculated by plotting the base 2 logarithm of the PSA value against time since diagnosis; the doubling time can be calculated as the reciprocal value of the slope of the regression lines through these points. PSA-DT <3 year was used as a recommendation to trigger intervention only after a minimum of four follow-up visits (i.e. after 1 year of follow-up). Baseline clinical characteristics (age at diagnosis, PSA, PSA-D, clinical T stage, number of biopsy cores and number of cores positive), and PSA-DT at the time of repeat biopsy were analysed in a multivariate logistic regression with respect to reclassification at repeat biopsy. PSA-D was calculated as PSA divided by total prostate volume. The odds ratio for PSA-D was reported per 0.10 units increase to facilitate clinical interpretation. Because of small numbers, clinical stage T2 was not further subdivided into specific categories. Kaplan-Meier analysis was used to evaluate active therapy-free survival (ATFS) over time. In addition, time to active treatment was examined with Cox regression analysis to evaluate baseline characteristics associated with switching to deferred therapy. To evaluate longer follow-up in our cohort, we selected a subgroup of patients who had been diagnosed at least 2.5 year before last follow-up (May 2012) and had been fol-

Table 1 | Participating countries in the PRIAS study

Country	**N (%)**
Netherlands	1129 (45.3)
Italy	364 (14.6)
Finland	288 (11.5)
Japan	243 (9.7)
Germany	110 (4.4)
France	93 (3.7)
Canada	87 (3.5)
Sweden	57 (2.3)
Spain	46 (1.8)
Australia	36 (1.4)
Norway	17 (0.7)
Czech Republic	12 (0.5)
Austria	8 (0.3)
Switzerland	2 (0.1)
Turkey	1 (0.04)
Belgium	1 (0.04)
New-Zealand	0*
Total	**2494 (100)**

**Only recently joined PRIAS*

lowed on AS for at least 6 months. Clinical T stage (T1c or T2) and PSA-DT (negative and >10 year, 3-10 year, <3 year) were stratified into groups; other characteristics were used as continuous variables. P values were calculated using the Mann-Whitney U test (continuous variables) and the Chi-square test (categorical variables). Statistical analyses were performed using SPSS statistical software v.17.0. (IBM Corp., Armonk, NY, USA). All statistical tests were 2-sided with p <0.05 considered to be statistically significant.

RESULTS

Up to May 2012, 2494 men (median age 65.8 year) meeting all inclusion criteria were included in PRIAS. The distribution across participating countries is shown in table 1. Median follow-up for the overall cohort was 1.6 year (25-75p: 1.0-2.8 year). Baseline characteristics of the study group are shown in table 2.

A total of 1858 repeat biopsies were performed in 1480 men. A first repeat biopsy was done in 1480 patients (79.7%), 308 patients (16.6%) underwent a second repeat

Table 2 | Patient characteristics at baseline

	All patients (N=2494)	**No treatment (N=1967)**	**Active treatment (N=527)**	***p value***
	Median (25-75p)	*Median (25-75p)*	*Median (25-75p)*	
Age, years	65.8 (61.0-70.4)	66.0 (61.1-70.6)	64.9 (60.9-69.8)	0.09
PSA, ng/ml	5.6 (4.4-7.0)	5.5 (4.3-7.0)	5.6 (4.6-6.9)	0.51
Prostate volume, ml	44 (35-57)	45 (35-58)	41 (34-53)	<0.001
PSA-D, ng/ml/ml	0.13 (0.09-0.16)	0.12 (0.09-0.16)	0.14 (0.11-0.17)	<0.001
Number of cores	10 (8-12)	10 (8-12)	10 (8-12)	<0.001
	N (%)	*N (%)*	*N (%)*	
Clinical stage				0.09
T1	2122 (85.1)	1692 (86.0)	430 (81.6)	
T2	372 (14.9)	275 (14.0)	97 (18.4)	
T2A	*324 (87.1)*	*240 (87.3)*	*84 (86.6)*	
T2B	*34 (9.1)*	*25 (9.1)*	*9 (9.3)*	
T2C	*14 (3.8)*	*10 (3.6)*	*4 (4.1)*	
Positive cores				<0.001
1	1717 (68.8)	1404 (71.4)	313 (59.4)	
2	777 (31.2)	563 (28.6)	214 (40.6)	

PSA, prostate-specific antigen; PSA-D, PSA density

biopsy, 60 patients (3.2%) had 3 and 10 patients (0.5%) received 4 repeat biopsies. A total of 687 (37.0%) biopsies were negative for PCa, which represented 542 of the first repeat biopsies (36.6%). In total, 415 patients receiving one or more repeat biopsies (28.0%) were reclassified during follow-up; 89 patients (21.4%) demonstrated Gleason score upgrading, 212 patients (51.1%) were reclassified based on the number of positive cores and 114 patients (27.5%) had a combination of both. Median time to the first repeat biopsy was 1.1 year (25-75p: 1.0-1.3 year). Compliance with the first repeat biopsy (defined as undergoing the repeat biopsy within 1.5 year from initial diagnosis) in men followed for at least 1.5 year was found to be 81%. Of all 415 patients with an unfavorable repeat biopsy result, 305 patients (73.5%) received active treatment, whereas 110 patients (26.5%) chose to continue on AS despite protocol recommendation (of these patients, 60% were reclassified based on only number of positive cores and 40% showed upgrading).

Predictors for reclassification (i.e. Gleason score >6 and/or more than two positive cores) on the first repeat biopsy and for any reclassification on repeat biopsy during follow-up are listed in table 3. PSA-D and the number of positive cores at diagnosis

Table 3 | Multivariate analysis of possible predictors for reclassification at repeat biopsy

	First repeat biopsy (N=1480)		**All repeat biopsies (N=1858)**	
Baseline characteristics	*OR (95% CI)*	*p value*	*OR (95% CI)*	*p value*
Age at diagnosis	1.03 (1.01-1.05)	0.02*	1.02 (1.00-1.04)	0.02*
PSA	0.9 (0.82-0.95)	0.002*	0.9 (0.84-0.96)	0.002*
PSA-D†	3.0 (2.14-4.28)	<0.001*	2.5 (1.87-3.45)	<0.001*
Clinical stage				
T1C	-	-	-	-
T2	1.3 (0.92-1.80)	0.14	1.1 (0.81-1.49)	0.56
Total biopsy cores	1.0 (0.90-1.00)	0.05	1.0 (0.92-1.00)	0.07
Positive cores				
1	-	-	-	-
2	2.2 (1.67-2.81)	<0.001*	2.1 (1.69-2.69)	<0.001*
PSA-DT**				
negative or >10 yr	-	-	-	-
3-10 yr	1.3 (0.93-1.70)	0.14	1.3 (1.01-1.70)	0.04*
<3 yr	1.6 (1.20-2.25)	0.002*	1.7 (1.27-2.29)	<0.001*

OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen; PSA-D, PSA density; PSA-DT, PSA doubling time

† OR for PSA-D is reported per 0.10 units increase

** significant result (p <0.05).*

*** separate analyses were performed with PSA-DT added to the baseline characteristics; the significance of the other outcomes remained unchanged*

- reference group

were found to be the most important predictors, while age and baseline PSA value also turned out to be significantly associated with reclassification on repeat biopsy. When PSA-DT at the time of repeat biopsy was added to the analysis, values between 3 year and 10 year and, even more so, <3 year also showed an association with reclassification.

In total, 1885 patients (75.6%) continued on AS, 527 patients (21.1%) underwent active therapy, 43 patients (1.7%) were lost to follow-up, 21 patients (0.8%) have switched to watchful waiting because of increasing co-morbidity, and 18 patients (0.7%) died of causes other than PCa. The median time to active therapy was 1.2 year (25-75p: 1.0-1.6 year), while the median time free from intervention for the rest of the cohort was 1.9 year (25-75p: 1.0-3.1 year). Figure 1 shows the ATFS. The ATFS at 2-year and 4-year was 77.3% and 67.7%, respectively.

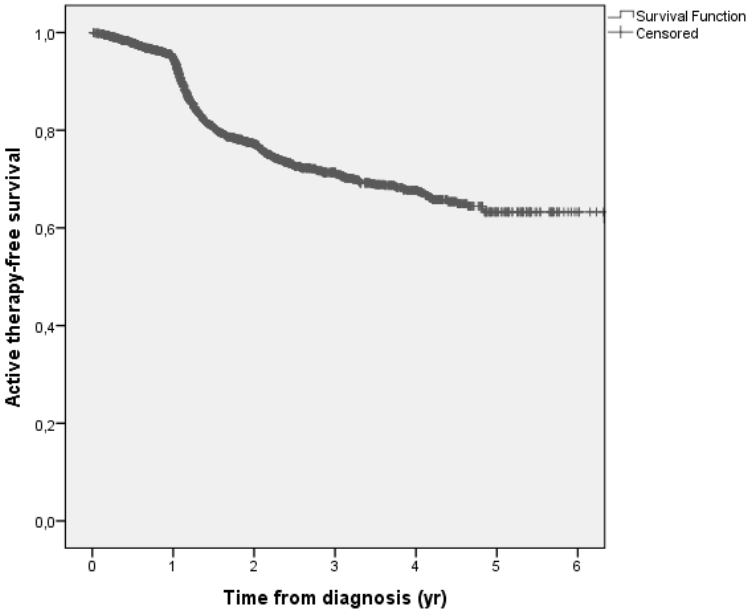

Figure 1 | Active therapy-free survival over time.

Of all men undergoing deferred treatment, 387 men (73.4%) had a protocol-based reason to do so, 47 men (8.9%) switched because of anxiety and 93 men (17.6%) had another reason, such as a solitary PSA increase, urinary symptoms or patient's preference. Of all patients with protocol-based reasons, 79% were biopsy-related whereas the remaining 21% had a PSA-DT <3 year (table 4). Cox analysis showed PSA-D, the number of positive cores (two compared with one) and the total number of cores at baseline to be predictive for the likelihood of being switched to active treatment during follow-up (table 5). The majority of patients underwent radical prostatectomy or radiotherapy as

Table 4 | Type and reason of deferred therapy in 527 treated patients

Treatment type	**N (%)**
Radical prostatectomy	253 (48.0)
Radiotherapy	238 (45.2)
Hormonal therapy	8 (1.5)
Other* or unknown therapy	28 (5.3)
Reason for treatment	
Protocol-based	387 (73.4)
Gleason score >6**	61 (15.8)
>2 positive cores	146 (37.7)
Gleason score >6 and >2 positive cores	99 (25.6)
PSA-DT <3 yr	81 (20.9)
Anxiety	47 (8.9)
Other***	93 (17.6)

**4 patients received high intensity focused ultrasound therapy*
***one patient was reclassified after review of the specimen of a prediagnostic transurethral resection of the prostate*
****other reasons comprised increase in PSA with PSA-DT >3 yr, lower urinary tract symptoms, patient's wish, and unknown reasons*

Table 5 | Association of baseline characteristics with deferred active treatment over time

Baseline characteristics	**Deferred active therapy (N=527)**	
	HR (95% CI)	*p value*
Age at diagnosis	1.0 (0.98-1.01)	0.62
PSA	1.0 (0.92-1.02)	0.22
PSA-D†	2.1 (1.68-2.70)	<0.001*
Clinical stage		
T1C	-	-
T2	1.1 (0.86-1.34)	0.55
Total biopsy cores	0.95 (0.91-0.98)	0.002*
Positive cores		
1	-	-
2	1.7 (1.43-2.04)	<0.001*

HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; PSA-D, PSA density
† HR for PSA-D is reported per 0.10 units increase
** significant result (p <0.05).*
- reference group

deferred treatment in quite evenly distributed amounts (table 4), 8 men switched to hormonal therapy, 4 men received high-intensity focused ultrasound and in 24 other men the type of final therapy was unknown. The outcomes of 167 men undergoing radical prostatectomy after initial surveillance within the study were recently published

[6]. A separate report on radiotherapy results will be the subject of a subsequent manuscript. There have been no PCa deaths in our cohort, however, 2 cases of metastatic disease were reported. The overall survival at 2-year and 4-year was 97.1% and 86.5%, respectively.

In all, 1071 patients were eligible for the evaluation of longer follow-up in our cohort. Median follow-up was 3.1 year (25-75p: 1.8-4.0 year). This subgroup showed results that were very similar to the results in the complete cohort regarding baseline characteristics, reclassification on repeat biopsy (25%), predictors for reclassification and active treatment, and ATFS at 2-year (76%) and 4-year (66%).

DISCUSSION

We report updated results from the largest prospective AS cohort for low-risk PCa that acquires data from over 100 medical centres worldwide. Our analyses show that besides age and PSA at diagnosis, both PSA-D and the number of positive cores at diagnosis (two compared with one) are important predictors for reclassification at repeat biopsy. The latter two predictors are also shown to be associated with the likelihood of switching to active therapy during follow-up. The majority of patients remained free from therapy, and it is important to note that, while 18 men died from other causes, no patients died from PCa.

As a response to increasing overdiagnosis and subsequent overtreatment, several AS studies have been initiated worldwide [7-11]. Our data are consistent with the data previously reported regarding reclassification, ATFS and favorable disease-specific outcomes [7-11]. Although follow-up in most cohorts is still relatively short, it has been shown that this alternative management strategy for carefully selected patients is associated with a disease-specific mortality of less than 3% at 10 year [7]. It was found that AS was associated with the greatest quality adjusted life expectancy when compared with active treatment of low-risk PCa [12]. These data reinforce the use of AS as an alternative to the radical treatment of favorable-risk, localized PCa. Our results for data with longer follow-up (median 3.1 year) are similar to our results with relatively short follow-up.

In our cohort, active therapy was triggered by a protocol-based reason in 73.4% of patients, the majority of these patients had biopsy-related reasons and 20.9% of the patients switched because of short PSA-DT. PSA kinetics are not used as a trigger for intervention in all AS series [9-11]. In the long-term follow-up series described by Klotz et al. [7], PSA-DT was used to identify patients for definitive therapy. Their results also showed an 8.5-fold greater risk of PSA progression after active therapy in men with a PSA-DT <3 year compared with men with longer PSA-DT, indicating the relevance of PSA-DT as a marker for more aggressive disease. However, defining the exact triggers for

deferred intervention, as well as selecting favorable-risk disease at diagnosis, remains difficult in the absence of hard endpoints such as PCa mortality. As yet, Gleason score might be one of the most important predictors for disease-specific outcome [13, 14]. However, although Gleason score 6 is considered to represent low-risk disease, it is important to note that this classification is not as clear-cut and not all patients harbouring Gleason 3+4 disease will be better off receiving radical therapy [15]. The number of positive cores used as a proxy for tumor volume as described by Stamey et al. and Epstein et al. [16, 17] is another point of debate, since the effect of tumor volume on PCa outcome has been discussed and several studies have shown no independent predictive value [18, 19]. Also, a recent study [20] showed that the PCa volume threshold for insignificant disease is 1.3 ml, which is more than twice as high as the 0.5 ml originally described by Stamey et al. [16]. This finding implies that a cut-off of 2 positive cores to define low-risk disease might be too restrictive and additional research is necessary to focus on adjusting and extending AS criteria regarding histological features of the disease without compromising the window of opportunity for cure.

In total, 27% of the cohort experienced disease reclassification at repeat biopsy during follow-up. We know that prostate biopsies are subject to misclassification, which was previously demonstrated by the levels of reclassification at repeat biopsy [21] and radical prostatectomy [6] in our AS cohort. Regarding the protracted course of PCa, especially in low-risk disease [22], this phenomenon is very likely attributable to initial misclassification instead of true disease progression. It is hoped that in the future better markers and imaging modalities, such as multiparametric resonance imaging (MRI), will contribute to more accurate staging and grading. For now, repeat biopsies are vital to either confirm favorable-risk disease or recognize potential aggressive disease in time to preserve a good prognosis. Our data show that the protocol is not always strictly followed, which resulted in skipping scheduled repeat biopsies in approximately 19% of the cases. Moreover, we found that one-quarter of patients continue on AS despite a biopsy-based recommendation for active therapy. These observations should alert treating physicians, especially in the presence of clinical characteristics predicting for adverse features and potentially aggressive disease, to urge patients to follow a strict monitoring protocol.

The strongest predictors for reclassification at repeat biopsy in our cohort were the number of positive cores and PSA-D, which correspond to a previous report we published on 757 first repeat biopsies [21]. When we evaluated Gleason score upgrading as the single outcome of unfavorable repeat biopsy, we found that these predictors, including PSA-DT <3 year, maintained their significant association (data not shown).

We found the same baseline characteristics to be associated with switching to active therapy over time. Since the number of positive cores is also a trigger for intervention, it might be expected that this factor would play a role in the likelihood of eventually

undergoing treatment in our series. On the contrary, PSA-D seems to be an important independent predictor for adverse findings, which has repeatedly been shown in other studies on histological disease progression on repeat biopsy [23-25]. Also, PSA-D was found to be predictive of insignificant PCa at radical prostatectomy [26, 27]. This observation is debated in literature: smaller prostates are associated with more aggressive disease [28, 29]; however, this observation could also be attributable to PSA performance characteristics [30]. Other factors such as BMI and ethnicity could potentially influence PCa prognosis, but data on these factors are lacking in our cohort.

Although we observed a 100% disease-specific survival, longer follow-up clearly is needed to answer the question of the impact of AS on survival, also given the relatively high overall survival rate in our cohort. We know from screening trials that even 10 year is too short to evaluate PCa mortality [2], which holds even more for patients who are considered low-risk and usually have longer life expectancies. It is hoped that with longer follow-up we will be able to improve the strategy of AS by increasing its availability in a safe way and thereby preventing, or at least delaying, overtreatment in as many patients as possible.

Ongoing research efforts must focus on improving selection for AS and early identification of occult high-risk PCa. New markers and imaging modalities such as MRI seem promising, but more work is needed to evaluate them in an AS setting. Immediate repeat biopsies, as well as template and MRI-guided biopsies might help to improve patient classification, however, an important caveat in AS remains the lack of validated measures of outcome. The indicators of risk reclassification that are currently used as a surrogate for outcome in most AS programs still require further study to which our prospective AS data can hopefully contribute with longer follow-up.

CONCLUSIONS

In an era of widespread availability of PSA-based screening, AS is of growing interest as an alternative to treatment of low-risk PCa. PRIAS is the largest observational prospective study evaluating AS worldwide and our data support AS as a feasible strategy to reduce overtreatment, at least in the short-term, without compromising curability.

Clinical characteristics and PSA kinetics can be used to predict who will be reclassified to higher risk during follow-up and who is more likely to switch to deferred active therapy over time. Caution is warranted in patients harbouring these higher risk features and strict monitoring of their histological and biochemical features is essential. The limitations of predicting the outcome of PCa using surrogate endpoints and markers

should be recognized. Nonetheless, the majority of patients in this study remain free from any therapy and adverse events are rare, although follow-up is still too short to draw definitive conclusions.

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11 Active surveillance for low-risk prostate cancer

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ABSTRACT

Active surveillance (AS) is an important management strategy for men diagnosed with low-risk prostate cancer (PCa). The need for AS is increasing due to the awareness that many PCa are identified that show a low growth potential and therefore are likely to remain clinically asymptomatic during the lifetime of an individual. Currently there is no good method to prevent the overdiagnosis of indolent cancers upfront. During the last decade, several studies on AS around the world have made observations that feed the discussion on how to select and monitor these patients, how to proceed with the research to develop a better and more precise clinical definition of indolent cancers and how to manage men under AS clinically. Furthermore, patients' perspectives have become clearer, and quality of life studies give direction to the practical approach and care for patients and partners. This paper reflects the consensus on the state of the art and the future direction of AS, based on the Inside Track Conference "Active Surveillance for low risk prostate cancer" (Chairmen: C.H. Bangma, NL, and L. Klotz, CA; Co-Chairmen: L.J. Denis, BE, and C. Parker, UK; Scientific Coordinators: M. J. Roobol, NL, and E.W. Steyerberg, NL), organized by the European School of Oncology in collaboration with Europa Uomo in Rotterdam, the Netherlands in January 2012. Topics for discussion were the optimisation of patient selection based on indolent disease definition, the incorporation of therapeutic agents into AS programs, the optimisation of patient care, and the application of emerging technologies and biomarkers.

INTRODUCTION

Due to the increasing number of patients diagnosed with potentially indolent cancers through prostate-specific antigen (PSA)-based screening, active surveillance (AS) is of growing interest for patients and physicians as an alternative to the treatment of low-risk prostate cancer (PCa). Although world statistics are incomplete, the number of men with PCa being registered in studies on AS and in population based registries (e.g. SEER) is increasing. AS has become an accepted management strategy in various guidelines [1-4] and is supported by patient organisations.

Increased awareness of health, prevention and disease risks, together with the widespread availability of diagnostic technologies, have changed the classification or identification of 'disease' in such a way that many patients may never develop symptomatic disease during their life span. This is true for cancerous diseases, like breast, thyroid, and even some lung cancers, as well as for PCa, and urges us to redefine the word 'cancer' and its emotional weight. Because of the increased capacity to detect cancers at an even earlier stage of development, the gap between the clinical and histopathological meaning of the term "cancer" is widening. Whereas the pathological term "cancer" is merely based on well-established morphological criteria, the clinical term "cancer" is associated with the notion of an inevitably progressive metastatic process, which may ultimately run a fatal clinical course. However, overdiagnosed PCa may never cause clinical symptoms in men, let alone death. Moreover, curative and controlling treatment options have been improved, which tends to make PCa a chronic disease more often than a fatal one. Treating all PCa can lead to overtreatment with very significant (potentially lifelong) side-effects and costs. Although this may be warranted for life-threatening disease, it is worrying when these radical therapies are applied to men harboring insignificant disease [5].

REDUCTION OF OVERDIAGNOSIS IN POPULATION BASED AND INDIVIDUAL SCREENING

Overdiagnosis of indolent PCa -predominantly as a result of PSA-based screening and extended-pattern biopsy schemes- has been highlighted during recent years [6, 7]. The high incidence of asymptomatic or latent histological proven cancers was, however, long known as a result of histopathologic examination of prostates obtained during autopsy [8]. Population based screening programs, like the European Randomized Study of Screening for Prostate Cancer (ERSPC), identified the size of the problem in the PSA era, estimating that 30-50 % of men in the general population could experience overdiagnosis of indolent disease [7].

A reduction in the diagnosis of indolent cancers might be achieved when a risk-based approach would be used limiting prostatic biopsies to men at higher risk of PCa. Instruments like the Prostate Cancer Risk Calculator predicting indolent PCa (www.prostatecancer-riskcalculator.com) have been validated in various populations [9, 10]. To make population based screening acceptable, a reduction is needed in the number needed to screen and in the number needed to treat [11]. Both numbers are dependent on the selection of risk groups for biopsies, while the number needed to treat with radical therapies can be decreased by implementing AS. Additionally, because overdiagnosis and the associated risk of overtreatment inevitably reduce the quality adjusted life years (QALY) in screen-detected cases, a strategy of AS is essential to counteract this negative effect.

THE PROBLEM OF UNCERTAINTY

Much of the controversy associated with the use of AS as a patient management alternative lies in the inability to predict critical outcomes in men with PCa. If outcomes in individual patients could accurately be predicted, AS would be a much more attractive choice. More specifically, an individual patient needs predictions of various outcomes, such as long-term survival, impotence, incontinence, and bowel problems as a consequence of his treatment choice (AS vs. various more aggressive therapies) [12]. This "grid" of predictions, tailored to the individual patient, is critically needed for many men to embrace AS as an alternative to treatment. Without such a grid of predictions, there is a chance that decisions are made on the basis of fear, clinician salesmanship, and other potentially irrational drivers. Decision making is a very complex phase for patients and specialists involved in PCa care. Patients should be empowered to take responsibility to chose amongst equally effective therapeutic strategies and they should be supported in order to deal with misconceptions, misbelieves and prejudices. A multidisciplinary setting in which the specialists acknowledge the equivalence of the therapies in certain risk classes may facilitate the patient's acceptance of AS. The development of robust and accurate diagnostic and prognostic "markers" (including imaging), cleaner data collection, and more sophisticated statistical modelling can all improve the situation. Unfortunately, many, if not most, add additional expense and time, and they require evidence collection on large-scale datasets. For this purpose, cooperation among the study groups collecting data is urged, and an international registry would be of high value.

PROGRESS OF AS STUDY INITIATIVES WORLD WIDE

Various studies on AS ongoing around the world include well-defined protocols on selection and eligibility criteria, monitoring, and triggers for treatment shift towards therapy [13-18]. Excellent reviews on these programs and quality of life (QOL) studies with recent updates will become available in 2012. Most prospective studies on AS are observational. The START trial, one of two randomised studies in the USA, was closed preliminary due to poor accrual. Another research program, the Men's Eating and Living study (MEAL) in which men harbouring PCa are randomised for dietary interventions, is still recruiting [19]. In North America, two trials are including MRI imaging in their work up for risk stratification; the Active Surveillance Magnetic Resonance Imaging Study (ASIST) and the Biological Investigations in Active Surveillance study (BIAS), respectively, which are still recruiting. In a Dutch sub-study of PRIAS, MR-PRIAS, patients undergo multiparametric MR imaging followed by MR-guided prostate biopsy of cancer suspicious regions for risk re-stratification at inclusion and at 12 and 48 months of follow-up. The first results of this study are expected shortly.

Surrogate endpoints like the outcome of radical prostatectomy (RP) are increasingly becoming available. Of the189 RPs performed in patients who discontinued PRIAS due to risk reclassification on biopsy (47 %) or PSA doubling time (14 %) or both (15 %), 19 % showed a pT3 classification and 14 % a Gleason score of 4+3 or higher [20]. This is in line with previous reports, and underlines the uncertainty with regard to the overall long term results of AS. When compared to immediate RP, no differences in pathologic outcome and PSA recurrence-free survival were observed in several series [21-24]. Also, a nationwide cohort study in the United States showed similar rates for PCa mortality [25]. Furthermore, disease-specific mortality and metastatic disease are reported to be uncommon in prospective AS series [13-15, 17, 18], while the majority remains free from active treatment. However, the PSA failure rate in a long-term follow-up study [14] was found to be as high as 50% in radically treated patients, which corresponded to 13% of the overall cohort. Longer follow-up is needed to determine the impact of the PSA failure rate on PCa mortality.

BIOBANKING AND CORRELATIVE MOLECULAR-GENETIC STUDIES AND CENTRAL REGISTRY

Of further notice are the activities on creating biobanks containing tissue, serum and urine samples within these well-controlled AS trials. These biobanks will allow for the study on molecular and genetic profiles of the initially diagnosed cancers, and their changes over time (e.g. the observational Prostate Active Surveillance Study (PASS) in

the USA, in which 1000 men will be recruited before 2014 [26]). A correlative science component is now also incorporated in the ASIST trial in Toronto. Biobanking has been identified as a high priority for research funding by international granting agencies. Exchange of biobanked samples among researchers would facilitate the search and validation of new biomarkers in an AS setting. The collective number of men participating in studies for AS world wide is approximately 5000. The feeling at the conference was that this would give the opportunity of a research registry of all data which might be a useful source for comparison between various cultural settings, genetic backgrounds, age cohorts, etc, in order to further tailor AS to patients' characteristics and preferences. Analysis of underlying risks in a large registry might offer a better validation of current outcome parameters and protocols, while also providing information on cost-efficiency and intervention strategies.

DEFINITION OF INDOLENT CANCER IN RELATION TO PROGNOSTIC MODELS

Cancers that remain asymptomatic have been labelled traditionally by terms such as 'clinically insignificant', 'minimal', and 'indolent' disease. While originally defined by histological criteria, clinical characteristics, such as clinical stage, prostate volume and PSA level have been added to the definition in order to select men that are likely to have small volume low Gleason score PCa. The histological criteria for indolent PCa (Gleason score 6 or less, pathological stage T2, and tumor volume less than 0.5 ml) designed by and named after Stamey [27] and Epstein [28], are based on a small series of pre-PSA era radical cystoprostatectomies and RPs for cancers detected by a 5 core biopsy procedure. Based on the above histological criteria, clinical (pre-treatment) criteria for indolent PCa were developed, based on biopsy and clinical findings. The histological Epstein criteria have been questioned recently in a data set of 325 RP specimens of men diagnosed with PCa in a large screening study, which showed the relative minor influence of tumor size on the clinical outcome of a low grade tumor [29]. The study suggested an index tumor volume of 1.3 ml as a cut-off for indolence in Gleason score 6 adenocarcinomas (stage T1-2). Since current AS schemes are based on the 0.5 ml tumor volume as originally defined in 1994 [27, 28], the new findings imply that the maximum number of positive cores that classifies for starting AS might have to be revisited. Furthermore, it is now considered that the modification of the biopsy Gleason score might be reason for recalibration. Tumor grading remains the most influential predictive factor, but it was felt that with the increased reporting of Gleason grade 4 subsequent to the ISUP Gleason score modification in 2005 [30], a low percentage of secondary Gleason grade 4 in the biopsy specimen should not necessarily lead to immediate exclusion from AS programs.

Also, nomograms predicting indolence based on biopsy criteria might have to be revisited due to a changed definition of indolence, as they are constructed on predefined populations, often with a surrogate outcome like freedom of biochemical recurrence after 10 years of follow-up. Improvement could be obtained by redefining indolent tumors, based on the long-term clinical outcome of these tumors instead of their short-term histological characteristics. Nomograms that utilise the presently available risk factors outperform classification based on fixed criteria. Such risk models also allow for updating and incorporation of forthcoming risk factors [9, 10, 31, 32].

Prospective validation of volume and grading might be performed in studies that map the prostate by template guided mapping as carefully as possible, thus covering all areas, and then follow these patients with AS [33, 34]. This intensive biopsy scheme would become obsolete as soon as multiparametric MRI, or any other imaging modality, could prove to be equivalent or better. In a comparison of accuracy in detecting relevant lesions between MRI targeting and template biopsies, no difference was observed in 115 procedures, while the number of biopsies needed to detect a cancer decreased dramatically, i.e. 7-fold less biopsies using MRI [35].

DEVELOPMENT OF MARKER AND IMAGING TECHNOLOGY FOR SELECTION AND FOLLOW-UP

If only the traditional histological diagnosis could be combined with a better prognostic molecular marker than Gleason grade, the definition of indolent disease could be developed independent of the variability between grading by pathologists. However, this appears not to be around the corner yet. Genomic research might offer new approaches in the longer term, but the profiling of tumors remains connected to the issue of tumor heterogeneity and sampling bias.

Future tissue-based biomarkers

Starting with 1 genome sequenced in 13 years (Human Genome Project, 2000), currently one can sequence 1 genome for $3000 in a few days with the promise in a few years from now to perform this for 100 euro in 15 minutes; more than 100.000 times faster and cheaper than a decade ago. The increase in information on individual tumors needs a computing capacity that is unavailable at present if one aims at implementing sequencing for many patients in the clinic. Furthermore there still is hardly any understanding of the link between the genetic profiles and the biology behind it. At present, genetic alterations and identification of fusion genes are frequently observed in prostate tumors, but they are shared between individuals only at low frequency [36]. Except for the well known ETS fusion events, most aberrations are tumor-specific and the gap between the

observed genetic changes and the meaning for personalized medicine is enormous. It is therefore unlikely that this genomic information, although highly promising, will provide a large number of risk factors in the short term. In the long run, sequence analysis of genomic areas of interest is expected to become a standard procedure for personalized oncology [37]. A modest start has been made by measuring DNA content [38].

Biomarkers in serum and urine

PSA and its change over time appears to be a trigger to shift towards active therapy less frequently compared to the changes of repeated staging biopsies in the various programs using these parameters. The exact value of PSA doubling time (PSADT) remains difficult to assess, as in these studies PSADT is directly involved in the intermediate outcome of starting active therapy. PSADT is the single trigger of treatment in approximately 10-20 % of cases [20]. PSADT remains appropriate as a trigger for repeat biopsy, or eventually for MRI in the programs using it. PSADT $\leq$3 years at the time of standard 1-year repeat biopsy was shown to be associated with adverse characteristics on repeat biopsy in an AS cohort [39]. However, in the Hopkins and UCSF series in which biopsy results were the most common interventional trigger, PSA changes were not related to reclassification or adverse histological results at surgery [40, 41].

No markers developed recently have been validated as relevant prognostic factors. However, isoforms of PSA, especially the combination of free PSA and -2ProPSA [38] need further analysis. Other available tests, like urinary PCA3, appear to be predictive of tumor volume [42], but no significant association was found with biopsy progression in an AS cohort [43, 44].

Imaging technology as a future tool for improved selection

In addition to tissue, serum or post digital rectal examination (DRE) urine biomarkers, imaging modalities are currently being assessed for their potential role in AS. Multiparametric MRI (T2 weighted imaging combined with Diffusion Weighted Imaging and/or Dynamic Contrast Enhanced MR imaging and/or proton MR spectroscopy) was reported to rule out clinically important lesions very accurately with a negative predictive value of 95% [45], while detecting lesions larger than 0.5 ml in more than 90%. Multiparametric MRI also shows correlation to Gleason score, but still with considerable overlap between grades [46].

In order to have a reliable and reproducible examination with sufficient availability, standardisation of the technology and methods acquiring MRI images and their interpretation is needed. Therefore, guidelines were developed describing both minimal and optimal imaging acquisition protocols and a structured standardized reporting system (PI-RADS) for prostate MRI [47].

Localization accuracy of multiparametric MR imaging is used to target biopsies to defined cancer suspicious regions. MRI guided biopsies (median 4 cores instead of 12 for random biopsy cores) on cancer suspicious regions in men with previous negative transrectal ultrasound-guided biopsy sessions are reported to have PCa detection rates of 41%, predominantly detecting clinically significant cancer (87%) [48].

In multiparametric MRI, the acceptable size of a lesion might have to be chosen in relation to the intrinsic properties of MRI, realising that sparsely growing or lower Gleason grade (components of) cancers are relatively less well detected on MRI and therefore an MR visible lesion is not equivalent to histological tumor size [49]. However, Gleason grade 4 components, thanks to its increased cellular density, will often be accurately recognized on multiparametric MRI. Moreover, missing small or sparse Gleason grade 3 tumors may be regarded as an advantage in reducing overdiagnosis.

To increase availability of MR guidance of prostate biopsies, efforts are made to fuse MRI images to ultrasonography. When current issues like intra-procedural motion correction and accurate elastic registration for prostate deformation will be improved, MR-Ultrasound fusion guided biopsy may combine the localization accuracy of prostate MRI with the availability and practicality of an ultrasound examination.

Combined multiparametric MR imaging and MR guided biopsy may be of value for AS patient risk reclassification at inclusion or during follow-up based on Gleason grade criteria. Multiparametric MRI-based MR-biopsy Gleason grade concordance for the highest Gleason 3, 4 and 5 components upon prostatectomy were respectively 100%, 91% and 73%. MR-biopsy concordance rates were significantly higher compared to TRUS biopsy Gleason grade concordance rates: 94%, 46% and 30%, respectively [50]. However when it comes to evaluating tumor volume using MRI, using imaging criteria only is not desirable. False-positive lesions and lower detection rates of sparsely low-grade cancer (components) prohibit accurate tumor delineation. MR guided biopsy cancer core-lengths, however, may contribute in estimating cancer volume.

Although research in ultrasound-based techniques like contrast-enhanced ultrasound and elastography is still in an early stage, both techniques seem promising for PCa localization [51, 52].

THE ROLE OF HEALTH CARE PROVIDERS AND PATIENTS IN THE DISEASE MANAGEMENT

Many patients and physicians consider information on screening and AS for PCa variable and non-transparent. Nevertheless, AS as a concept for disease management and treatment timing is growing in attention. In a survey performed in 500 health care providers in 26 countries, 95 % of physicians mentioned to discuss AS with their patients, while

50 % reported that also patients bring up the subject [53]. In total, 98 % of urologists follow internationally accepted inclusion criteria. The most influential factors of decision making were patient wish and guidelines.

With regard to QOL there are a few indications that men on AS have a better long term QOL compared to those that underwent radical treatment [54]. While short term QOL is regarded as excellent [55-57], there is a need for long term data assessed with validated questionnaires [58]. There are only a few men (<10%) that shift towards active therapy due to their main fear, that is of disease progression, once started on AS. It can be seen that most men are not anxiously concerned about disease progression and adjustment to their cancer further improves over time [57]; patients who are more distressed may need some support to learn effective strategies aimed at coping with their fears [59]. In depth interviews with participants on AS in the ProtecT study showed the important role of self management, for example by adjusting diet as part of their lifestyle, in which the role of their partners also appeared prominent [60, 61]. Although a considerable number of men rely heavily on their physician's advice, over 80% of men (as well as physicians) are compliant to risk based treatment advices (nomograms) when offered [62].

The awareness that AS is an acceptable strategy for many men with low-risk PCa is growing around the world. It is a concept that primarily involves the timing of treatment and that might not be suitable for every man. Because of the inflated results of invasive (often commercial) therapies, alternative strategies like watchful waiting in those men with significant competing co-morbidities with regard to QOL or mortality are often not mentioned during consultations. Our incomplete understanding of the biology and the lack of long term results in AS justify a request for more research in the area of low-risk PCa. In this, patient organisations (e.g. Europa Uomo) as well as scientists need to act as a team to reduce the burden of PCa.

INTERVENTIONS IN ACTIVE SURVEILLANCE PROGRAMS

The relative uncertainty on the biologic outcome of low-risk PCa and the intermediate results of AS studies justify the evaluation of interventions by 5-alpha reductase inhibitors, lifestyle (exercise and dietary supplements), and maybe even statins. The practical assessment of such interventions can only be performed by phase II or III studies with intermediate endpoints like grade progression, PSA changes, imaging, or a combination offered by risk evaluation, as the outcome of randomised studies take over a decade.

Patients with small volume low-grade cancer foci who have been diagnosed by PSA-based screening often have benign hyperplasia of the prostate [17, 63]. Moreover, AS protocols tend to select patients with large prostates by applying a cut-off for PSA

density at inclusion. The prescription of 5-alpha reductase inhibitors is not an exception in these men. From this point of view, positive results reported from the REDEEM study, showing that dutasteride reduces the rate of reclassification towards higher risk on repeat biopsy in AS patients [64], could encourage us to consider 5-alpha reductase inhibitors in patients followed on AS.

Recommendations from the ESO Inside Track Conference on Active Surveillance	
1	To create an international registry of AS data from European, American and Asian trials
2	To introduce individualised risk assessment before prostate biopsies for screening
3	To redefine indolent disease and to construct improved nomograms including patient and cancer characterisitics
4	To validate multiparametric MRI for selection and follow-up of AS patients
5	To validate molecular markers during life style interventions or relevant drugs in AS
6	To deliver care for AS patients in multidisciplinary settings

CONCLUSIONS

1. An international group of health professionals and patient representatives who met in Rotterdam in January 2012 recommend an international registry of AS data from Europe, America, and Asia for research purposes.
2. The increased incidence of low-risk PCa is partly due to overdiagnosis of indolent disease, which should be reduced by risk based avoidance of diagnostic biopsies.
3. Redefinition of indolent disease should be based on current observations of intermediate outcome next to traditional histological criteria, in order to reduce the burden of cancer diagnosis, and to select men for AS.
4. Technological developments of cancer markers and imaging by multiparametric MRI for selection and follow up are of considerable interest but will need to be validated.
5. Studies with lifestyle interventions including food additives or relevant drugs in which biorepositories are constructed for molecular evaluation, are to be promoted.
6. Patient and partner care should be delivered in a multidisciplinary and multiprofessional team implementing results of QOL studies in AS.

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V | General Discussion

12 | General discussion

INTRODUCTION

The rationale for prostate cancer (PCa) screening is obvious since PCa is the most common cause of cancer and the sixth leading cause of cancer death among men worldwide with an estimated 899.000 new PCa diagnoses and 258.400 disease-specific deaths in 2008 [1]. Several trials have been published with respect to PCa screening [2-6], however, due to substantial methodological limitations, only two randomized controlled trials [2,3] can be considered suitable to provide an answer to the question whether or not screening is capable of reducing PCa mortality at an acceptable price. The European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a 20% mortality reduction after 9 years follow-up [7], which was further enhanced up to 31% after adjustment for both non-compliance (in the screening arm) and contamination (i.e. use of screening by individuals in the control arm) [8]. In 2012, results with 11 year follow-up were published [2], which showed a consolidation of the previous findings with 21% reduction in PCa mortality after 2 more years of follow-up and 29% after adjustment for non-compliance. In addition, the Göteborg screening trial [3], which is part of the ERSPC, published results with 14 year follow-up showing a 44% reduction in the intention-to-screen analysis, which was 56% after adjustment for non-compliance. While the intention-to-screen analysis is diluted by non-compliance and contamination it shows the effect on the study population as a whole, where the secondary analyses have the ability to give a better adjusted estimate of the effect of screening at the individual level for those men who are actually screened.

Longer follow-up is needed to confirm the ERSPC findings, since natural history studies have shown that, even in localized PCa, mortality rates can still increase after a follow-up period of 15 years [9].

CONTROVERSIES IN SCREENING

In response to the outcome of the ERSPC, several points of discussion have been brought up in literature concerning the usefulness of screening and the methodology of the ERSPC. In this thesis, several controversial points were addressed [10]. One of the issues raised by critics is the view that overall mortality would be a more appropriate endpoint than disease-specific mortality. However, to achieve significance on such an outcome, several million participants would be needed despite the relatively high incidence rate and significant reduction in PCa-specific mortality. Because the lifetime risk for a man to die from PCa is less than 3% [11], a reduction of 30% would not impact all cause mortality in a study such as the ERSPC, but could have an important effect with respect to nationwide screening. The main goal of health programs worldwide is to gain

improvements in mortality of different types of cancer that will in the end hopefully decrease the total burden of cancer mortality.

As discussed in this thesis [10], other issues raised by critics comprised methodological points that were anticipated and described in the ERSPC monitoring plan [12], and the potential treatment related effect due to possible differences in treatment between the screening and control arms. It was shown previously that the effect of differences in treatment between trial arms in the ERSPC is only minor [13], which rejects the idea that the mortality reduction is based on unequal treatment.

From the Prostate Cancer Prevention Trial (PCPT) we have learned that PCa, including high-grade PCa, is present even among men with prostate-specific antigen (PSA) levels of 4 ng/ml or less [14]. A cut-off value of 3.0 ng/ml was shown to lead to missing 67.8% of biopsy detectable PCa and 42.4% of potentially aggressive ones [15]. This implies that, although the risk of having PCa is related to the PSA level, there is no "normal" PSA level at which a patient can be reassured of a true negative test result. A cut-off of PSA $\leq$3 ng/ml in the ERSPC will therefore lead to a substantial number of missed cancers, but we should keep in mind that more aggressive screening will inevitably lead to the detection of a lot of insignificant PCa, which will increase overdiagnosis and potentially overtreatment.

Overdiagnosis

Although the controversy surrounding screening for PCa has not yet been fully elucidated, there is no doubt that screening results in overdiagnosis and overtreatment in many men. Overdiagnosis is one of the major downsides of PCa screening with rates estimated to be no less than 50% in the ERSPC [16]. Definitions used in literature to indicate insignificant PCa vary greatly, but indolent and insignificant are the most commonly reported terms. Indolent cancer is more likely defined by strict pathological criteria, which refer to disease that will never –regardless of the patient's lifespan- become clinically significant. Insignificant disease comprises more than just pathological features and also factors in patient age and co-morbidity to better reflect the natural history of the disease in an individual patient [17]. Data from the United States show that over 93% of men with localized PCa in a contemporary cohort elected active therapy over expectant management [18]. Their data show slightly improving trends over more recent years, but these results strongly suggest overtreatment of low-risk disease. The most recent 11-year follow-up report of the ERSPC [2] showed an initial active treatment rate of 80% for all diagnosed PCa. However, in a previous study on ERSPC data [19], it was shown that men with organ-confined disease more frequently chose expectant management as their initial strategy of disease management. In the control arm the

rates for expectant management increased from 14.8% in the initial years of the study (1994-1998) to 22.6% later on (2003-2006), while these rates increased from 17% to 35.9% in the screening arm.

Besides the potential psychological burden of a PCa diagnosis, it is the risk of side-effects of radical treatment [20,21] that makes overdiagnosis a major point of concern. To tackle the issue of overdiagnosis we would need to be able to better select those men who will profit from screening. Ideally only those cancers that will eventually become aggressive would need to be detected in an early stage that would allow for curative treatment, while those with insignificant disease can safely be left undiagnosed.

PSA as a predictor

We now know that on the one hand PSA-based screening can reduce PCa-specific mortality, but on the other hand screening for PCa based on solely a PSA cut-off results in considerable overdiagnosis and large numbers of unnecessary biopsies, while still missing PCa in men with values below the cut-off. Our focus should be on how to improve the selection of screening and screening algorithms.

PSA was found to be an important predictor for the lifetime risk of metastatic disease and PCa death in unscreened men [22]. Almost all PCa deaths in that study (90%) occurred in the top quartile of PSA (≥2 ng/ml) measured at age 60, while the risk of death for men with a PSA below the median (≤1 ng/ml) was only 0.2%. In this thesis, we analyzed the incidence and disease-specific mortality for PCa in men with an initial PSA <3 ng/ml within the Rotterdam screening arm of the ERSPC [23]. The overall risk of PCa death in this cohort was very low with 0.15% at 11 year median follow-up. The risk of PCa and aggressive PCa, as well as for disease-specific death significantly increased with higher PSA values. Men were 150-fold more likely to die of causes other than PCa. The risk of PCa in men with a PSA <1.0 ng/ml was only 1.8%, with a 0.04% risk of PCa death.

These results suggest that risk-stratification based on PSA values would improve the outcomes in terms of decreasing unnecessary biopsies and overdiagnosis. To contribute to decreasing PCa mortality by means of screening, a large number of PCa deaths would need to be prevented, which can not be found in the lowest PSA ranges. Given the prognostic value of an initial PSA test, it might play an important role in individualized risk stratification where further screening could be based on baseline PSA values. Interval-detected PCa had a substantial role in the incidence of aggressive PCa and disease-specific deaths in the study described in this thesis [23]. Although shortening of the screening interval from 4 to 2 years might induce a reduction of the incidence of aggressive PCa, it will inevitably lead to an increase in overall PCa diagnoses and low-risk PCa [24]. Therefore, individualized screening algorithms to better identify those men who can benefit from more frequent screening should be improved in order to define the optimal screening interval. The favorable prognosis among men with a PSA

level <1.0 ng/ml supports a prolonged screening interval of 8 years, which would lead to a considerable decrease in screening visits with a minimal risk of missing aggressive cancer at a curable stage [25].

As was reported in this thesis, men aged 55-74 years with initial PSA values <3.0 ng/ml were shown to be at low risk for PCa-specific mortality and initial PSA screening values were shown to be useful for risk stratification [23]. It has been suggested that baseline PSA testing at a young age (<60 years) may contribute to risk stratification. Men with PSA levels above the age-specific median were not only found to have a greater risk of PCa diagnosis, but PSA was also found to be strongly predictive of aggressive disease, metastases and disease-specific mortality [26]. Despite that the optimal age to start screening and the optimal screening interval remain unknown, this age-related concept should certainly be taken into account for the risk stratification of patients and individualization of screening protocols.

Ultimately, it is clear that although PSA is good as a screening test, it is far from ideal. The deployment of additional predictors and the development of molecular and genetic biomarkers should be further investigated to improve identification of men with potentially aggressive disease who are better off receiving early treatment while sparing men with low-risk PCa from the exposure to the side-effects of radical therapy.

SCREENING IN THE FUTURE

If screening for PCa was to be implemented as nationwide health programs, it would have to effectuate mortality reduction at a reasonable price. This 'price' comprises a number of considerations that can be considered priority issues of screening that need to be tackled.

The harms and benefits of PSA screening have been modelled by Heijnsdijk et al. [27]. They quantified the effects of screening on PCa mortality and on quality of life, using a model based on the ERSPC data [2]. Without the adjustment for quality of life the number of life years gained from screening was estimated to be 73 over the lifetime of 1000 men who underwent annual screening between ages 55 and 69, which was 56 years after the adjustment for quality of life effects. A substantial part of this 23% reduction was caused by overdiagnosed cancers, which reinforces the importance of strategies to reduce overdiagnosis. To assess long-term quality of life, longer follow-up data on the impact of various treatments and active surveillance are essential. These data together with longer-term follow-up from the ERSPC – after all, the Göteborg screening trial showed 44% reduction in PCa mortality after 14 years [3] – will hopefully give us better insight in what should be recommended regarding a policy of nationwide PCa screening. At this moment patients seeking screening should be informed about the possible

risks and uncertainties as well as the benefits and both the patient and the physician should have an important role in the decision making.

Risk calculators in decision making

As discussed earlier, testing for PCa should be made more selective by means of individualized screening. Addressing the issue of overdiagnosis and overtreatment, various nomograms have been developed to reduce the number of unnecessary biopsies [28-34]. These decision tools use additional prebiopsy information besides PSA level, such as age, prostate volume, digital rectal exam and transrectal ultrasound in a model to improve the predictive value of screening.

These risk modifying techniques can also be used to better identify cancers in patients that are likely to be low-risk and for whom radical treatment will not lead to improved prognosis, but only to the unnecessary exposure of possible adverse therapy effects.

The PCa risk calculator (www.prostatecancer-riskcalculator.com), which was based on ERSPC data, is one of these decision tools. It is a graphical device that was developed to predict the probability of an event that can be modelled by means of logistic regression analysis [35]. It can be used to predict the chance of a positive sextant biopsy and the degree of aggressiveness, as well as the chance of having an insignificant tumor. It was found that applying the risk calculator in a screening setting with a PSA cut-off level of 3.0 ng/ml in combination with a probability cut-off of 12.5% to undergo sextant biopsies would lead to a reduction of a third of the biopsies, which would increase the positive predictive value from 29% to 38% [33]. Using this strategy, only very few PCa cases would have been missed for which diagnosis at a subsequent screening visit might be too late for treatment with curative intent. The PCa risk calculator used here has also been validated in external populations [36] and has shown to have superior discrimination for the prediction of PCa compared to other calculators that do not include prostate volume in their algorithm [37,38]. Besides predicting the outcome of a biopsy, the risk calculator can be used to predict insignificant cancer (defined as pathological Gleason score 6 or less, tumor volume less than 0.5ml and organ-confined disease). The area under the curve was found to be 0.76 for the prediction of insignificant PCa in a screening setting [39], and when it was validated in a clinical cohort it performed equally well [40]. These data further establish the role of nomograms for clinical decision-making and for managing screen-detected PCa. The PCa risk calculator has shown to outperform a PSA- and DRE-based approach in the decision to perform a biopsy in a Dutch clinical setting [41], and, in the same setting, it has shown to be useful in treatment decision-making in patients with localized PCa [42].

So these individualized screening algorithms might contribute to counteract two of the most important side-effects of screening, namely unnecessary invasive testing and overdiagnosis with the related overtreatment. The risk calculator mentioned above is

a step in the right direction, but since it was developed with ERSPC data, it is based on cancer length in PCa samples from sextant biopsies. This limits its use for contemporary practice where often extended biopsy regimens are used.

In this thesis data from autopsy studies was analyzed in order to allow for predictions based on 12 and 18-core biopsy regimens [43]. Data from 33 autopsied men showed that correction factors of 2.72 and 2.03 would be appropriate to adjust the risk calculator for 18 and 12-core schemes, respectively. These findings give direction to the improvement of the clinical applicability of the risk calculator, because contemporary biopsy regimens often comprise more than 6 cores. Although extended biopsy regimens result in significantly higher detection rates as compared to sextant protocols [44], the incidence of PCa is not equally distributed throughout the prostate with the peripheral zone being affected more often [45,46]. This underlines the importance of defining correction factors to adjust for extended biopsy schemes. The correction factors found in our study are indicative, however, these data still need to be validated before they can be implemented. Since none of the men in this study had a history of PCa, they can by definition be considered to have had insignificant disease despite of their actual tumor characteristics, which causes this study population to not exactly match the screening population on which the original risk calculator was developed. Further validation is essential to justify the use of these correction factors in contemporary practice. Ideally, data on a large cohort of men would be needed in whom extended biopsies were performed following a strict template in order to be able to validate correction factors and compare the biopsy template used in the ERSPC (i.e. lateralized sextant biopsy) to the more extended regimens.

Markers and imaging in screening

Other strategies to reduce overdiagnosis are development of new markers and improved imaging techniques. A novel biomarker is required to be specific for PCa, differentiate between aggressive versus non-aggressive PCa, and should not be expressed in other organs or diseases. A marker that might be of additional value is prostate cancer gene 3 (PCA3). Its clinical value as an isolated first-line diagnostic tool is limited, however, PCA3 could be of additional value in risk stratification using a combination of clinical characteristics to aid decision-making [47]. Another promising marker in urine is TMPRSS2:ERG, but results regarding its prognostic ability are contradictory and the screening sensitivity is variable [48]. The advantage of urine-based testing is that it is non-invasive and easily available which makes it a promising source of biomarkers. Other PSA-related derivatives and subforms, such as precursor forms of PSA and the Prostate Health Index (phi) are currently under study and will need to be further validated in large, multicentre, prospective trials. Yet, the perfect marker for PCa screening still has to be found and further development in this research area is urgently needed.

NATURAL COURSE OF SCREEN-DETECTED PROSTATE CANCER

Most of the published data on the natural course of PCa and the impact of radical treatment is based on cases detected clinically, before the PSA era [49-52]. In 2005, Albertsen et al. [49] reported on the 20-year survival of men who were diagnosed with clinically localized PCa and treated with observation or androgen withdrawal therapy alone. All 767 cancers were diagnosed between 1971 and 1984, thus well before the widespread use of PSA as a marker for the early detection of PCa [53]. After a median follow-up of 24 years, the PCa-specific mortality for men with a Gleason score equal to or smaller than 6 was found to be around 19%, while the majority had died of competing causes.

These findings may not be applicable to contemporary practice however, since the introduction of PSA-based screening has induced lead-time that causes bias in the interpretation of screening results. The lead-time (i.e. the time with which cancer diagnosis is advanced by screening) within the Rotterdam arm of the ERSPC was found to be around 10 year, varying from 6 to 12 year depending on the age and frequency of screening, and it was estimated that around 50% of the screen-detected PCa cases were overdiagnosed [16]. Another adjustment that considerably changed the description of contemporary low-risk disease, is the adaptation of the Gleason grading system in 2005 [54]. In the modified criteria ill-defined glands with poorly formed lumina and large cribiform glands with smooth borders, classically described as Gleason pattern 3, were redefined as Gleason pattern 4, while Gleason scores 2-5 are almost never being given anymore at biopsy. This alteration, also known as the 'Will Rogers phenomenon', causes contemporary Gleason 6 PCa to have a more favorable prognosis [55] than those presented in older studies [49-51,56,57].

A recent report from a population-based nationwide cohort study in Sweden [50] showed a 10-year disease-specific mortality of 3.6% in a group of 2021 expectantly managed men (including both active surveillance and watchful waiting) who had a mean age of 64.7 years and who were followed for a median of 8.2 years. The 10-year disease-specific mortality rates for low- and intermediate-risk men in that cohort were 2.4% and 5.2% respectively, while the overall mortality rate reached 20.4%. Another study presented results from the Surveillance, Epidemiology, and End Results (SEER) program [56] of men who had a median age of 78 years with T1 or T2 PCa in whom curative therapy was not attempted and of whom 42% had received androgen deprivation therapy. The 10-year disease-specific mortality was 8.3-9.1% for well- and intermediate-differentiated tumors, while the overall mortality rate was 51.7% after a median follow-up of 8.3 years. Although these data were obtained in the PSA era and already show substantially lower disease-specific mortality rates compared to the control arm of the SPCG-4 study (19.5-23.3%) in which only a small minority of patients had screen-detected disease [51,52],

the overall health and the age of the patients in this study are not representative for the majority of patients who opt for active surveillance in contemporary practice. Vickers et al. [58] modelled the SPCG-4 data to show that surgery was not beneficial in Gleason 6, T1 disease or in patients >70 years, while the benefit of treatment for Gleason 6, T2 and Gleason 7, T1 was also questionable, but dependent on other clinical findings (e.g. number of positive cores and co-morbidity) and patient preference. Recently, results from the randomized Prostate cancer Intervention Versus Observation Trial (PIVOT) were presented [57], showing that radical prostatectomy did not reduce disease-specific survival compared to observation through at least 12 years in men with clinically localized PCa that had been diagnosed in the era of PSA testing. Results were particularly robust in men who had low PSA values (<10 ng/ml) and those who had low-risk disease (PSA <10 ng/ml, Gleason score ≤6, clinical stage T1-T2a). These findings add to the evidence suggesting a favorable natural course of disease in patients who are considered to be at low-risk and support a strategy of expectant management, or active surveillance, in these cases. Moreover, patients followed on active surveillance nowadays are offered active treatment in case of risk reclassification or disease progression, which would reduce the risk associated with initial expectant management and would likely further reduce any benefit of surgery. The above-mentioned results should of course be interpreted cautiously, regarding existing differences with contemporary, mostly screen-detected, populations and increased life-expectancy.

RATIONALE FOR ACTIVE SURVEILLANCE

Although PCa has an important share in causing cancer-related deaths worldwide [59,60], the vast majority of men diagnosed with the disease die as a result of other causes. PSA-based screening has shown to reduce PCa-specific mortality [2,3], but has also shown to substantially increase the detection of cancers that would not cause impairment to quality or quantity of life if left undiagnosed [16,61]. These cases are said to be overdiagnosed. Autopsy studies in men who died of other causes have reported rates of potentially detectable PCa in up to 70% of men aged >60 years [62]. Detection of PCa in all these men would lead to a probability of overdiagnosis up to 94% [61], while the rate of overdetection in the ERSPC has been estimated to be around 50% [16]. Because a lot of men with low-risk PCa receive treatment, overdiagnosis has been associated with overtreatment: unnecessarily exposing men to the potential side-effects triggered by active therapy. The rate of men undergoing initial radical treatment for low-risk disease differs from over 90% in the United States [18] to 77-85% of men with organ-confined disease in the control arm of the ERSPC and 64-83% of men in the screening arm [19].

A Swedish sub study of the ERSPC trial showed the lowest rate of 40% [63] in low-risk cases.

The substantial rates of overdiagnosis and subsequent overtreatment support the need for a strategy that focuses on a more selective approach to treatment. Active surveillance is a management strategy for low-risk PCa, expectantly following patients by means of repeated PSA tests, DRE, and biopsies to avoid, or at least delay, treatment in whom it is possible, while selectively switching to radical treatment well within the window of opportunity for cure when higher risk disease is expected.

FEASIBILITY OF ACTIVE SURVEILLANCE

Since active surveillance is a relatively new management strategy for low-risk PCa, most prospective active surveillance studies have only short follow-up available. To evaluate long-term outcomes of expectant management in a contemporary screen-detected cohort of men, we evaluated men with low- and intermediate-risk PCa who initially elected expectant management. Results were reported in this thesis [64]. A total of 509 patients were studied, of whom 381 (75%) had low-risk PCa and 128 (25%) intermediate-risk. Radical treatment was avoided in the majority of patients for at least 6.8 years. Importantly, the rate of adverse events was very low in this study after a median follow-up of 7.4 years. The 10-year disease-specific survival rate was 98.4% despite a considerable share of intermediate-risk patients. Only 2 patients who died of PCa received deferred treatment with curative intent and potentially missed the window of curability because of initial expectant management, which was only 0.4% of our cohort and 2% of the overall deaths. These data substantiate the feasibility of a strategy of active surveillance for low-risk PCa. No significant difference in adverse PCa-specific events was demonstrated between the risk groups, indicating that active surveillance criteria could potentially be extended to selected patients with more adverse disease features.

Another study also found intermediate-risk patients to show favorable outcomes when followed on active surveillance [65]. Although intermediate-risk patients showed more adverse features at diagnosis, as was the case in our cohort, they did not undergo more active therapy or experience more progression, indicating that selected candidates with intermediate-risk features can be followed on active surveillance, preserving favorable prognosis. A report by Godtman et al. [63] also showed favorable results in a screen-detected cohort choosing active surveillance instead of immediate active treatment. Although no strict follow-up protocol was used, no distant metastases or PCa deaths were reported in the low-risk groups and only 1 PCa death and 1 case of distant metastasis occurred in the intermediate-risk group after a median follow-up of 6 years.

Although these retrospective data on expectant management in a screening setting show results with longer follow-up than most active surveillance series, still long-term follow-up is essential to evaluate the outcomes in men with longer life expectancy. We know that lead-time, or the time with which the cancer diagnosis is advanced due to screening, has been estimated at up to 11 years in low-risk disease [16], which implies that a follow-up well beyond that time is necessary before definitive conclusions regarding the long-term safety of active surveillance can be drawn, especially in younger men with no co-morbidities. Long-term outcomes of contemporary active surveillance studies will take considerable time to mature, which makes retrospective analysis of the pathologic characteristics of patients fulfilling active surveillance criteria the only current option for validation of these criteria.

Delayed versus immediate treatment

To assess the risk of deferred radical treatment for men undergoing initial active surveillance, several studies examined oncologic outcomes in radical prostatectomy series comparing delayed to immediate interventions. Dall'Era et al. [66] reported that Gleason upgrading, positive surgical margins or non-organ-confined disease showed no association with the time to treatment, which was either immediate (<6 months) or delayed (median 18 months). Similar results on these intermediate outcomes were found in another study [67] that also showed comparable tumor volumes and biochemical recurrence rates in a similar setting. Warlick et al. [68] supported these findings by showing that a >75% risk of "non-curable" cancer was not significantly different for delayed and immediate intervention groups. Accordingly, in a Swedish study [69], among low- and intermediate-risk patients, no difference was observed for any one or more of three adverse pathology features of Gleason score upgrading, positive surgical margins and extracapsular extension. Also, a nationwide cohort study in the United States showed similar rates for PCa mortality among men with low-risk disease who opted for deferred treatment and those who were initially treated [70].

Conflicting results have been reported by others who showed increased rates of PSA progression [71,72] and Gleason score upgrading in low-risk patients undergoing deferred therapy before or after 6 months. However, both studies identified low-risk patients according to the D'Amico classification [73], which results in less strict criteria to define low-risk disease than those used in most contemporary active surveillance studies. Although the aforementioned studies attempt to throw light on the risk of applying active surveillance, it should be kept in mind that selection bias in the deferred treatment groups is likely because reasons for switching from active surveillance to active treatment often include signs of risk reclassification (e.g., on repeat biopsy). Another downside of these studies is their retrospective and nonrandomized nature. To be able to evaluate whether a delay in treatment after risk reclassification or true

disease progression will compromise cure, prospective randomized trials comparing active surveillance to radical treatment would be required.

However, as yet, no results from studies randomizing for active surveillance and active therapy are available. The prospective START (Standard Treatment Against Restricted Treatment) trial [74] was closed prematurely due to problems in patient accrual. The ProtecT (Prostate testing for cancer and Treatment) study is an ongoing trial for the treatment of localized PCa that offers randomization to external beam radiotherapy, radical prostatectomy, or active surveillance to patients with screen-detected disease [75]. The aim of the trial is to provide information on the effectiveness of these strategies for localized PCa. The main trial publication with 10-year follow-up results is expected to be published in 2016.

Regarding the considerable difficulties in implementing randomized trials for radical treatment and active surveillance, prospective active surveillance studies will play an important role in finding answers to important questions on long-term mortality, and inclusion and follow-up criteria for active surveillance.

CONTEMPORARY ACTIVE SURVEILLANCE STUDIES

Worldwide, several institutions have initiated prospective active surveillance studies, which are shown in table 1. In total, data has been reported on 4700 men [76-81]. PRIAS is the largest cohort with over 2500 men in 17 countries and over 100 participating centres [81]. However, most studies only have short- to intermediate-term follow-up available, which does not allow drawing definitive conclusions regarding mortality risk. Results with the longest median follow-up time were reported by Klotz et al. [76], who showed a low rate of PCa mortality (10-year disease-specific survival 97.2%). Only one out of patients who died from PCa in their cohort was treated after a prolonged period of observation and subsequently experienced progression to metastases and death. They did find a relatively high PSA failure rate (50%) in patients who were treated after reclassification to higher risk, for which a short PSA doubling time (PSA-DT) was found to be predictive. Overall, 13% of their complete cohort showed PSA failure, which is comparable to rates described after radical surgery or radiotherapy in patients with favorable-risk disease [76]. Results described in this thesis [81] show results for active surveillance with shorter follow-up. Reclassification on repeat biopsy was shown in 28% (415/1480) of cases, for which the number of positive cores and PSA density (PSA-D) were found to be predictive. The active therapy-free survival rate at 2 years was 77.3% and the disease-specific survival rate was 100% [81].

Table 1 | Summary of largest active surveillance studies.

Institution / study	No. of patients	Median age (years)	Inclusion criteria	Triggers for intervention	Median follow-up (years)	ATFS
University of Toronto[73]	450	70	PSA ≤10; GS ≤3+3 (until 2000 for men >70: GS ≤3+4, PSA ≤15)	PSA-DT <3 years; GS upgrading; T stage progression	6.8	70%
Royal Marsden[74]	326	67	T1-T2a; PSA <15; GS ≤7; ≤50% core involvement	PSA-V >1; primary GS ≥4; >50% core involvement	1.8	73%
Johns Hopkins*[75]	709	66	T1c; PSA-D <0.15; GS ≤6, ≤2 positive cores; ≤50% core involvement	GS ≥7 ; >2 positive cores; >50% core involvement	2.7	67%
University of Miami[76]	230	63	PSA ≤10; GS ≤6; ≤2 positive cores; ≤20% core involvement	GS ≥7; increase core involvement; increase positive cores	3.7	86%
University of California San Francisco**[77]	321	63	T1-T2a; PSA <10; GS ≤6; <33% positive cores	GS ≥7; PSA-V >0.75	3.6	76%
PRIAS[78]	2494	65	T1-T2; PSA ≤10; PSA-D <0.2; GS ≤6; ≤2 positive cores	GS ≥7; >2 positive cores; PSA-DT <3 years	1.6	76%

ATFS, active therapy-free survival; PSA, prostate-specific antigen; GS, Gleason score; PSA-DT, PSA doubling time; PSA-V, PSA velocity; PSA-D, PSA density

** 78% of cohort met low-risk criteria; **71% of cohort met low-risk criteria*

The majority of men on active surveillance remain without treatment during follow-up and disease-specific outcomes are favorable in all active surveillance cohorts so far, but long-term follow-up is needed to confirm these findings.

In a study that compared the ability of various active surveillance criteria to identify patients with certain pathologic tumor features based on prostate biopsy data, the PRIAS criteria and University of Miami criteria were found to have the best ability to predict pathologically insignificant disease at radical prostatectomy when compared to other sets of active surveillance eligibility criteria and Epstein criteria [82]. Yet, although precise criteria are of great importance, it is unrealistic to expect the same criteria to apply to all men on surveillance. Depending on factors such as age and co-morbidity, individual approaches and shared decision-making might lead to slightly diverging criteria for eligibility and to trigger intervention.

CHALLENGES IN ACTIVE SURVEILLANCE

In active surveillance, curative treatment is delayed in men who have low-risk disease until it is warranted based on defined indicators of disease progression. However, there are some challenges to face to achieve widespread acceptance of this management strategy, namely defining eligibility and identifying reclassification or true disease progression.

Patient selection and triggers for intervention

Contemporary active surveillance trials use slightly different inclusion criteria (table 1) to define low-risk PCa, which all aim to select low-volume, low-grade disease associated with low PSA, thereby attempting to find a balance between maximizing the number of patients who can avoid treatment and minimizing the number of aggressive PCa missed. The most commonly used criteria are based on the Epstein criteria for low-risk disease described in 1994 [83], which integrate clinical data with biopsy characteristics. These criteria are based on Epstein's definition of minimal PCa on radical prostatectomy, comprising organ-confined (pT2) disease $<0.5cm^3$ with a Gleason score ≤ 6. This definition was interpreted by Stamey et al. [84] as the 8% (i.e. lifetime risk) largest PCa volumes in 139 cystoprostatectomy specimens from bladder cancer patients in whom it was unknown whether they had PCa. This resulted in a 0.5ml threshold to identify clinically significant disease, under the assumption that PCa progression is propotional to cancer volume. Many contemporary criteria for low-risk disease are based on this histopathologic definition of insignificant PCa. However, this 0.5ml volume threshold might be considered much too restrictive. Previous studies have shown that, although tumor volume is associated with tumor stage and grade, it does not act as an independent predictor of PCa outcome [85,86]. Wolters et al. revisited the threshold issue with more contemporary data from the ERSPC screening trial following the method used in the original publication by Stamey et al. [87]. Although they could confirm the threshold of 0.5ml with their data, they also showed that when tumor grade (Gleason score 6) and stage (pT2) were considered as the most important prognostic factors for PCa aggressiveness instead of tumor volume, clinically insignificant PCa may include volumes up to at least 1.3ml. In their study, 98% of all Gleason score ≤ 6, pT2 cancers would comply with this updated threshold. Moreover, the study by Eggener et al. [88] showed a 15-year PCa-specific mortality rate of 0.2% for pathological Gleason 6 disease after radical prostatectomy, with only 3 of 9557 patients with organ-confined Gleason score 6 disease dying from PCa. These results would support less stringent criteria for inclusion in active surveillance programs regarding cancer volume in patients with well differentiated cancer (e.g. expand the maximum number of positive cores), provided that they can be accurately determined at diagnosis. Some even think that small, low-

grade (Gleason pattern 3) lesions could be regarded as non-malignant and should not be called cancer, but 'indolent lesions of epithelial origin (IDLE)' instead, of course given that these lesions could be accurately identified [89].

The most frequently used criteria include tumor stage (T1c-T2), PSA value (≤10 ng/ml), PSA-D (<0.15-0.20 ng/ml/ml), Gleason score (≤3+3=6), and extent of disease on biopsy. However, the validity of these criteria is open to debate and the risk of underestimation of the cancer regarding stage and grade remains. This is illustrated by a number of studies on the outcome at radical prostatectomy of men who would have been eligible for active surveillance following contemporary criteria. The rate of Gleason score upgrading in these studies varied between 21% and 36% [90-94], while high Gleason scores of 8-10 were found in 3-4%, extracapsular extension in 5-19%, PSA progression n 11-23%, and positive surgical margins in 14-35%. These results show that a considerable amount of men who are thought to have low-risk PCa according to clinical features at diagnosis, harbour more aggressive disease on radical prostatectomy.

The PRIAS criteria do not include information on the extent of tumor involvement, although it might have additional value in the prediction of the risk for aggressive PCa. The main reason for leaving tumor involvement out of the PRIAS eligibility criteria is to ensure applicability of the PRIAS protocol in peripheral clinics that do not have expert prostate pathologists and tumor involvement is not routinely reported. However, it has also been shown that the combination of other criteria (i.e. PSA ≤10, PSAD <0.2, GS ≤6 and ≤2 positive cores) rarely have large tumor volumes in these cores [82].

Because of the difficulty to determine the true nature of a cancer and selectively decide whether a patient harbours low-risk disease at diagnosis, repeat biopsy can be used to better identify patients with more aggressive disease. This is illustrated by the study of Berglund et al. [95] in which repeat biopsy within 3 months after diagnosis among men suitable for active surveillance showed 27% upgrading and/or upstaging. The study showing protocol-based 1-year repeat biopsy results in an active surveillance cohort described in this thesis [96] also reported a rate of 22% for reclassification to higher risk disease (9% Gleason upgrading). These results indicate that, regarding the short follow-up, it is more likely that misclassification at time of diagnosis occurs in a considerable group of men, instead of real upgrading and/or upstaging as a result of biologic progression during follow-up. Reclassification of risk during active surveillance follow-up is frequently described in literature, which reinforces the use of repeat biopsies during follow-up for active surveillance to check for correct classification of disease and monitor for potential reclassification over time. Although reclassification after a period of 1 year is not likely to compromise the opportunity for cure, it seems recommendable to confirm eligibility in an early stage.

Also, several clinical characteristics have been found to predict for unfavorable outcome at repeat biopsy. PSA-D was repeatedly found to be correlated with adverse histological outcomes [96-99], but the ideal cut-off value remains to be determined. The effect of PSA-D could be attributed to smaller prostate volumes that have been associated with higher grade disease in radical prostatectomy studies [100,101]. Nevertheless, this finding has been refuted by others [102] who say this observation is biased by PSA performance characteristics for high-grade PCa instead of true tumor biology being responsible. However, PSA-D seems to be an important prognosticator for higher risk disease. Furthermore, the number of positive cores and a PSA-DT <3 years were found to predict unfavorable repeat biopsy outcomes as described in this thesis [96]. These predictors for reclassification facilitate risk stratification to assess the likelihood of unfavorable short-term repeat biopsy results in patients with assumed low-risk PCa, and caution is warranted in case of a combination of unfavorable characteristics. However, it should be kept in mind that it is not yet known whether biopsy outcome is a valid measure to predict disease with unfavorable prognosis. There is considerable uncertainty as to the precise histological criteria (tumor size and grade) that should trigger intervention.

In long-term studies of outcome of localized PCa, Gleason score is consistently the most important prognostic factor. However, this grading system is also subject to interobserver variation [103] and sampling error due to the heterogeneity of PCa as is illustrated by the substantial amount of reclassification (22-28%) on short-term repeat biopsy in active surveillance settings [95,96,99,104].

Data on radical prostatectomy after initial active surveillance is scarce. In this thesis we have shown pathology results for a large group of 167 men in PRIAS [105]. Although the majority of men had organ-confined disease (81%) and favorable Gleason grading (Gleason score $\leq$3+4; 86%) on final pathology, reclassification of Gleason grading compared with the last biopsy results was not uncommon (31%). Unfavorable disease, defined as pT3-4 and/or Gleason score $\geq$4+3, was present in 29% of patients who underwent surgery after a median of 1.3 years after diagnosis, which underlines the importance of efforts to improve selection for active surveillance and decrease misclassification. Another study in 48 men who progressed on repeat biopsy by Duffield et al. [106] also showed favorable pathology of most tumors. They found that all 10 tumors with dominant nodules greater than 1ml were predominantly located in the anterior region of the prostate, indicating that this region should be sampled in men on active surveillance in order to improve patient selection.

There are several approaches that might improve our ability to select patients with low-risk disease for active surveillance. Prognosticators associated with misclassification at diagnosis, such as PSA-D and the number of positive cores, can be used to initiate repeat

biopsies in order to detect potential high-risk disease in an early stage. Ideally, nomograms will be developed to better predict individual risk of undersampling and/or true disease progression during follow-up. Extended biopsy schedules [107] and template biopsy mapping [108] will lead to better initial sampling of the prostate, which could potentially be improved by visualization of high-risk areas through imaging. Of course prostate biopsies are not without the risk of complications such as bleeding and infection [109], and even though serious complications are rare, the indication for a biopsy should be well-considered. It should also be kept in mind that using more stringent criteria will reduce misclassification, but will also limit the number of men eligible for active surveillance, while it remains unknown whether this would lead to an improved prognosis.

DEVELOPMENTS IN IMAGING TECHNIQUES AND BIOMARKERS

Clearly, there is an unmet need for a non-invasive method of disease monitoring during active surveillance. There is a growing interest in Magnetic Resonance Imaging (MRI) as a useful imaging technique that is being studied to evaluate its role in the selection and follow-up of PCa patients on active surveillance. Although transrectal ultrasound (TRUS) is still the mainstay for imaging of the prostate, underestimation of the tumor volume on TRUS or not being able to visualize the tumor at all and under sampling of Gleason score are potential causes for inadequate identification of PCa aggressiveness. Functional MRI techniques and MRI-guided biopsies can be used for detection and localisation of PCa, as well as to optimize the staging accuracy, which might prove valuable for the future selection and follow-up of active surveillance patients [110,111]. Results of two studies on diffusion-weighted MRI in patients managed by active surveillance showed significant differences in apparent diffusion coefficients in those who showed signs of progression compared to those who did not, supporting the potential of this technique to monitor patients with low-risk PCa and to help identify those who might be better off with radical treatment [112,113]. Another study showed that MRI did not improve the prediction of unfavorable disease features in the radical prostatectomy specimen of active surveillance suitable patients, when these patients were selected based on an extended 21-core biopsy scheme and the most stringent inclusion criteria for active surveillance [114]. Within the PRIAS study, a cohort of men in the region of Nijmegen (The Netherlands) is submitted according to protocol for multiparametric MRI since 2010. Preliminary results show a reclassification rate of 27% within 3 months from diagnosis and a rate of 44% negative biopsies in suspect lesions (unpublished data [115]). Although the use of MRI might be promising for active surveillance and in the future potentially will be included in active surveillance protocols to replace or complement

repeat biopsies, further validation is warranted to confirm its contribution to improved patient selection.

Another imaging technique that might support detection and characterisation of PCa is computer-aided ultrasonography (HistoScanning) [116]. First results showed accurate detection of PCa foci with a volume ≥0.5ml [117], but further validation of this technique is needed to evaluate its use in PCa screening and active surveillance. Preliminary results of a study in active surveillance initiated in 58 men in the PRIAS study show that patients with adverse biopsy findings after one year of follow-up also have a significantly larger tumor volume measured by Histoscanning at 12 months compared to those with favorable biopsy outcomes (S. van den Heuvel, personal communication, Dec 2011). This technique is still under development, as standardization of assessment and reporting during active surveillance has to be implemented.

The need for better biomarkers, that can be used to predict PCa behavior and indicate in whom treatment is indicated, is very real. Within the ERSPC a limited number of evaluations of potential new prognostic biomarkers has been performed. The prognostic value of the molecular markers EZH2, MIB-2, p27(kip1) and BMI-1 on biopsy cores from men with low-risk PCa who were subsequently treated with radical prostatectomy showed that a high EZH2 and a low p27(kip1) expression were predictive for significant disease [118], which could improve the pre-treatment risk assessment and the selection of men with insignificant disease. Results on the ability of PCA3 to predict PCa staging and grading are contradictory [47]. Tosoian et al. [119] studied the value of PCA3 within an active surveillance cohort; they found no association with short-term biopsy progression. Further analysis is necessary to define the role of PCA3, possibly in combination with other biomarkers, in active surveillance programs.

DEVELOPMENTS IN RISK STRATIFICATION

With the growing number of observations of men on active surveillance programs, the precision of prediction of potential insignificant cancers increases. Various prognostic models have been designed to predict insignificant PCa in a screening setting [39,120]. These nomograms predict the probability of clinically insignificant PCa by incorporating multiple clinical variables besides PSA, such as prostate volume, biopsy Gleason score, and length of noncancerous and cancerous tissue in biopsy cores, in order to support patients and clinicians when considering different treatment options. These individualized screening algorithms can help to identify substantial groups of PCa cases that are likely insignificant and can therefore be considered for active surveillance. Implementation of such risk assessment tools has been validated recently in a study analysing the use of the ERSPC Prostate Cancer Risk Calculator (www.prostatecancer-riskcalculator.com).

It was shown that the compliance to follow an advice for active surveillance in case of a prediction on the presence of an insignificant cancer of >70% amongst physicians as well as patients was 82% [42]. Further validation and improvement of these nomograms can be achieved with longer follow-up of active surveillance programs and potential addition of novel biomarkers or imaging results. As the risk calculator mentioned was validated successfully in cohorts originating from different countries, application within PRIAS as an entry criterium might be an option to improve the specificity and decrease the number of participants that need to shift towards radical treatment in the first couple of years due to misclassification.

More personalized risk assessments during follow-up of patients on active surveillance may be achieved by developing dynamic decision models [121] that consider updated clinical information, such as changing PSA values or imaging results over time, to optimize the timing of biopsies and the choice for deferred treatment. A project with the aim of developing a dynamic model and incorporating it into the PRIAS web tool is ongoing. The possibility of obtaining such updated predictions will allow for more individualized management of patients according to the evolution of his disease along the follow-up, based on outcomes of survival, quality of life and costs.

FOCAL THERAPY

The rationale for active surveillance is, in large part, based on the morbidity of current radical treatments. If a therapy would become available that had minimal or no side-effects, this could be a good replacement for active surveillance. Studies focussing on focal therapy aim to reach this goal by treating only the cancer-containing region of the prostate. However, these studies have to deal with the same challenges as those of active surveillance, namely patient selection and identification of the dominant cancer focus. Studies evaluating the accuracy of extended biopsy schemes in predicting unilateral disease in radical prostatectomy specimens show that only 22-27% of the unilateral positive cores also had unilateral disease on final pathology [122]. Another study also showed that roughly 25% of the PCa with the most favorable characteristics at diagnosis showed small volume, unilateral disease in the pathology specimen [123].

Moreover, regarding the favorable natural course of low-risk disease, it will be hard to demonstrate that focal therapy improves prognosis in these cases. When better imaging techniques allow us to more reliably define PCa and rule out significant missed disease, focal therapy may play a role in treating patients with localized disease, unsuitable for surveillance.

5α REDUCTASE INHIBITORS

Two randomized, placebo-controlled trials showed a reduction of approximately 25% in overall incidence of PCa among men using 5α reductase inhibitors (5-ARI) [124,125]. Although these data might give hope for a chemopreventive agent for PCa, these studies also showed a 0.5% increase in high-risk disease in 5-ARI users. The REDEEM (Reduction by Dutasteride of Clinical Progression Events in Expectant Management) study on the safety and efficacy of 5-ARI in men who already received a PCa diagnosis and who considered to be at low-risk, showed a reduced risk of disease progression in the 5-ARI group after 3 years [126]. Additional advantages of the use of 5-ARI in active surveillance could be the simultaneous treatment of symptoms from often coexisting benign prostatic hyperplasia and stabilization of PSA levels, which can be a source of disease-related anxiety in men. Although this might indicate a potential role for 5-ARI in the prevention of disease progression, trials with longer follow-up are required to obtain more robust data.

QUALITY OF LIFE

The potential side-effects of radical treatment have their impact on patients' quality of life (QoL). It is imaginable, however, that having to live with PCa that remains untreated also influences a man's wellbeing. Therefore, QoL is an important area of research in active surveillance for low-risk disease.

Within PRIAS the effects of expectantly managing PCa on patients' QoL have been studied. It was shown that men have good perception of their disease and the potential risks and benefits of their management strategy [127]. Furthermore, favorable levels of anxiety and distress were reported up to 9 months after diagnosis among men on active surveillance, showing comparable, or even more favorable results for depression and (disease-specific) anxiety than men who underwent other treatments for localized PCa [128,129]. Another study by Hayes et al. [130] examined the QoL benefits and risks of active surveillance compared with initial treatment for men with low-risk, clinically localized PCa. They found that active surveillance was associated with the greatest quality adjusted life expectancy and that individual preferences play a central role in the decision whether to treat or to pursue active surveillance. Patients undergoing radical prostatectomy in the PRIAS study chose deferred treatment based on anxiety in approximately 9% of the cases [81], which indicates that individual preferences play an important role in treatment decision-making. QoL will be subject to further prospective evaluation within PRIAS and other active surveillance studies to fulfil the need for long-term data assessed with validated questionnaires and we have to work towards a

multidisciplinary approach to support patients who might be more distressed to learn effective strategies aimed at coping with their fears.

EPILOGUE

FUTURE PERSPECTIVES

In the contemporary practice of widespread PSA testing many screen-detected PCa that would never have become clinically apparent if it was not for screening are diagnosed, leading to overdiagnosis. Until strategies aimed at preventing overdiagnosis have been developed, active surveillance will play an important role in the management of insignificant disease. However, there are challenges in screening as well as in active surveillance that need to be addressed in order to improve individualized screening strategies and decrease overdiagnosis on the one hand, and to optimize active surveillance strategies on the other.

Protocols used to monitor patients on surveillance vary between different studies and are currently not evidence based. The natural course of PCa is not yet completely understood, however, studies reporting on the outcome of low-risk disease after expectant management are quite favorable, even showing similar disease-specific survival when compared to radical prostatectomy, especially in older men. Therefore the rationale for active surveillance is clear, but it remains challenging to distinguish insignificant from aggressive disease based on histology at diagnosis. Although misclassification at diagnosis has been showed to be quite common, it is likely that many of the PCa harbouring more aggressive disease than initially assumed will be found during follow-up through repeated histological evaluation. The acceptance of active surveillance as a management strategy for PCa would surely improve if staging and grading could be predicted with more accuracy in an early stage. Therefore, in the future we have to keep working towards improving risk stratification by means of extended biopsy schemes, novel biomarkers and advanced imaging techniques, which could contribute to this effort. In this thesis, we have reflected on the controversy associated with the use of active surveillance and the possibilities for optimisation of patient care and the application of emerging technologies and biomarkers [131]. Future studies on the use of already existing algorithms that incorporate multiple clinical characteristics to predict the chance of harbouring insignificant disease, will contribute to the individual management of patients. Furthermore, research on new molecular and genetic biomarkers is needed to improve the differentiation between potentially aggressive and insignificant PCa. Ide-

ally, only those men who will truly benefit from radical treatment should be subjected to active therapy with its subsequent side-effects.

Retrospective series with longer follow-up [63,64] add to the evidence that active surveillance for low-risk PCa seems to be a safe approach and that, in the short en medium term, it could be a viable option for many men with intermediate-risk PCa. Up till now, results from PRIAS and other prospective active surveillance studies have been encouraging and only very small numbers of adverse events have been reported. However, follow-up in most series is quite short and there are still challenges to be tackled regarding optimal selection of patients and triggers for intervention. Selection of men suitable for active surveillance should be improved, thereby optimizing the number of potential active surveillance candidates, increasing the active therapy-free survival and preserving quality of life, and preventing treatment delay of potentially aggressive tumors beyond the so-called window of opportunity for cure. Priority should be given to research focused on how to reduce the high misclassification rates and the role of imaging and biomarkers in risk stratification and as a proxy for biopsy. Longer follow-up in active surveillance series is warranted to validate the safety of this approach in terms of PCa survival and to support further optimisation the inclusion and follow-up criteria for active surveillance.

THE PRIAS STUDY

Important research goals for the PRIAS study comprise the validation of eligibility criteria and triggers for treatment. Longer follow-up will provide us with more solid information for validation of these criteria, as well as the strategy as a whole, such as biochemical recurrence after treatment, metastatic disease, and PCa-specific death. However, in the recent publications, as well as the next few years, we have to use surrogate endpoints such as repeat biopsy results and active therapy-free survival. These surrogate endpoints show that our selection of patients might be too restrictive, since a substantial number of patients is recommended to switch to deferred treatment over time, while the long-term prognosis of low-risk, and even intermediate-risk patients, on expectant management has shown to be rather favorable. Although not all patients with intermediate-risk disease should be offered active surveillance, the question of expanded criteria will be an important area of investigation in the coming years. Selected men who do not meet the current or low-risk criteria for active surveillance, might still want to consider it as their initial strategy, with the understanding that it might come down to delayed rather than avoided treatment. Eventually, we have to attempt to find

a balance between maximizing the number of patients, who can safely avoid (or delay) radical treatment, while minimizing the number of aggressive PCa missed.

Other issues that the PRIAS study data will hopefully shed more light on in the years to come are international differences in patient characteristics, reclassification rates, and more solid disease-specific endpoints. Of special interest is the development of dynamic models that allow for more individualized management of patients by obtaining updated predictions according to the changing clinical characteristics over time. PRIAS data can be used for this purpose to support further validation, implementation and improvement of active surveillance as a management strategy for low-risk PCa. These risk assessment tools will enable a more individualized approach to the management of a patient with PCa and will hopefully lead to a further decrease in overtreatment with its subsequent risk of side-effects, thereby attenuating the largest negative side-effect of screening and increasing the quality of life. Nested side studies on the use of MRI in active surveillance will be another point of interest. Finally, an important joint effort with the other large active surveillance cohorts will be an international collaboration combining all available data in a registry to enable thorough research to deal with important endpoints for active surveillance by means of meta-analysis.

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VI | Appendices

SUMMARY

The *first part* of this thesis comprises an introduction to prostate cancer and screening (**chapter 1**). The European Randomized study of Screening for Prostate Cancer (ERSPC) has shown an effect of screening on prostate cancer mortality in favor of the screening population, however, controversies remain. One of the most important side-effects of screening is overdiagnosis with subsequent overtreatment, which has led to the introduction of active surveillance as an alternative to the radical treatment of prostate cancer (**chapter 2**). With active surveillance, patients with supposedly low-risk tumors receive expectant management and are strictly followed over time. In case of reclassification to higher risk or signs of true disease progression, the patient will switch to deferred radical treatment. Because active surveillance is a relatively new management strategy, its feasibility and the short-term outcomes are the main focus of this thesis (**chapter 3**).

The *second part* of this thesis focuses on low-risk prostate cancer. In **chapter 4** the main findings of the ERSPC are described and the controversial points in prostate cancer screening are discussed, as well as how these issues should be dealt with. Overdiagnosis and overtreatment are indicated as major worries, but less aggressive screening methods, risk modifying calculators and the use of active surveillance can decrease the impact of these side-effects and, if applied, will lead to a better risk-benefit ratio in screening. In **chapter 5**, it is shown that the risk of developing prostate cancer, aggressive prostate cancer and prostate cancer death in men with initial PSA values <3.0 ng/ml in the Rotterdam screening arm of the ERSPC increased with higher initial PSA levels. However, prostate cancer mortality in this cohort was relatively low, compared to men with initial levels ≥3.0 ng/ml (11-fold higher) and compared to the risk of other causes of death (150-fold higher). Especially men with PSA <1.0 ng/ml at first screen had a minimal risk to die from prostate cancer during an 11 year period. This finding supports the idea to prolong the screening interval to at least 8 years in this group. The overall outcomes of this study contribute to risk stratification and individual management of men in PSA-based screening programs. The long-term feasibility of expectant management as a proxy for active surveillance in contemporary practice is assessed in **chapter 6** by evaluating outcomes of men with screen-detected localized prostate cancer who initially elected to withhold radical treatment for either low- or intermediate-risk disease. Although intermediate-risk men, by definition, had more unfavorable disease characteristics at diagnosis, their 10-year disease-specific survival rates did not differ from the low-risk group. The overall outcomes were favorable with a 98.4% disease-specific survival rate for the overall cohort, while radical treatment was avoided in a majority of cases. These results support the feasibility for active surveillance on the longer-term and even show that selected patients with intermediate-risk disease might profit from this strategy.

In *part three*, **chapter 7**, an effort is made to calculate correction factors based on autopsy data for the use of the prostate cancer risk calculator in contemporary practice. The original risk calculator is based on sextant biopsies, while nowadays often more biopsy cores are taken. Adjustments correcting for this increase would lead to a more accurate prediction of the probability of indolent cancer. Correction factors for 12 and 18-core schemes were calculated; however, the small number of patients and the lack of validation hamper implementation of the results and reinforce the need for further study.

Part four shows the results of the Prostate Cancer Research International: Active Surveillance (PRIAS) trial. **Chapter 8** focuses on the outcome of the routinely obtained 1-year repeat biopsies and identifying prognosticators for unfavorable results. Risk reclassification to higher risk was found in 163 out of 757 (21.5%) repeat biopsies. The outcome was found to be significantly associated with the number of positive cores (2 vs. 1) and PSA density at diagnosis, as well as PSA doubling time at the time of repeat biopsy. Though reclassification is quite common and more likely due to misclassification than to actual disease progression, the relatively high rate emphasizes the difficulty of patient selection and the need for continued evaluation in active surveillance. Results of this study show that clinical features at baseline and during follow-up can be used in risk stratification of men for the prediction of unfavorable features at repeat biopsy. Radical prostatectomy results after initial active surveillance are described in **chapter 9**. The majority of men showed organ-confined disease and favorable Gleason grading ($\leq$3+4) in a majority of cases. Nevertheless, 29% (49/167) were found to have an unfavorable radical prostatectomy outcome. Since median time to surgery was quite short (1.3 years), it is likely that that most of the cases with unfavorable outcome were misclassified at diagnosis. More than 75% of this cohort switched to surgery based on a protocol recommendation, which may, at least in part, explain the relatively high rate of unfavorable findings due to the self-selection of men who start on active surveillance and receive surgery because of reclassification during follow-up. These results again show the importance of improvement in patient selection for active surveillance. **Chapter 10** gives an up-to-date overview of the PRIAS study. Short-term data confirm the feasibility of active surveillance in the reduction of overtreatment and the use of a web-based tool to facilitate worldwide inclusion of patients. Clinical characteristics at baseline and PSA kinetics are again shown to be predictive for reclassification, as well as for switching to deferred treatment. The active therapy-free survival after 2 and 4 years was found to be 77.3% and 67.7%, respectively. The disease-specific survival rate was 100%, but follow-up is still too short to draw definitive conclusions. Finally, in **chapter 11**, an overview is presented of key issues in active surveillance that need to be tackled and emerging technologies and markers that will hopefully lead to optimization of patient selection and care in the near future.

The *fifth part* of this thesis summarizes and discusses the key findings of the studies described in all previous chapters and puts them into perspective (**chapter 12**). The rationale for active surveillance and the feasibility of this strategy are discussed in more detail. An overview of contemporary active surveillance trials is presented and the areas of improvement are indicated. Eventually, a balance needs to be found between maximizing the number of patients who can avoid treatment and minimizing the number of aggressive prostate cancer missed. The improvement of screening strategies and developments in the technologies for radical treatment in the future might lead to decreased rates of overdiagnosis and virtual disappearance of side-effects, which in turn would reduce the need for active surveillance as an alternative to radical treatment. Until then, research aimed at improving active surveillance strategies will continue and we will carry on providing the best care available today to our patients.

SAMENVATTING

In het *eerste deel* van dit proefschrift wordt een introductie gegeven over prostaatkanker en screening van prostaatkanker (**hoofdstuk 1**). De Europese gerandomiseerde studie naar screening op prostaatkanker (ERSPC) heeft een effect laten zien op de vermindering van sterfte aan prostaatkanker ten gunste van de screeningarm. Echter, het invoeren van prostaatkankerscreening blijft omstreden. Eén van de meest belangrijke neveneffecten van screening is overdiagnostiek en daarmee gepaard gaande overbehandeling, wat heeft geleid tot de introductie van het actief afwachtend beleid (ofwel 'active surveillance') als een alternatief voor de radicale behandeling van prostaatkanker (**hoofdstuk 2**). Bij active surveillance wordt bij patiënten met een vermeend laag-risico tumor een afwachtend beleid gevoerd, waarbij zij volgens een strikt protocol in de tijd worden gevolgd. Wanneer er sprake blijkt van reclassificatie naar een hoger risico of wanneer er aanwijzing is voor daadwerkelijke progressie van ziekte, is uitgestelde radicale behandeling geïndiceerd. Omdat active surveillance een relatief nieuwe management strategie is, zijn de haalbaarheid van een dergelijke aanpak en de kortetermijn uitkomsten ervan de belangrijkste onderwerpen van dit proefschrift (**hoofdstuk 3**).

Het *tweede deel* van dit proefschrift richt zich op laag-risico prostaatkanker. In **hoofdstuk 4** worden de belangrijkste resultaten van de ERSPC beschreven en worden omstreden onderwerpen bediscussieerd. Overdiagnostiek en overbehandeling worden hierbij aangegeven als belangrijke problemen veroorzaakt door screening, maar minder agressieve screening, het gebruik van risicowijzers en het toepassen van active surveillance kunnen de invloed van deze neveneffecten verminderen en zullen dan ook leiden tot een betere verhouding tussen baten en lasten. In **hoofdstuk 5** wordt getoond dat het risico op het ontwikkelen van (agressieve) prostaatkanker en sterfte aan prostaatkanker bij mannen met een initieel PSA <3.0 ng/ml in de Rotterdamse screeningarm van de ERSPC toeneemt met een hogere initiële PSA waarde. De sterfte aan prostaatkanker was in dit cohort echter relatief laag in verhouding met de mannen die een initieel PSA ≥3.0 ng/ml hadden (11 keer hoger risico) en in verhouding met de sterfte aan andere oorzaken (150 keer hoger risico). Vooral mannen met een PSA <1.0 ng/ml bij de initiële screening hadden een minimaal risico om te overlijden aan prostaatkanker binnen een periode van 11 jaar. Deze bevinding ondersteunt het idee om het screening interval in deze groep naar 8 jaar op te schuiven. De uitkomsten van deze studie dragen bij aan de risicostratificatie en het individuele management van mannen die in een op PSA gebaseerd screeningprogramma zitten. De haalbaarheid van een afwachtend beleid op de lange termijn wordt bekeken in **hoofdstuk 6** door de uitkomsten te evalueren van mannen met een door screening gedetecteerde, gelokaliseerde prostaatkanker, bij wie in eerste instantie een expectatief beleid werd gevoerd. Er werd zowel naar de uitkomsten van laag-risico als naar die van matig-risico patiënten gekeken. Hoewel mannen met

matig-risico ziekte per definitie slechtere ziekte karakteristieken hadden bij diagnose, was de ziekte-specifieke overleving over 10 jaar in deze groep vergelijkbaar met die in de laag-risico groep. De uitkomsten lieten verder gunstige overlevingskansen zien voor het gehele cohort (98.4%), terwijl radicale behandeling in het merendeel van de gevallen kon worden vermeden. Deze resultaten laten zien dat active surveillance als management strategie voor prostaatkanker op de langere termijn haalbaar is en dat, naast laag-risico tumoren, mogelijk ook goed geselecteerde mannen met een matig risico voor deze aanpak in aanmerking kunnen komen.

In *deel drie*, **hoofdstuk 7**, worden correctiefactoren berekend op basis van gegevens verkregen in een autopsie studie. Deze factoren zijn bedoeld om de prostaatkanker risicowijzer verder toe te kunnen spitsen op het gebruik in de huidige praktijk, waarbij vaak uitgebreider wordt gebiopteerd dan de sextante biopten waarop de risicowijzer is gebaseerd. Factoren om te corrigeren voor deze uitgebreidere biopten leiden tot een preciezere voorspelling van de kans op een indolente tumor. Er werden correctiefactoren voor schema's van 12 en 18 biopten berekend, maar de kleine aantallen en het gebrek aan validatie belemmeren directe implementatie van de resultaten. Verder onderzoek is dus noodzakelijk.

In *deel vier* worden resultaten getoond van de PRIAS studie. In **hoofdstuk 8** ligt de nadruk op de uitkomst van het herhalingsbiopt dat, volgens studieprotocol, na 1 jaar is gepland. Ook werd gekeken naar voorspellers van een slechte uitkomst. Reclassificatie van het risico naar een hoger risico werd gevonden in 163 van de 757 herhalingsbiopten (21.5%). Een slechte uitkomst bleek significant geassocieerd te zijn met het aantal positieve biopten (2 versus 1) en de PSA dichtheid bij diagnose, alsook met de PSA verdubbelingstijd ten tijde van het herhalingsbiopt. Reclassificatie komt regelmatig voor en lijkt meer verband te houden met initiële misclassificatie dan met daadwerkelijke progressie van ziekte. Het relatief hoge percentage laat zien dat het lastig kan zijn om patiënten goed te selecteren en geeft ook aan dat continue evaluatie in het geval van active surveillance belangrijk is. De resultaten laten zien dat klinische karakteristieken bij diagnose en tijdens follow-up gebruikt kunnen worden voor de risicostratificatie van patiënten voor het voorspellen van ongunstige karakteristieken bij het herhalingsbiopt. Radicale prostatectomie resultaten na initiële active surveillance worden besproken in **hoofdstuk 9**. Het merendeel van de mannen heeft bij pathologische evaluatie gelokaliseerde ziekte en een gunstige Gleason score ($\leq$3+4). Desalniettemin wordt in 29% (49/167) van de gevallen een ongunstige uitslag gevonden. Gezien de korte tijd tot operatie (mediaan 1.3 jaar), is het het meest waarschijnlijk dat de meeste van deze gevallen niet juist geclassificeerd zijn bij diagnose. Ruim 75% van het cohort onderging een radicale prostatectomie op basis van een protocollaire aanbeveling voor behandeling. Dit kan (deels) een verklaring geven voor het relatief hoge percentage ongunstige resultaten, doordat een geselecteerde groep ontstaat van mannen die beginnen met

active surveillance, maar op basis van reclassificatie gedurende follow-up toch kiezen voor definitieve behandeling. Deze resultaten benadrukken wederom de relevantie van de noodzaak tot verbeterde selectie voor active surveillance. **Hoofdstuk 10** geeft een overzicht van de PRIAS studie. De kortetermijn resultaten laten zien dat active surveillance een goede aanpak is om overbehandeling tegen te gaan en dat het gebruik van een webportaal de inclusie en follow-up van patiënten wereldwijd vergemakkelijkt. Reclassificatie en de overstap naar actieve therapie zijn significant geassocieerd met klinische karakteristieken bij diagnose en PSA kinetiek. De actieve therapie-vrije overleving na 2 en 4 jaar was respectievelijk 77.3% en 67.7%. De ziekte-specifieke overleving was 100%, maar de follow-up is nog te kort om hier harde conclusies aan te verbinden. In **hoofdstuk 11** wordt een overzicht gegeven van de te verbeteren kernpunten binnen active surveillance en de vooruitgang in onderzoek naar beeldvorming en biomarkers die hopelijk in de nabije toekomst tot een optimalisering van de selectie van en zorg voor patiënten gaan leiden.

In het *vijfde deel* van dit proefschrift worden de belangrijkste bevindingen van de voorgaande hoofdstukken bediscussieerd en in perspectief geplaatst (**hoofdstuk 12**). The rationale en haalbaarheid van active surveillance worden in meer detail besproken. Er wordt een overzicht gegeven van de huidige active surveillance studies en van de punten waarop verbetering te behalen is. Uiteindelijk moet een balans worden gevonden tussen het maximaliseren van het aantal patiënten bij wie radicale behandeling kan worden voorkomen en het minimaliseren van het aantal patiënten bij wie agressieve prostaatkanker wordt gemist. Het verbeteren van screening strategieën en de ontwikkeling van behandeltechnologieën zou in de toekomst kunnen leiden tot een vermindering van de overdiagnostiek en het verdwijnen van bijwerkingen van behandeling, waardoor de noodzaak van active surveillance als alternatief voor radicale behandeling steeds meer af zal nemen. Tot die tijd zal onderzoek naar het verbeteren van active surveillance nodig zijn en zullen we de best beschikbare zorg mogelijk maken voor de huidige generatie patiënten.

CURRICULUM VITAE

Meelan Bul werd op 29 maart 1981 geboren in Rotterdam. Zij groeide op in Capelle aan den IJssel en ging hier ook naar de middelbare school. In 1999 begon zij, na uitloten voor geneeskunde, met de studie biomedische wetenschappen in Leiden en behaalde hiervoor haar propedeuse. In 2000 kon zij dan toch van start met de studie geneeskunde in Rotterdam aan de Erasmus universiteit. Tijdens de co-schappen werd al snel duidelijk dat de snijdende kant van het artsenvak het meest trok. Na een laatste co-schap in Zuid-Afrika begon zij als arts-assistent chirurgie in ziekenhuis Walcheren in Vlissingen. Ook deed zij chirurgische ervaring op in het Albert Schweitzer ziekenhuis in Dordrecht en in het Academisch Medisch Centrum in Amsterdam, alvorens de keuze te maken voor de urologie. Nadat zij vijf maanden als arts-assistent urologie in het Erasmus MC in Rotterdam had gewerkt, begon zij in 2010 met haar driejarig promotietraject op het screeningbureau urologie van het Erasmus MC, onder leiding van professor Bangma, professor Schröder en Monique Roobol. In januari 2013 is Meelan begonnen met haar heelkundige vooropleiding in het Albert Schweitzer ziekenhuis in Dordrecht en in 2015 zal zij haar opleiding urologie voortzetten in het Erasmus MC in Rotterdam. In haar vrije tijd houdt zij zich graag bezig met diverse sporten, waaronder fitness, wielrennen, boulderen, hockeyen en mountainbiken en is zij regelmatig als RPM-instructeur (indoor cycling) te vinden op de sportschool.

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Meelan

ERASMUS UNIVERSITEIT ROTTERDAM

PhD PORTFOLIO

Name PhD student	Meelan Bul
Erasmus MC	Department of Urology
PhD period	2010-2012
Promotor	Prof. dr. C.H. Bangma
Supervisors	Prof. dr. F.H. Schröder
	Dr. M.J. Roobol

PhD training	**Year**	**Workload (ECTS)**
General courses		
Biomedical English writing	2010-2011	4
Erasmus summer programme (NIHES)	2010	5.5
Seminars and workshops		
Department Urology journal club	2010-2012	1
Department Urology internal course	2010-2012	1
Department Urology PhD meeting	2010-2012	0.5
Multi-disciplinaire behandeling prostaatkanker	2010	1
Presentations		
Voorjaarsvergadering NVU	2010	0.5
Masterclass EUomo, Krakow	2010	1
Najaarsvergadering NVU	2010	0.5
SEOHS symposium, Rotterdam	2010	0.5
Genitourinary cancers symposium, ASCO, Orlando	2011	1
Annual meeting EAU, Vienna (*best poster*)	2011	1
ERSPC meeting, Peschierra	2011	1
Annual meeting AUA, Washington	2011	1
Active surveillance symposium, Rotterdam	2012	0.5
Annual meeting EAU, Paris (*best poster*)	2012	1
ERSPC meeting, Yllasjärvi	2012	1
Pomeranian Uro-Oncology meeting, Jastzrebia Gora	2012	1
Annual meeting AUA, Atlanta	2012	1
Prostate Action Forum, Rotterdam	2012	1

International conferences		
Annual ERSPC meetings	2010-2012	1.0
Annual PRIAS study user meetings	2010-2012	1.0
NVU biannual meetings	2010-2012	0.5
Masterclass EUomo	2010	0.5
SEOHS symposium	2010	0.5
ASCO	2011	0.5
Annual meetings EAU	2011-2012	1.0
Annual meetings AUA	2011-2012	1.0
Active surveillance symposium	2012	0.5
Pomeranian Uro-Oncology meeting	2012	0.5
Prostate Action Forum	2012	0.5
Global congress on prostate cancer	2012	0.5
Lecturing		
PRIAS study user meetings	2010-2012	1
Physician education PRIAS, Hilversum	2010	1
Urology working group IKZ, Eindhoven	2011	1
Total ECTS	**36**	

ABBREVIATIONS

NIHES	Netherlands Institute for Health Sciences
NVU	Nederlandse Vereniging voor Urologie
SEOHS	Symposium Experimenteel Onderzoek Heelkundige Specialismen
ASCO	American Society of Clinical Oncology
ERSPC	European Randomized Study of Screening for Prostate Cancer
EAU	European Association of Urology
AUA	American Urological Association
PRIAS	Prostate Cancer Research International: Active Surveillance